Systematic Review and Meta-analysis of Deaths Attributable to Antimicrobial Resistance, Latin America

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Antimicrobial resistance is a pressing global health concern, leading to 4.95 million deaths in 2019. We conducted a systematic review and meta-analysis to assess the lethality attributed to infections caused by multidrug-resistant organisms (MDROs) in Latin America and the Caribbean. A comprehensive search of major databases retrieved relevant studies from 2000–2022. We included 54 observational studies, primarily from Brazil, Argentina, and Colombia. The most commonly studied organism was methicillin-resistant *Staphylococcus aureus*. The overall unadjusted case fatality rate related to MDROs was 45.0%; higher adjusted lethality was observed in persons infected with MDROs than in those infected with other pathogens (adjusted odds ratio 1.93, 95% CI 1.58–2.37). A higher lethality rate was seen in patients who did not receive appropriate empirical treatment (odds ratio 2.27, 95% CI 1.44–3.56). These findings underscore the increased lethality associated with antimicrobial resistance in Latin America and the Caribbean.

Antimicrobial resistance (AMR) is a growing public health problem that affects health, the economy, and human development (*1*). A 2016 review of AMR showed that drug-resistant infections will kill 10 million persons annually by 2050 and cause a cumulative economic loss of US $100 trillion if proactive solutions to slow the rise of drug resistance are not implemented (*2*). Although some persons have criticized this forecast, numerous researchers agree that the spread of AMR is an urgent problem, one that will require a global, coordinated action plan to solve (*3*,*4*).

Recently, a study using statistical predictive models based on a comprehensive systematic review estimated 4.95 million deaths related to AMR, including 1.27 million deaths attributable to AMR, occurred across 204 countries and territories in 2019 (*5*). The highest burden of AMR is seen in low-resource settings. AMR was the third leading underlying cause of death for 2019 in the Institute for Health Metrics and Evaluation's Global Burden of Disease study (https://www.healthdata.org/research-analysis/gbd). In addition, deaths attributable to AMR surpassed deaths caused by HIV, tuberculosis, and malaria. Understanding the effects of AMR is crucial for building policy resolutions, particularly regarding antimicrobial and diagnostic stewardship and infection prevention and control programs. This study, in which we defined attributable lethality as the excess lethality of patients with infections caused by resistant organisms compared with patients with infections caused by the same susceptible pathogens, represents an essential contribution to knowledge of the effects of AMR on lethality. However, because the estimations were performed for 2019, data related to the effects of the COVID-19 pandemic could not be part of this study. In addition, estimates of attributable lethality for the Latin America region were based principally on data from Brazil, Colombia, and Mexico; information from other countries in the region was limited (*5*). The incidence of multidrug-resistant organisms (MDROs) increased during the COVID-19 pandemic because of widespread use of antimicrobial drugs and breaches in infection control practices (*6*–*8*). During 2020–2021, Latin American and

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Caribbean (LAC) countries reported clinical emergence of carbapenemase-producing Enterobacterales that had not been previously characterized locally, increased prevalence of carbapenemases that had been previously detected, and coproduction of multiple carbapenemases in some isolates (*9*).

Several studies have estimated the effects of antibiotic resistance on incidence, deaths, length of hospital stay, and healthcare costs for MDROs (*1*,*2*,*10*), but systematic research on the effects of AMR in the LAC region for a wide range of bacteria and infections is lacking. We conducted a systematic review to address this evidence gap.

Materials and Methods

Search Strategy and Selection Criteria

We performed a systematic review and meta-analysis using Cochrane methods (*11*) and the PRISMA (*12*) statement for reporting systematic reviews and meta-analysis. We searched records published during January 1, 2000–March 29, 2022, in the databases CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, Embase, LILACS (Latin American and Caribbean Health Sciences Literature), and CINAHL (Cumulative Index to Nursing and Allied Health Literature), without language restriction and with geographic scope of LAC countries (Appendix, https://wwwnc.cdc.gov/EID/article/29/11/23-0753-App1.pdf).

We included cohort studies, case–control studies, cross-sectional and control arms of randomized and quasi-randomized controlled trials, with ≥20 inpatient or outpatient participants, irrespective of age and sex, that assessed case-fatality rate (i.e., number of deaths among diagnosed cases only) within 30 days postinfection by any of the following resistant organisms: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE, including *Klebsiella pneumoniae*, *Enterobacter*, *Escherichia coli*, *Proteus*, and *Serratia*), carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA), carbapenem-resistant *Acinetobacter baumannii* (CR-AB), or azole/echinocandin-resistant *Candida* spp. (*1*). We have incorporated the MDRO category, which encompasses a diverse array of microorganisms (MRSA, VRE, ESBL-E, CRE, CR-PA, CR-AB). MDRO definitions and appropriate empirical treatment varied among primary studies. We accepted the definitions given by each study author.

We planned to include economic evaluations to assess resource use, including hospital stays and loss of health-related quality of life. We considered systematic reviews and meta-analyses only as sources for primary studies. When we found data or data subsets reported in >1 publication, we selected the most recent study or the study with the larger sample size. We searched databases containing proceedings of regional congresses and doctoral theses. We also consulted websites from the main regional medical societies, experts, and associations related to the topic (Appendix).

Statistical Analysis

Pairs of reviewers independently selected articles by evaluating titles and abstracts of identified studies and then performing full-text review using Covidence software (https://www.covidence.org). One reviewer performed data extraction and a second verified data by using a prespecified extraction online form previously piloted in 10 studies. The same reviewers independently assessed the risk for bias using a checklist for observational studies developed by the US National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). All authors resolved discrepancies by consensus.

We extracted study information consisting of type of publication, year of publication, authors, population, geographic location, study design, methods, pathogen–drug combinations, counterfactual data, and outcomes of interest. We classified population risk as high risk if they met ≥1 of the following characteristics: intensive care unit (ICU) setting or >50% of enrolled patients from ICU; median Charlson Comorbidity Index of >3 (if not reported, >50% of the patients with >1 comorbidity); or patients referred from high-risk wards (i.e., hematology, oncology, burns, transplantation, and infectious diseases, including HIV units). Otherwise, we classified the population as average risk. If study authors provided no data, we categorized the population risk as unknown.

To analyze our data, we used descriptive statistics and performed proportional meta-analysis using the random effects model whenever possible, employing methods to stabilize variance given the degree of expected heterogeneity. We applied the arcsine transformation to stabilize the variance of proportions using inverse arcsine variance weights for the random effects model with the metagen function (*13*,*14*). We used the restricted maximum-likelihood estimator to calculate the heterogeneity variance τ^2 across the studies and I^2 statistic as a measure of the proportion

of the overall variation that was attributable to between-study heterogeneity (*15*,*16*).

The primary outcome was deaths attributable to AMR. Mortality rates describe the incidence of deaths among a specific population over a specific time. In this study, the population under investigation consisted of infected persons; although the accurate term is lethality (number of deaths among infected patients), we occasionally use the term mortality, which is more commonly used in the literature. We have included adjusted measures, such as odds ratio (OR), relative risk (RR), or hazard ratio (HR), when they were available for ≥10 events in the susceptible or resistance group. We included the longest time-point in-hospital lethality reported in each study in the analysis. We also performed a random-effects meta-analysis to estimate the pooled unadjusted OR when possible. Otherwise, we calculated ORs and 95% CIs using the information provided in each study. We report all effects estimates with a 95% CI. We describe the remaining results narratively and in tables.

We performed subgroup analysis by recruitment year and pathogen-drug combination. We performed a sensitivity analysis to assess the effect of risk for bias on the results of the primary analyses by limiting the analysis to a low risk for bias for the primary domains. We also used Knapp-Hartung adjustments to estimate 95% CIs around the pooled effect as a sensitivity analysis (*17*).

To further explore heterogeneity, we conducted a meta-regression analysis to examine whether adjusted and unadjusted effect estimates differed notably by year of study recruitment, population severity, resistance mechanisms or type of resistance, and appropriate empirical antibiotic treatment. We also planned a sensitivity analysis on the basis of the type of adjustment performed and considered it appropriate if the authors controlled in the final model ≥1 variable in each of these categories: variables related to the patients' baseline status, variables related to the infection, and variables related to the treatment (*18*).

We visually inspected the funnel plot for asymmetry to assess publication bias and performed Begg's test. We used R software version 4.0.3 for all analyses (*19*). The protocol of this study is registered in PROSPERO (https://www.crd.york.ac.uk/prospero; identification no. CRD42022322795).

Results

We identified 1,141 records from databases and 204 records from other sources; after the selection process, 54 studies met our inclusion criteria (Figure 1). The articles were published during January 1, 2000–March 29, 2022; the inclusion period of participants was 1991–2020. We excluded 19 studies at the extraction stage (Appendix Table 6). Most included studies were cohort studies (50/54 [92.6%]); 36 were retrospective studies. The studies provided data on AMR mainly from Brazil (29 [53.7%]), Argentina (8 [14.8%]), Colombia (6 [11.1%]), and Mexico (6 [11.1%]). Of the 54 included studies, participants in 38 (70.4%) were adults (adults and elderly patients), and 6 (11.1%) studies included only children (neonates and pediatric patients). In the 49 studies that reported the source of patients, all participants were hospitalized, 18 (36.7%) consisted of ICU patients, and 20 (40.9%) included both ICU and non-ICU patients. High-risk populations were included in 43 (79.6%) studies. The most frequently evaluated individual microorganism was MRSA in 16 (29.6%) studies (Appendix Table 12). We identified a fair risk of bias in 24 (44.4%) of 54 studies (Appendix Tables 7, 8). We noted additional characteristics of individual included studies (Appendix Table 9).

We assessed lethality and association measures of the individual studies (Appendix Table 13). The overall unadjusted case-fatality rate related to MDRO was 45.0% (95% CI 40.0–50.0; I^2 85.0%) (Appendix Figure 1). We found higher lethality among participants infected with MDRO than among participants infected with nonresistant organisms, grouped according to the type of resistance (pooled adjusted OR [aOR] 1.93, 95% CI 1.58–2.37; I^2 0%) (Figure 2). Although that trend was maintained in studies that reported RR or HR as adjusted measures, the difference was not statistically significant. We found no evidence of publication bias among studies reporting aOR or adjusted HR (Appendix Figures 2, 3).

Higher lethality was also observed in those who did not receive appropriate empirical treatment (OR 2.27, 95% CI 1.44–3.56) than in those who did (OR 1.59, 95% CI 0.99–2.56), although the test for subgroup differences was not statistically significant (p = 0.57). We also found no statistically significant difference (p = 0.75) between resistance and lethality in those studies that included appropriate empiric antibiotic treatment as a covariate in the adjusted model (Figure 3; Appendix Figure 4).

We report the association between unadjusted lethality and type of resistance (Table). The pooled unadjusted lethality associated with resistant infections was significantly higher (OR 1.86, 95% CI 1.55–2.23) than that associated with susceptible infections but with high heterogeneity (I^2 71%) (Appendix Figure 5). We identified a downward trend (p = 0.463) of this pooled OR of lethality over time (Figure 4). We also

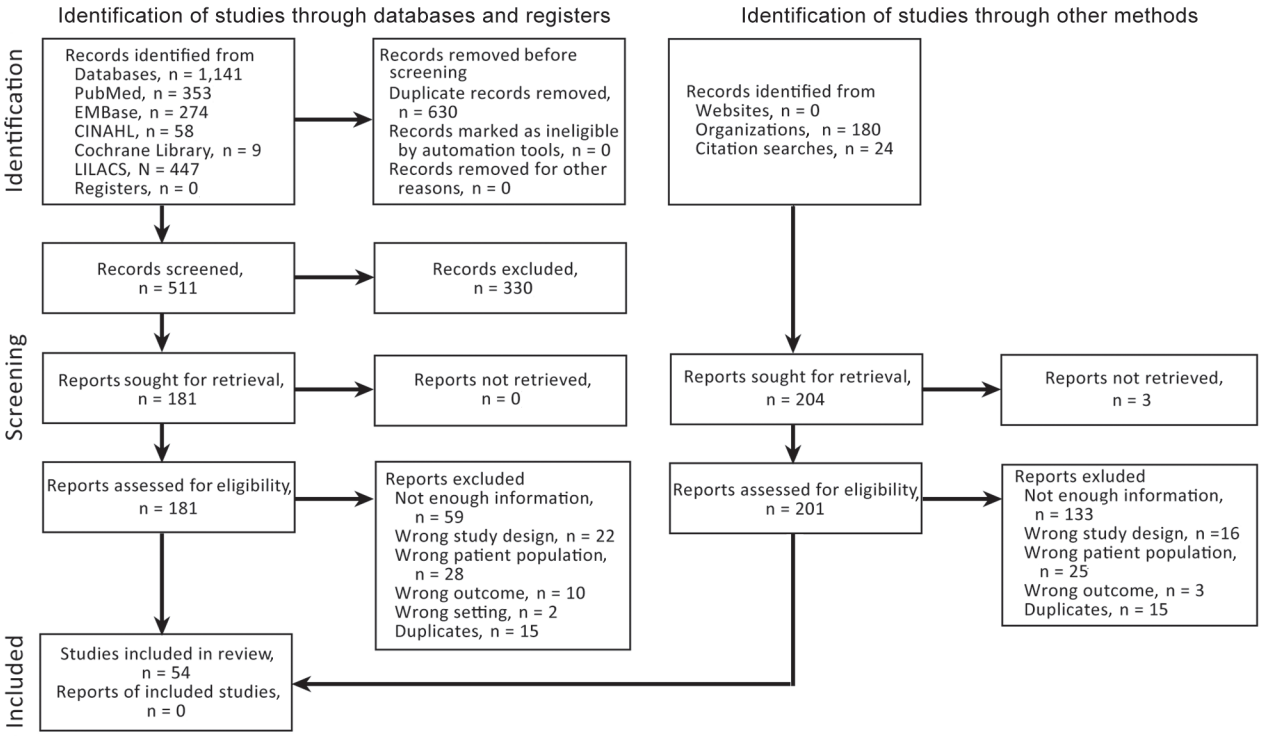

Figure 1. Flowchart demonstrating identification process of studies for systematic review and meta-analysis of deaths attributable to antimicrobial resistance, Latin America. CINAHL, Cumulative Index to Nursing and Allied Health Literature; LILACS, Latin American and Caribbean Health Sciences Literature).

presented a forest plot of unadjusted OR for lethality by year of study recruitment (Appendix Figure 6). The results of a meta-regression analysis showed no significant differences in effect estimates (Appendix Table 10).

We analyzed the difference between the pooled unadjusted and adjusted lethality associated with resistance between studies that reported both measures (Appendix Figure 7). The magnitude of the effect was larger when looking at the unadjusted measures, but the differences between subgroups were not statistically significant (p = 0.360).

We performed a sensitivity analysis based on the type of multivariate model adjustment reported in the studies. Although the aOR was larger when the adjustment was appropriate, we found no statistically significant subgroup differences (p = 0.56) (Appendix Figure 8). As a sensitivity analysis, we report the 95% CI around the pooled effect with Knapp-Hartung adjustments in those studies that report adjust measures. We found no major differences with or without this method (Appendix Table 11).

In all but 2 reports where hospitalization stay was documented, patients with resistant microorganisms exhibited longer length of stay relative to those with susceptible strains (Appendix Table 9). We did not find any information related to loss of health-related quality of life attributable to MDRO in the region. Length of stay was not reported because data were scarce and heterogeneous.

Discussion

This systematic review and meta-analysis offers a thorough and current evaluation of how infection with a wide range of antimicrobial-resistant bacteria affects the lethality rates for infectious diseases during hospitalization in LAC countries. We established the unadjusted and adjusted lethality attributable to MDRO within this region. A previous study reported estimations using predictive statistical modeling to produce estimates of AMR burden for all locations, including for locations with no data. However, the methodologic approach used in this study differed substantially (*5*).

Although unadjusted case-fatality rates varied across different MDROs, the lowest values were observed for ESLB-E. That finding might be because of the increased use of carbapenems as appropriate initial empirical treatments, especially for healthcare-associated infections, which some studies have demonstrated in the region (*34*).

Similar to previous researchers (*35*,*36*), we also report that drug resistance might lead to an increased

attributable risk for death. However, our findings should be interpreted with caution because of substantial heterogeneity in effect estimates across studies and other methodologic limitations. The heterogeneity was partially explained by the fact that some studies were adjusted for confounding variables, but others were not. When we analyzed studies adjusted for confounding variables separately, the results for each group were no longer heterogeneous. The adjustment decreased the association strength,

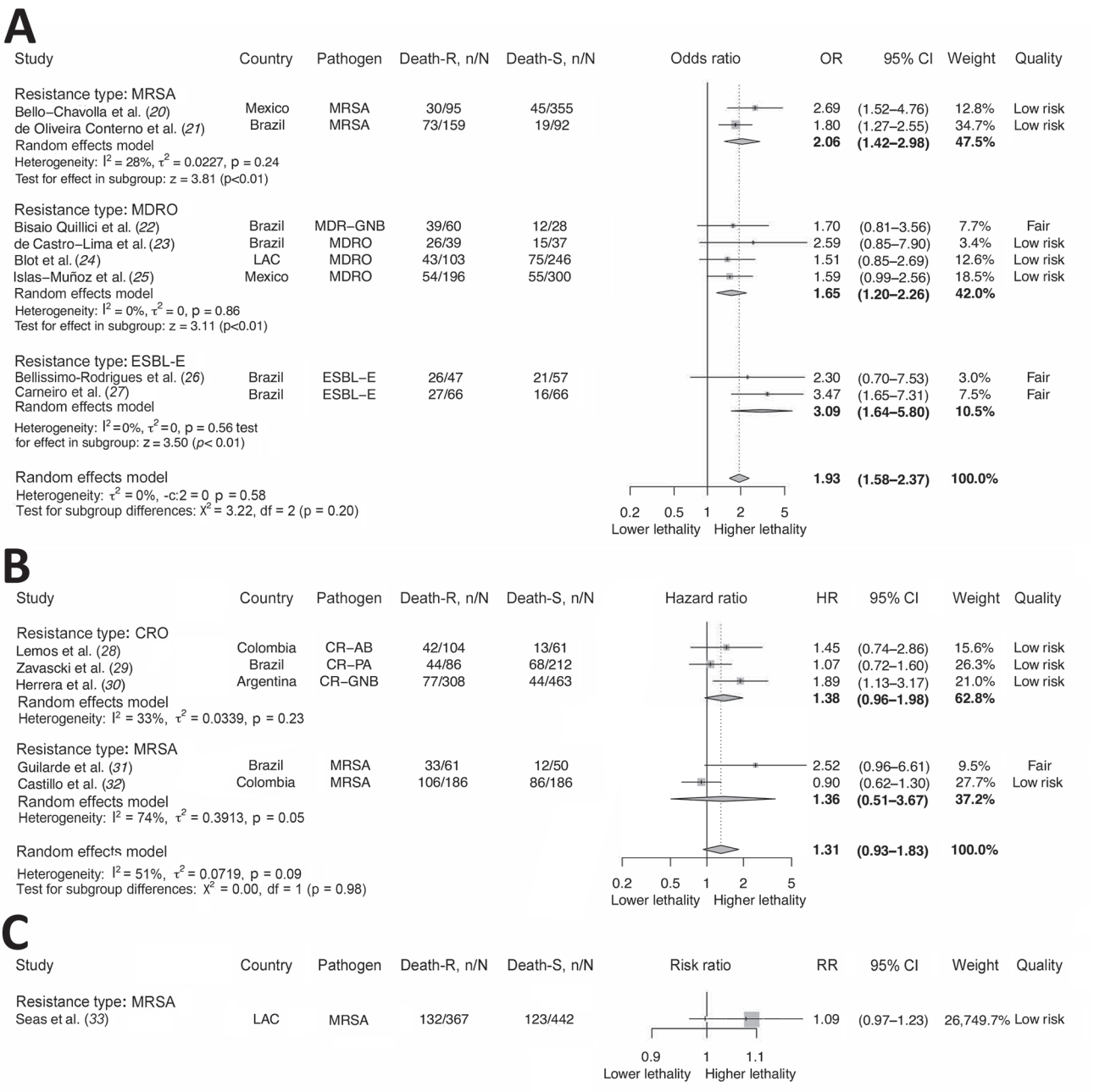

Figure 2. Association between antimicrobial resistance and lethality by the type of resistance in systematic review and meta-analysis of deaths attributable to antimicrobial resistance, Latin America. Adjusted measures are shown as adjusted odds ratio (A), adjusted hazard ratio (B), and adjusted risk ratio (C). Death-R indicates death in the resistant group; Death-S indicates death in the susceptible group. Error bars indicate 95% CIs. CR-AB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CR-GNB, carbapenem-resistant gram-negative bacteria (including CRE, CR-PA, CR-AB); CR-PA, carbapenem-resistant *Pseudomonas aeruginosa*; CRO, carbapenem-resistant organisms; ESBL-E, extended-spectrum β-lactamase–producing Enterobacterales; HR, hazard ratio; LAC, Latin American and Caribbean; MDR-GNB, multidrug-resistant gram-negative bacilli (including ESBL-E, CRE, CR-PA, CR-AB); MDRO, multidrug-resistant organisms (including MRSA, vancomycin-resistant *Enterococcus*, ESLB-E, CRE, CR-PA, CR-AB); MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; RR, risk ratio.

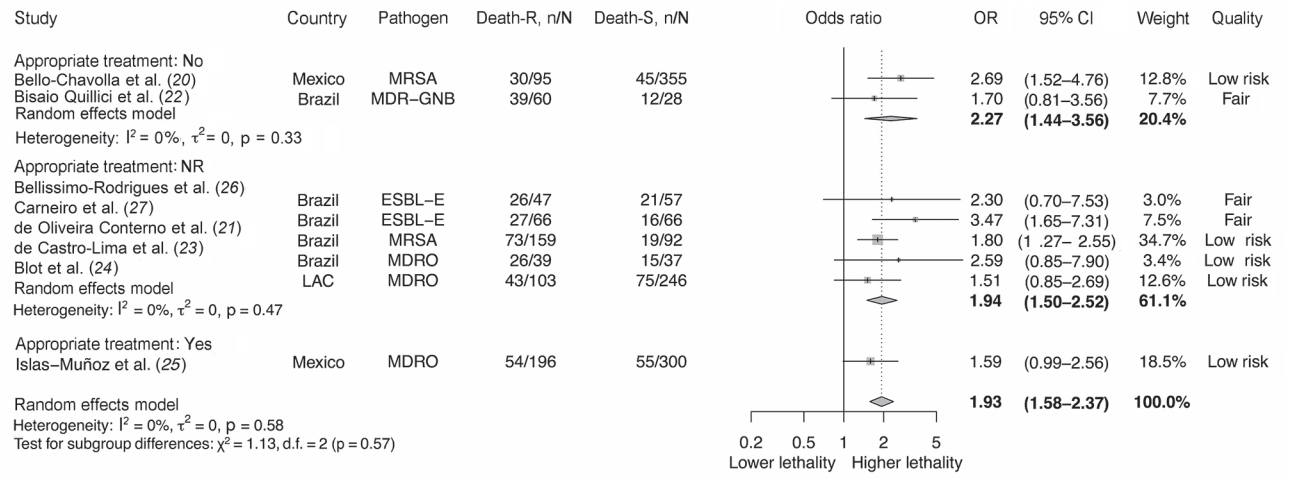

Figure 3. Adjusted odds ratios between antimicrobial resistance and lethality by appropriate empirical antibiotic treatment (considering the definition of appropriate empirical treatment given by each author) in systematic review and meta-analysis of deaths attributable to antimicrobial resistance, Latin America. Death-R indicates death in the resistant group; Death-S indicates death in the susceptible group. Error bars indicate 95% CIs. CR-AB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CR-PA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-E, extended-spectrum β-lactamase–producing Enterobacterales; MDR-GNB, multidrug-resistant gram-negative bacilli (including ESBL-E, CRE, CR-PA, CR-AB); MDRO, multidrug-resistant organisms (including MRSA, vancomycin-resistant Enterococcus, ESLB-E, CRE, CR-PA, CR-AB); MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; OR, odds ratio.

although the subgroup differences were not statistically significant. The downward trend of pooled unadjusted lethality OR and resistance by calendar recruitment period was not statistically significant, but this finding still might reflect a better understanding of the resistance mechanisms and an improved empirical treatment.

As in previous reports (*37*,*38*), our report found 2 times higher attributable lethality associated with MRSA infections than with non-MRSA infections. As in our study, the heterogeneity was explained by the fact that some studies were adjusted for confounding variables, but others were not. When those studies that were adjusted for confounding variables were analyzed separately from studies that were not adjusted, the results for each group were no longer heterogeneous (Appendix Figure 7). Of note, several studies have identified the association of inappropriate empirical antibiotic treatment with increased lethality among patients with MRSA bacteremia (*39*,*40*).

Table. Pooled unadjusted odds ratio for the association between antimicrobial resistance and lethality by type of resistance, Latin America*

Type of resistance	OR (95% CI)	I^2
Carbapenem-resistance	2.86 (2.07–3.95)	61%
Extended-spectrum β-lactamase	1.28 (0.95–1.74)	38%
Methicillin-resistance	1.78 (1.29–2.45)	63%
MDRO†	1.64 (1.16–2.30)	68%
Azol-resistant	1.41 (0.59–3.35)	-
Vancomycin-resistant	4.09 (2.40–6.97)	0%
Random effect model	1.86 (1.55–2.23)	71%

*MDRO, multidrug-resistant organisms; OR, pooled odds ratio.
†Multidrug-resistant organisms include methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant *Enterococcus* spp, extended-spectrum β-lactamase producing Enterobacterales, carbapenem-resistant Enterobacterales (including *Klebsiella, Enterobacter, Escherichia coli, Proteus, Serratia*), carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii* and azole/echinocandin-resistant *Candida* spp.

In our study, patients with VRE infections were 4-fold (unadjusted) more likely to die than patients infected with vancomycin-susceptible *Enterococcus* spp. A previous meta-analysis indicated that vancomycin resistance was an independent predictor of death among patients with enterococcal bacteremia (2.5-fold adjusted) (*41*). Some plausible explanations for this association difference, besides the adjustment of the last estimation, might include type of infection, suboptimal activity, or dosing among the antimicrobials used against VRE, a systematic delay in the initiation of antimicrobial agents active against VRE, and differences in intrinsic virulence among vancomycin-resistant and vancomycin-susceptible species of enterococci.

In our study, infections by ESBL-E were associated with higher lethality than for non–ESBL-E. Other studies have found that ESBL-E bacteremia is associated with higher lethality than bacteremia with non–ESBL-E, although the estimate of this association is affected by adjustment procedures. Adjustment for adequate empirical therapy or delay in effective therapy leads to reduced ORs, indicating that higher

lethality is likely to be partly mediated through this phenomenon (*42*–*44*).

We found a significant attributable lethality associated with carbapenem-resistant organisms in 11 studies included in our meta-analysis. A previous study showed that KPC-producing *K. pneumoniae* was independently associated with 3 times higher in-hospital lethality (*45*).

A meta-analysis of 15 studies consisting of 3,201 cases of *P. aeruginosa* infection demonstrated a 2-fold higher lethality rate among patients infected with the multidrug-resistant strain than those with a non–multidrug-resistant strain, especially in patients with bloodstream infection, immunosuppression, and inadequate antimicrobial therapy (*35*). Other meta-analyses showed that appropriate initial antibiotic therapy was associated with lower unadjusted lethality for *P. aeruginosa* infections than was inappropriate initial antibiotic therapy. The association with lethality persisted in sensitivity meta-analysis of low-risk bias studies (*46*).

In a meta-analysis that included 16 observational studies, patients with CR-AB had a significantly 2-fold higher risk for lethality than patients with non–carbapenem-resistant strain in the pooled analysis, although substantial heterogeneity was evident. The association remained significant in the pooled aOR of 10 studies. Compared with patients with non–carbapenem-resistant strains, patients with CR-AB were more likely to have a severe underlying illness and to receive inappropriate empirical antimicrobial treatment, which increases the risk for lethality (*47*).

In our meta-analysis, 4 studies evaluating attributable lethality showed that MDRO had significantly higher lethality than non-MDRO. Although different microorganisms and site infections were represented, we did not find statistical heterogeneity.

For gram-negative infections, a meta-analysis showed that lethality was higher in patients with multidrug-resistant infections than those with non–multidrug-resistant infections (*48*). The meta-analysis demonstrated that septic shock, ICU stay, pneumonia, isolation of multidrug-resistant gram-negative bacteria, inappropriate empirical and definitive treatment, and male sex were more common in patients who died than patients who survived (*48*). In addition, several studies have reported inappropriate empirical and definitive treatment as independent variables associated with attributable lethality (*35*,*39*–*44*,*46*–*49*)

As the incidence of AMR rises, a corresponding increase in the likelihood of inappropriate empirical treatment occurs. Our meta-analysis revealed that persons who did not receive appropriate empirical treatment had a higher lethality rate than those who did. However, the lack of information regarding the adequacy of antimicrobial therapy in many studies might explain the absence of statistically significant differences between subgroups.

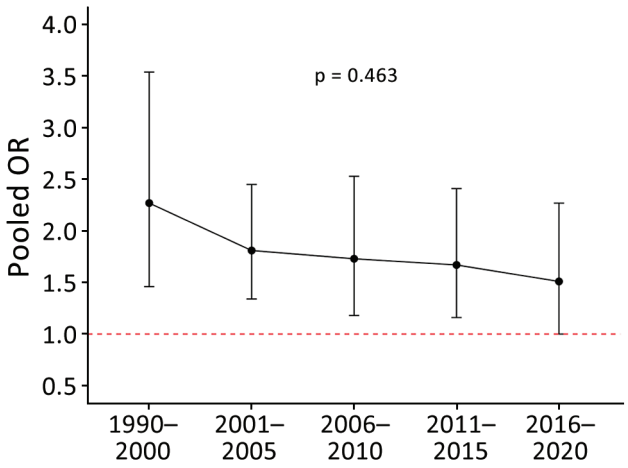

Figure 4. Pooled unadjusted OR between antimicrobial resistance and lethality by calendar recruitment period in systematic review and meta-analysis of deaths attributable to antimicrobial resistance, Latin America. Data points depict pooled lethality estimates from random effects meta-analysis models. Error bars indicate 95% CIs. OR, odds ratio.

The first limitation of our study is that of the 41 cohort studies included, only 14 were prospective. Incomplete collection in surveys in retrospective cohort studies limits confidence in their estimates. Other limitations include the lack of data for most countries in the LAC region and the number of included studies with small samples. For example, most data were obtained from a few tertiary centers in each country, which are likely to report higher rates of resistance than their national averages. Methods for reporting, collection, and analysis might also differ among laboratories, countries, and surveillance networks. Other limitations included the type of infections (which might vary across included studies), the type of antimicrobial drugs administered for the infection, the type of bacteria, and the mechanism of resistance, which might lead to differences in lethality.

In conclusion, our systematic review and meta-analysis demonstrate that MDROs are associated with higher attributable lethality across different periods in LAC than sensitive organisms, even after adjusting for confounding variables. More studies on AMR-attributable lethality would be needed in the region, with adjustment by confounders and larger sample sizes. Rather than relying solely on new drug development to address the problem of AMR, we should focus efforts on preventing the emergence and transmission of these organisms through the One

Health initiative, principally in low-income settings (*50*). Future studies that involve many healthcare centers and that adjust for potential confounding variables should be undertaken to address the impact of AMR. In addition, expanding microbiology laboratory capacity and data collection systems are necessary to improve our understanding of this critical human health threat.

Acknowledgments

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The data used for this analysis can be made available upon reasonable request once all relevant substudies from the consortium are reported and completed. The data dictionary can be made available upon request to the corresponding author.

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R.Q., A.C., and C.E. conceptualized the study. Data were curated by M.S., E.N., and C.P. Formal analysis was performed by A.C., A.B., M.S., E.N., and C.P., R.Q., and C.E. acquired funding. R.Q., A.C., A.B., M.S., E.N., C.P., and C.E. conducted the investigation. R.Q., A.C., A.B., M.S., E.N., C.P., and C.E. constructed the methodology. Project administration was performed by A.C. A.C., A.B., and R.Q. supervised the study. R.Q., A.C., A.B., M.S., E.N., C.P., and C.E. participated in the writing of the original draft. R.Q., A.C., A.B., M.S., E.N., C.P., and C.E. performed review and editing.

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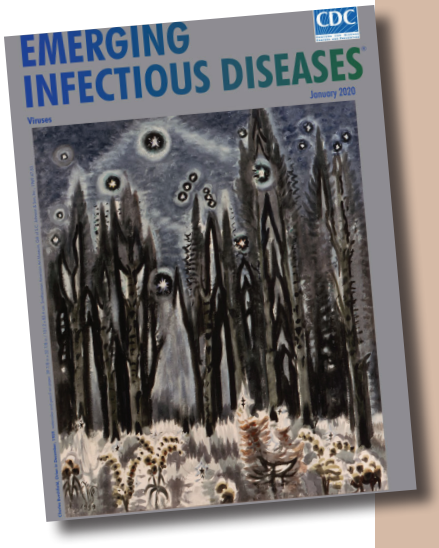
etymologia revisited

Picobirnavirus [pi-ko-burr′nə-vi″rəs]

Picobirnavirus, the recently recognized sole genus in the family *Picobirnaviridae*, is a small (*Pico*, Spanish for small), bisegmented (*bi*, Latin for two), double-stranded RNA virus. Picobirnaviruses were initially considered to be birna-like viruses, and the name was derived from birnavirus (bisegmented RNA), but the virions are much smaller (diameter 35 nm vs. 65 nm).

Picobirnaviruses are reported in gastroenteric and respiratory infections. These infections were first described in humans and black-footed pigmy rice rats in 1988. Thereafter, these infections have been reported in feces and intestinal contents from a wide variety of mammals with or without diarrhea, and in birds and reptiles worldwide.



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https//wwwnc.cdc.gov/eid/article/26/1/et-2601_article

Article DOI: https://doi.org/10.3201/eid2911.230753

Systematic Review and Meta-analysis of Deaths Attributable to Antimicrobial Resistance, Latin America

Appendix

Search Strategy

Appendix Table 1. Terms used in PubMed search, 26 March 2022

Search	Query
#67	#4 AND #29 AND #50 AND #65 AND #66 Filters: from 2000/1/1 - 3000/12/12
#66	(Americas[MeSH Terms:noexp] OR Latin America[Mesh] OR Latin America*[tiab] OR Latinamerica*[tiab] OR Latinoamerica*[tiab] OR Hispanoamerica*[tiab] OR Iberoamerica*[tiab] OR Ibero Americ*[tiab] OR Panamerican*[tiab] OR Central America[Mesh] OR Central America*[tiab] OR Centroamerica*[tiab] OR Mesoamerica*[tiab] OR Meso America*[tiab] OR Middle America*[tiab] OR South America[Mesh] OR South America*[tiab] OR Southamerica*[tiab] OR Sudamerica*[tiab] OR "America del sur"[tiab] OR Caribbean Region[Mesh] OR Caribbean[tiab] OR Caribe*[tiab] OR West Indies[Mesh] OR West Indi*[tiab] OR Antill*[tiab] OR Indians, South American[Mesh] OR Indians, Central American[Mesh] OR Amerindian*[tiab] OR Indians[tiab] OR American Indian*[tiab] OR Native America*[tiab] OR Patagoni*[tiab] OR Andes[tiab] OR Andean*[tiab] OR Amazon*[tiab] OR Argentin*[ad] OR Argentin*[tiab] OR Argentina[pl] OR Bolivia*[ad] OR Bolivia*[tiab] OR Bolivia[pl] OR Brazil*[ad] OR Brasil*[ad] OR Brazil*[tiab] OR Brasil*[tiab] OR Brazil[pl] OR Colombia*[ad] OR Colombia*[tiab] OR Colombia[pl] OR Chile*[ad] OR Chile*[tiab] OR Chile[pl] OR Ecuador*[ad] OR Ecuator*[ad] OR Ecuador*[tiab] OR Ecuador[pl] OR Guiana*[ad] OR Guiana*[tiab] OR French Guiana[pl] OR Guyan*[ad] OR Guyan*[tiab] OR Guyana[pl] OR Paraguay*[ad] OR Paraguay*[tiab] OR Paraguay[pl] OR Peru*[ad] OR Peru*[tiab] OR Peru[pl] OR Surinam*[ad] OR Surinam*[tiab] OR Surinam*[pl] OR Uruguay*[ad] OR Uruguay*[tiab] OR Uruguay[pl] OR Venez*[ad] OR Venez*[tiab] OR Venezuela[pl] OR Belize*[ad] OR Belize*[tiab] OR Belize[pl] OR Costa Ric*[ad] OR Costarric*[ad] OR Costaric*[ad] OR Costa Ric*[tiab] OR Costarric*[tiab] OR Costaric*[tiab] OR Costa Rica[pl] OR Salvador*[ad] OR Salvador*[tiab] OR El Salvador[pl] OR Guatemal*[ad] OR Guatemal*[tiab] OR Guatemala[pl] OR Hondur*[ad] OR Hondur*[tiab] OR Honduras[pl] OR Nicaragu*[ad] OR Nicaragu*[tiab] OR Nicaragua[pl] OR Panam*[ad] OR Panam*[tiab] OR Panama[pl] OR Mexico[Mesh] OR Mexic*[ad] OR Mexic*[tiab] OR Mejic*[tiab] OR Mexico[pl] OR Baham*[ad] OR Baham*[tiab] OR Bahamas[pl] OR Cuba*[ad] OR Cuba*[tiab] OR Cuba[pl] OR Dominic*[ad] OR Dominic*[tiab] OR Dominican Republic[pl] OR Haiti*[ad] OR Haiti*[tiab] OR Haiti[pl] OR Jamaic*[ad] OR Jamaic*[tiab] OR Jamaica[pl] OR Puerto Rico[Mesh] OR Puerto Ric*[tiab] OR Puertorric*[tiab] OR Puertoric*[tiab])
#65	#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64
#64	Hospital Stay*[tiab]
#63	"Length of Stay"[tiab]
#62	Stay Length*[tiab]
#61	Length of Stay[Mesh]
#60	DALY*[tiab]
#59	Disability Adjusted[tiab]
#58	Adjusted Life[tiab]
#57	QALY*[tiab]
#56	Quality Adjusted[tiab]
#55	Quality-Adjusted Life Years[Mesh]
#54	Fatality Rate*[tiab]
#53	Death Rate*[tiab]
#52	Mortalit*[tiab]

Search	Query
#51	Mortality[Mesh]
#50	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#49	ICU Infect*[tiab]
#48	ICU Associated[tiab]
#47	ICU Acquired[tiab]
#46	Community Infect*[tiab]
#45	Community Associated[tiab]
#44	Community Acquired[tiab]
#43	Healthcare Associated[tiab]
#42	Healthcare Infect*[tiab]
#41	Healthcare Acquired[tiab]
#40	Intrahospital Acquired[tiab]
#39	Intrahospital Associated[tiab]
#38	Intrahospital Infect*[tiab]
#37	Hospital Infect*[tiab]
#36	Hospital Associated[tiab]
#35	Hospital Acquired[tiab]
#34	Nosocomial Acquired[tiab]
#33	Nosocomial Associated[tiab]
#32	Nosocomial Infect*[tiab]
#31	Cross infect*[tiab]
#30	Cross Infection[Mesh]
#29	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#28	Enterobacter*[tiab]
#27	Enterobacteriaceae[Mesh]
#26	Enterococc*[tiab]
#25	Enterococcus[Mesh]
#24	Staphylococcus Aure*[tiab]
#23	Staphylococcus Aureus[Mesh]
#22	Herellea*[tiab]
#21	Acinetobacter*[tiab]
#20	Acinetobacter[Mesh]
#19	Pseudomona*[tiab]
#18	Pseudomonas[Mesh]
#17	Jadinii[tiab]
#16	Monilia*[tiab]
#15	Candid*[tiab]
#14	Candida[Mesh]
#13	Carbapenemase-Producing Enterobacter*[tiab]
#12	Carbapenem Resist*[tiab]
#11	Carbapenem-Resistant Enterobacteriaceae[Mesh]
#10	Cephalosporin Resist*[tiab]
#9	Vancomycin Resist*[tiab]
#8	Vancomycin-Resistant Enterococci[Mesh]
#7	MRSA[tiab]
#6	Methicillin Resist*[tiab]
#5	Methicillin-Resistant Staphylococcus Aureus[Mesh]
#4	#1 OR #2 OR #3
#3	AMR[tiab]
#2	Resist*[all]
#1	Drug Resistance, Microbial[Mesh]

Appendix Table 2. Terms used in EMBase (OVID) search, 28 March 2022 (Embase Classic+Embase <1947 to 2022 March 28>)

#	Query
1	exp antibiotic resistance/
2	Resist*.mp.
3	AMR.ti,ab.
4	or/1–3
5	exp methicillin resistant Staphylococcus aureus/
6	(Methicillin adj3 Resist*).ti,ab.
7	MRSA.ti,ab.
8	exp vancomycin resistant Enterococcus/
9	(Vancomycin adj3 Resist*).ti,ab.
10	(Cephalosporin adj3 Resist*).ti,ab.
11	exp carbapenem-resistant Enterobacteriaceae/
12	(Carbapenem adj3 Resist*).ti,ab.
13	(Carbapenemase-Producing adj3 Enterobacter*).ti,ab.
14	exp Candida/
15	Candid*.ti,ab.
16	Monilia*.ti,ab.
17	Jadinii.ti,ab.
18	exp Pseudomonas/
19	Pseudomona*.ti,ab.
20	exp Acinetobacter/
21	Acinetobacter*.ti,ab.
22	Herellea*.ti,ab.
23	exp Staphylococcus aureus/
24	Staphylococcus Aure*.ti,ab.
25	exp Enterococcus/
26	Enterococc*.ti,ab.
27	exp Enterobacteriaceae/
28	Enterobacter*.ti,ab.
29	or/5–28
30	exp cross infection/
31	(Cross* adj1 infect*).ti,ab.
32	(Nosocomial adj1 Infect*).ti,ab.
33	(Nosocomial adj1 Associated).ti,ab.
34	(Nosocomial adj1 Acquired).ti,ab.
35	(Hospital* adj1 Acquired).ti,ab.
36	(Hospital* adj1 Associated).ti,ab.
37	(Hospital* adj1 Infect*).ti,ab.
38	(Intra?hospital adj1 Infect*).ti,ab.
39	(Intra?hospital adj1 Associated).ti,ab.
40	(Intra?hospital adj1 Acquired).ti,ab.
41	(Health?care adj1 Acquired).ti,ab.
42	(Health?care adj1 Infect*).ti,ab.
43	(Health?care adj1 Associated).ti,ab.
44	(Community adj1 Acquired).ti,ab.
45	(Community adj1 Associated).ti,ab.
46	(Community adj1 Infect*).ti,ab.
47	(ICU adj1 Acquired).ti,ab.
48	(ICU adj1 Associated).ti,ab.
49	(ICU adj1 Infect*).ti,ab.
50	or/30–49
51	exp mortality/
52	Mortalit*.ti,ab.
53	Death Rate*.ti,ab.
54	Fatality Rate*.ti,ab.
55	exp quality adjusted life year/
56	(Quality adj1 Adjusted).ti,ab.
57	QALY*.ti,ab.
58	exp disability-adjusted life year/
59	(Disability adj1 Adjusted).ti,ab.
60	(Adjusted adj1 Life).ti,ab.
61	DALY*.ti,ab.
62	exp “length of stay”/
63	(Stay adj3 Length*).ti,ab.
64	(Hospital* adj3 Stay*).ti,ab.
65	or/51–64
66	(exp South/ and Central America/) or (Latin adj1 America*).ti,ab. or Latinamerica*.ti,ab. or Latinoamerica*.ti,ab. or Hispanoamerica.ti,ab. or Iberoamerica*.ti,ab. or (Ibero adj1 Americ*).ti,ab. or Panamerica*.ti,ab. or (South adj1 America*).ti,ab. or Southamerica*.ti,ab. or Sudamerica*.ti,ab. or (America adj1 Sur).ti,ab. or (Central adj1

#	Query
	America*).ti,ab. or Centroamerica*.ti,ab. or Mesoamerica*.ti,ab. or (Meso adj1 America*).ti,ab. or (Middle adj1 America*).ti,ab. or exp Caribbean Islands/ or Caribbean*.ti,ab. or Caribe*.ti,ab. or (West adj1 Indi*).ti,ab. or Antill*.ti,ab. or exp American indian/ or Amerindian*.ti,ab. or Indians.ti,ab. or (Native adj1 America*).ti,ab. or Patagoni*.ti,ab. or Andes.ti,ab. or Andean*.ti,ab. or Amazon*.ti,ab. or exp Argentina/ or Argentin*.ti,ab. or exp Bolivia/ or Bolivia*.ti,ab. or exp Brazil/ or Brazil*.ti,ab. or Brasil*.ti,ab. or exp Colombia/ or Colombia*.ti,ab. or exp Chile/ or Chile*.ti,ab. or exp Ecuador/ or Ecuador*.ti,ab. or exp French Guiana/ or Guiana*.ti,ab. or exp Guyana/ or Guyan*.ti,ab. or exp Paraguay/ or Paraguay*.ti,ab. or exp Peru/ or Peru*.ti,ab. or exp Suriname/ or Surinam*.ti,ab. or exp Uruguay/ or Uruguay*.ti,ab. or exp Venezuela/ or Venez*.ti,ab. or exp Belize/ or Beliz*.ti,ab. or exp Costa Rica/ or (Costa adj1 Rica).ti,ab. or Costarric*.ti,ab. or Costaric*.ti,ab. or exp El salvador/ or Salvador*.ti,ab. or exp Guatemala/ or Guatemal*.ti,ab. or exp Honduras/ or Hondur*.ti,ab. or exp Nicaragua/ or Nicaragu*.ti,ab. or exp Panama/ or Panam*.ti,ab. or exp Mexico/ or Mexic*.ti,ab. or exp Cuba/ or Cuba*.ti,ab. or exp Dominican Republic/ or Dominica*.ti,ab. or exp Haiti/ or Haiti*.ti,ab. or exp Jamaic/ or Jamaic*.ti,ab. or exp Puerto Rico/ or (Puerto adj1 Ric*).ti,ab. or Puertoric*.ti,ab. or Puertorric*.ti,ab.
67	4 and 29 and 50 and 65 and 66
68	limit 67 to yr = ”2000 -Current”

Appendix Table 3. Terms used in CINAHL Complete (EBSCO) search, 29 March 2022

#	Query
S70	S4 AND S31 AND S51 AND S66 AND S69 Limiters - Published Date: 20000101–20220331
S69	S67 OR S68
S68	AB (Latin N1 America*) OR Latinamerica* OR Latinoamerica* OR Latin* OR Hispanic Americans OR Iberoamerica* OR (Ibero N1 Americ*) OR Panamerican* OR (Central N1 America*) OR Centroamerica* OR Mesoamerica* OR (Meso N1 America*) OR (Middle N1 America*) OR (South N1 America*) OR Southamerica* OR Sudamerica* OR (America N1 Sur) OR Caribbean OR Caribe* OR (West N1 Indi*) OR Antill* OR Amerindian* OR Indians OR (American N1 Indian*) OR (Native N1 America*) OR Patagoni* OR Andes OR Andean* OR Amazon* OR Argentin* OR Bolivia* OR Brazil* OR Brasil* Colombia* OR Colombia* OR Colombia OR Chile* OR Ecuador* OR Guiana* OR Guyan* OR Guyan* OR Paraguay* OR Paraguay* OR Peru* OR Surinam* OR Surinam* OR Uruguay* OR Venez* OR Belize* OR (Costa N1 Ric*) OR Costarric* OR Costaric* OR Costa Ric* OR Costarric* OR Salvador* OR Salvador* OR Guatemal* OR Guatemal* OR Guatemala OR Hondur* OR Nicaragu* OR Panam* OR Mexic* OR Cuba* OR Dominic* OR Dominic* OR Haiti* OR Jamaic* OR (Puerto N1 Ric*) OR Puertorric* OR Puertoric*
S67	TI (Latin N1 America*) OR Latinamerica* OR Latinoamerica* OR Latin* OR Hispanic Americans OR Iberoamerica* OR (Ibero N1 Americ*) OR Panamerican* OR (Central N1 America*) OR Centroamerica* OR Mesoamerica* OR (Meso N1 America*) OR (Middle N1 America*) OR (South N1 America*) OR Southamerica* OR Sudamerica* OR (America N1 Sur) OR Caribbean OR Caribe* OR (West N1 Indi*) OR Antill* OR Amerindian* OR Indians OR (American N1 Indian*) OR (Native N1 America*) OR Patagoni* OR Andes OR Andean* OR Amazon* OR Argentin* OR Bolivia* OR Brazil* OR Brasil* Colombia* OR Colombia* OR Colombia OR Chile* OR Ecuador* OR Guiana* OR Guyan* OR Guyan* OR Paraguay* OR Paraguay* OR Peru* OR Surinam* OR Surinam* OR Uruguay* OR Venez* OR Belize* OR (Costa N1 Ric*) OR Costarric* OR Costaric* OR Costa Ric* OR Costarric* OR Salvador* OR Salvador* OR Guatemal* OR Guatemal* OR Guatemala OR Hondur* OR Nicaragu* OR Panam* OR Mexic* OR Cuba* OR Dominic* OR Dominic* OR Haiti* OR Jamaic* OR (Puerto N1 Ric*) OR Puertorric* OR Puertoric*
S66	S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65
S65	TI (Stay N3 Hospital*) OR AB (Stay N3 Hospital*)
S64	TI (Stay N3 Length*) OR AB (Stay N3 Length*)
S63	(MH “Length of Stay”)
S62	TI DALY* OR AB DALY*
S61	TI (Disability N1 Adjusted) OR AB (Disability N1 Adjusted)
S60	(MM “Disability-Adjusted Life Years”)
S59	TI (Adjusted N1 Life) OR AB (Adjusted N1 Life)
S58	TI QALY* OR AB QALY*
S57	TI (Quality N1 Adjusted) OR AB (Quality N1 Adjusted)
S56	(MM “Quality-Adjusted Life Years”)
S55	TI (Fatality N1 Rate*) OR AB (Fatality N1 Rate*)
S54	TI (Death N1 Rate*) OR AB (Death N1 Rate*)
S53	TI Mortalit* OR AB Mortalit*
S52	(MH “Mortality+”)
S51	S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50
S50	TI (ICU N1 Acquired) OR AB (ICU N1 Acquired)
S49	TI (ICU N3 Infect*) OR AB (ICU N3 Infect*)
S48	TI (Community N3 Infect*) OR AB (Community N3 Infect*)
S47	TI (Community N1 Associated) OR AB (Community N1 Associated)
S46	TI (Community N1 Acquired) OR AB (Community N1 Acquired)
S45	TI (Healthcare N1 Associated) OR AB (Healthcare N1 Associated)
S44	TI (Healthcare N1 Infect*) OR AB (Healthcare N1 Infect*)
S43	TI (Healthcare N1 Acquired) OR AB (Healthcare N1 Acquired)
S42	TI (Intrahospital N1 Acquired) OR AB (Intrahospital N1 Acquired)
S41	TI (Intrahospital N1 Associated) OR AB (Intrahospital N1 Associated)

#	Query
S40	TI (Intrahospital N1 Infect*) OR AB (Intrahospital N1 Infect*)
S39	TI (Hospital* N1 Infect*) OR AB (Hospital* N1 Infect*)
S38	TI (Hospital* N1 Associated) OR AB (Hospital* N1 Associated)
S37	TI (Hospital* N1 Acquired) OR AB (Hospital* N1 Acquired)
S36	TI (Nosocomial N1 Acquired) OR AB (Nosocomial N1 Acquired)
S35	TI (Nosocomial N1 Associated) OR AB (Nosocomial N1 Associated)
S34	TI (Nosocomial N1 Infect*) OR AB (Nosocomial N1 Infect*)
S33	TI (Cross N1 Infect*) OR AB (Cross N1 Infect*)
S32	(MH “Cross Infection+”)
S31	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30
S30	TI Enterobacter* OR AB Enterobacter*
S29	(MH “Enterobacteriaceae+”)
S28	TI Enterococc* OR AB Enterococc*
S27	(MH “Vancomycin Resistant Enterococci”)
S26	(MH “Enterococcus+”)
S25	TI (Staphylococcus N1 Aure*) OR AB (Staphylococcus N1 Aure*)
S24	(MH “Vancomycin-Resistant Staphylococcus Aureus”)
S23	(MH “Staphylococcus Aureus+”)
S22	TI Herellea* OR AB Herellea*
S21	TI Acinetobacter* OR AB Acinetobacter*
S20	(MH “Acinetobacter Infections”)
S19	TI Pseudomona* OR AB Pseudomona*
S18	(MH “Pseudomonas”)
S17	TI Jadinii OR AB Jadinii
S16	TI Monilia* OR AB Monilia*
S15	TI Candid* OR AB Candid*
S14	(MH “Candida+”)
S13	TI (Carbapenemase-Producing N3 Enterobacter*) OR AB (Carbapenemase-Producing N3 Enterobacter*)
S12	TI (Carbapenem N3 Resist*) OR AB (Carbapenem N3 Resist*)
S11	(MH “Carbapenem-Resistant Enterobacteriaceae”)
S10	TI (Cephalosporin N3 Resist*) OR AB (Cephalosporin N3 Resist*)
S9	TI (Vancomycin N3 Resist*) OR AB (Vancomycin N3 Resist*)
S8	(MH “Vancomycin Resistant Enterococci”)
S7	TI MRSA OR AB MRSA
S6	TI (Methicillin N3 Resist*) OR AB (Methicillin N3 Resist*)
S5	(MH “Methicillin-Resistant Staphylococcus Aureus”)
S4	S1 OR S2 OR S3
S3	TI AMR OR AB AMR
S2	TW Resist*
S1	(MH “Drug Resistance, Microbial+”)

Appendix Table 4. Terms used in Cochrane Library search, 29 March 2022

ID	Search
#1	MeSH descriptor: [Drug Resistance, Microbial] explode all trees
#2	Resist*:ti,ab,kw
#3	AMR:ti,ab,kw
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Methicillin-Resistant Staphylococcus aureus] explode all trees
#6	(Methicillin NEAR/3 Resist*):ti,ab,kw
#7	MRSA:ti,ab,kw
#8	MeSH descriptor: [Vancomycin-Resistant Enterococci] explode all trees
#9	(Vancomycin NEAR/3 Resist*):ti,ab,kw
#10	(Cephalosporin NEAR/3 Resist*):ti,ab,kw
#11	MeSH descriptor: [Carbapenem-Resistant Enterobacteriaceae] explode all trees
#12	(Carbapenem NEAR/3 Resist*):ti,ab,kw
#13	(Carbapenemase-Producing NEAR/3 Enterobacter*):ti,ab,kw
#14	MeSH descriptor: [Candida] explode all trees
#15	Candid*:ti,ab,kw
#16	Monilia*:ti,ab,kw
#17	Jadinii:ti,ab,kw
#18	MeSH descriptor: [Pseudomonas] explode all trees
#19	Pseudomona*:ti,ab,kw
#20	MeSH descriptor: [Acinetobacter] explode all trees
#21	Acinetobacter*:ti,ab,kw

ID	Search
#22	Herellea*:ti,ab,kw
#23	MeSH descriptor: [Staphylococcus aureus] explode all trees
#24	(Staphylococcus NEAR/1 Aure*):ti,ab,kw
#25	MeSH descriptor: [Enterococcus] explode all trees
#26	Enterococc*:ti,ab,kw
#27	MeSH descriptor: [Enterobacteriaceae] explode all trees
#28	Enterobacter*:ti,ab,kw
#29	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30	MeSH descriptor: [Cross Infection] explode all trees
#31	(Cross NEAR/1 Infect*):ti,ab,kw
#32	(Nosocomial NEAR/3 Infect*):ti,ab,kw
#33	(Nosocomial NEAR/3 Associated):ti,ab,kw
#34	(Nosocomial NEAR/3 Acquired):ti,ab,kw
#35	(Hospital* NEAR/3 Acquired):ti,ab,kw
#36	(Hospital* NEAR/3 Associated):ti,ab,kw
#37	(Hospital* NEAR/3 Infect*):ti,ab,kw
#38	(Intrahospital* NEAR/3 Infect*):ti,ab,kw
#39	(Intrahospital* NEAR/3 Associated):ti,ab,kw
#40	(Intrahospital* NEAR/3 Acquired):ti,ab,kw
#41	(Healthcare NEAR/3 Acquired):ti,ab,kw
#42	(Healthcare NEAR/3 Associated):ti,ab,kw
#43	(Healthcare NEAR/3 Infect*):ti,ab,kw
#44	(Community NEAR/3 Acquired):ti,ab,kw
#45	(Community NEAR/3 Associated):ti,ab,kw
#46	(Community NEAR/3 Infect*):ti,ab,kw
#47	(ICU NEAR/3 Acquired):ti,ab,kw
#48	(ICU NEAR/3 Associated):ti,ab,kw
#49	(ICU NEAR/3 Infect*):ti,ab,kw
#50	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51	MeSH descriptor: [Mortality] explode all trees
#52	Mortalit*:ti,ab,kw
#53	(Death NEAR/1 Rate*):ti,ab,kw
#54	(Fatality NEAR/1 Rate*):ti,ab,kw
#55	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#56	(Quality NEAR/1 Adjusted):ti,ab,kw
#57	QALY*:ti,ab,kw
#58	(Adjusted NEAR/1 Life):ti,ab,kw
#59	(Disability NEAR/1 Adjusted):ti,ab,kw
#60	DALY*:ti,ab,kw
#61	MeSH descriptor: [Length of Stay] explode all trees
#62	(Stay NEAR/3 Length*):ti,ab,kw
#63	(Hospital* NEAR/3 Stay*):ti,ab,kw
#64	#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
#65	MeSH descriptor: [Latin America] explode all trees
#66	MeSH descriptor: [Central America] explode all trees
#67	MeSH descriptor: [South America] explode all trees
#68	MeSH descriptor: [Caribbean Region] explode all trees
#69	MeSH descriptor: [West Indies] explode all trees
#70	MeSH descriptor: [Indians, South American] explode all trees
#71	MeSH descriptor: [Indians, Central American] explode all trees
#72	MeSH descriptor: [Mexico] explode all trees
#73	MeSH descriptor: [Puerto Rico] explode all trees
#74	(Latin NEAR/1 America*) OR Latinamerica* OR Latinoamerica* OR Latin* OR Hispanic Americans OR Iberoamerica* OR (Ibero NEAR/1 Americ*) OR Panamerican* OR (Central NEAR/1 America*) OR Centroamerica* OR Mesoamerica* OR (Meso NEAR/1 America*) OR (Middle NEAR/1 America*) OR (South NEAR/1 America*) OR Southamerica* OR Sudamerica* OR (America NEAR/1 Sur) OR Caribbean OR Caribe* OR (West NEAR/1 Indi*) OR Antill* OR Amerindian* OR Indians OR (American NEAR/1 Indian*) OR (Native NEAR/1 America*) OR Patagoni* OR Andes OR Andean* OR Amazon* OR Argentin* OR Bolivia* OR Brazil* OR Brasil* Colombia* OR Colombia* OR Colombia OR Chile* OR Ecuador* OR Guiana* OR Guyan* OR Guyan* OR Paraguay* OR Paraguay* OR Peru* OR Surinam* OR Surinam* OR Uruguay* OR Venez* OR Belize* OR (Costa NEAR/1 Ric*) OR Costarric* OR Costaric* OR Costa Ric* OR Costarric* OR Salvador* OR Salvador* OR Guatemal* OR Guatemal* OR Guatemala OR Hondur* OR Nicaragu* OR Panam* OR Mexic* OR Cuba* OR Dominic* OR Dominic* OR Haiti* OR Jamaic* OR (Puerto NEAR/1 Ric*) OR Puertorric* OR Puertoric*
#75	#65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74
#76	#4 AND #29 AND #50 AND #64 AND #74 with Publication Year from 2000 to 2022, with Cochrane Library publication date Between Jan 2000 and Mar 2022, in Trials

Appendix Table 5. Terms used in LILACS (BVS Eng) search, 29 March 2022

Database:	LILACS
Search on:	(MH Drug Resistance, Microbial OR Resist$ OR AMR OR RAM) AND (MH Methicillin-Resistant Staphylococcus Aureus OR Methicillin OR Meticilin$ OR MRSA OR MH Vancomycin-Resistant Enterococci OR Vancomycin OR Vancomicin$ OR Cephalosporin OR Cefalosporin$ OR MH Carbapenem-Resistant Enterobacteriaceae OR Carbapenem OR ((Carbapenemas$) AND (Producing OR Produtor$ OR Productor$)) OR MH Candida OR Candid$ OR Monilia$ OR Jadinii OR MH Pseudomonas OR Pseudomona$ OR MH Acinetobacter OR Acinetobacter$ OR Herellea$ OR MH Staphylococcus Aureus OR Staphylococcus OR Estafilococ$ OR MH Enterococcus OR Enterococ$ OR Enterococc$ OR MH Enterobacteriaceae OR Enterobacter$) AND (MH Cross Infection OR ((Cross OR Cruzad$ OR Nosocomial OR Hospital$ OR Intrahospital$ OR Healthcare OR Community OR Comunidad$ OR ICU) AND (Acquired OR Adquirid$ OR Associated OR Asociad$ OR Associad$ OR Infect$ OR Infecc$))) AND (MH Mortality OR Mortalit$ OR Mortalidad$ OR ((Death OR Muerte$ OR Morte$) AND (Rate$ OR Tasa OR Taxa$)) OR MH Quality-Adjusted Life Years OR ((Quality OR Disability) AND (Adjusted)) OR QALY$ OR DALY$ OR MH Length of Stay OR Estadía$ OR Stay$) [Words] and 2000 OR 2001 OR 2002 OR 2003 OR 2004 OR 2005 OR 2006 OR 2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 [Country, year publication]

Grey literature sources

· IDWEEK – Infectious Diseases Society of America (IDSA) – USA (https://idweek.org/)

· European Congress of Clinical Microbiology and Infection Diseases (ECCMID) – Europa (https://www.eccmid.org/)

· Society of Healthcare Epidemiology of America (SHEA) – USA (https://shea-online.org/)

· International Conference on Prevention & Infection Control (ICPIC) – Suiza (https://www.icpic.com/)

· Asociación Panamericana de Infectología (API) – Latinoamérica (https://www.apiinfectologia.org/)

· Asociación Latinoamericana para el Control de Infecciones (ASLACI) – Latinoamérica (https://www.aslaci.org/)

· Sociedad Argentina de Infectología (SADI) – Argentina (https://sadi.org.ar)

· Sociedad Peruana de Enfermedades Infecciosas y Tropicales – Perú (https://speit.org.pe/)

· Sociedad de Enfermedades Infecciosas de Panamá (SEIP) – Panamá (https://seipma.com)

· Asociación Centroamericana y del Caribe de Infectología (ACENCAI) / Asociación Guatemalteca de Enfermedades Infecciosas (AGEI) – Guatemala (https://asociacionageiorg.wordpress.com/)

· Sociedad de Infectología Clínica del Uruguay – Uruguay (www.infectologia.edu.uy)

· Sociedad Chilena de Infectología – Chile (http://www.sochinf.cl/)

· Sociedade Brasileira de Infectologia – Brasil (https://infectologia.org.br/)

https://jic-abih.com.br/index.php/jic/issue/view/48

https://jic-abih.com.br/index.php/jic/issue/view/Suplemento%201

https://jic-abih.com.br/index.php/jic/issue/view/35

https://jic-abih.com.br/index.php/jic/issue/view/33

https://jic-abih.com.br/index.php/jic/issue/view/29

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https://jic-abih.com.br/index.php/jic/issue/view/17

https://jic-abih.com.br/index.php/jic/issue/view/JIC%20Vol%202%20Numero%201

https://jic-abih.com.br/index.php/jic/issue/view/9

https://infectologia.org.br/atualizacao/publicacoes-da-sbi/

Appendix Table 6. List of studies excluded at full-text screening stage

Study author and publication year	Reason for exclusion
Barrero et al (2014) (*1*)	Duplicate
CartaxoSalgado et al (2011) (*2*)	Wrong outcome
Lopez Luis et al (2019) (*3*)	Duplicate
Lucena et al (2014) (*4*)	Wrong patient population
Fiorentin Vandresen et al (2021) (*5*)	Wrong patient population
Furtado et al (2009) (*6*)	Wrong patient population
Mano et al (2021) (*7*)	Wrong patient population
Pinheiro et al (2008) (*8*)	Wrong patient population
Michelud (2021) (*9*)	Wrong outcome
Calvancanti Dantas et al (2014) (*10*)	Duplicate
Freire et al (2015) (*11*)	Wrong patient population
Bento Talizin et al (2020) (*12*)	Wrong outcome
Cassettari et al (2012) (*13*)	Wrong patient population
Cezario et al (2009) (*14*)	Wrong outcome
Cusmano et al (2013) (*15*)	Wrong patient population
Pinoni et al (2019) (*16*)	Wrong patient population
Superti et al (2009) (*17*)	Wrong outcome
Romi et al (2017) (*18*)	Wrong patient population
da Silva et al (2020) (*19*)	Wrong patient population

Appendix Table 7. Risk of Bias Assessment for Cohort Studies—Cross-Sectional studies*

	Evaluation														
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Final**
Arnoni et al (2007) (*20*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	POOR
Bellísimo-Rodrigues et al (2006) (*21*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Bello-Chavolla et al (2018) (*22*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NR	Yes	LOW-RISK
Quillici et al (2021) (*23*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Blot et al (2019) (*24*)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NA	Yes	Yes	LOW-RISK
Bravo et al (2017) (*25*)	Yes	No	CD	NR	No	Yes	Yes	NA	NR	NA	Yes	NA	NA	No	POOR
Caceres et al (2020) (*26*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	POOR
Carneiro et al (2012) (*27*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Cassettari et al (2005) (*28*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Castillo et al (2012) (*29*)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Copaja-Corzo et al (2020) (*30*)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Cornejo-Juarez et al (2016) (*31*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Cornejo-Juarez et al (2015) (*32*)	Yes	Yes	Yes	No	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Correa et al (2013) (*33*)	Yes	Yes	No	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
da Silva et al (2021) (*34*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Oliveira da Silva et al (2021) (*35*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	CD	NA	NA	No	POOR
Castro-Lima et al (2019) (*36*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Matos et al (2016) (*37*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Costa et al (2015) (*38*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
de Vedia et al (2017) (*39*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	No	NA	NA	No	POOR
Ducanteizelier et al (2017) (*40*)	Yes	Yes	CD	CD	No	Yes	Yes	NA	CD	NA	Yes	NA	NA	No	POOR
Echeverri-Toro et al (2012) (*41*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	No	Yes	LOW-RISK
Gañete et al (2021) (*42*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Gentile et al (2018) (*43*)	Yes	Yes	Yes	Yes	No	NA	NA	NA	Yes	NA	Yes	NA	NA	No	FAIR
Gomes et al (2006) (*44*)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
González et al (2014) (*45*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Guilarde et al (2006) (*46*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Herrera et al (2021) (*47*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	CD	Yes	LOW-RISK
Islas-Muñoz et al (2018) (*48*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Kallel et al (2020) (*49*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Karve et al (2018) (*50*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Lemos et al (2014) (*51*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK

Study	Evaluation														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Final**
Lipari et al (2021) (*52*)	Yes	Yes	CD	No	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	POOR
Lopez Luis et al (2019) (*3*)	Yes	Yes	CD	CD	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Marra et al (2006) (*53*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Michelud et al (2021) (*9*)	Yes	Yes	CD	CD	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	POOR
Moreira et al (2008) (*54*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Nassar et al (2021) (*55*)	Yes	Yes	Yes	No	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Naves et al (2012) (*56*)	Yes	Yes	No	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	FAIR
Neves et al (2017) (*57*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Patermina-de la Ossa et al (2018) (*58*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Pinhati et al (2016)	Yes	Yes	Yes	Yes	No	NA	NA	NA	Yes	NA	Yes	NA	NA	No	FAIR
Ponce de León et al (2010) (*59*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Porto et al (2013) (*60*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	POOR
Prata-Rocha et al (2012) (*61*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	POOR
Rossi Gonçalves et al (2017) (*62*)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	POOR
da Silva et al (2014) (*63*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Seas et al (2018) (*64*)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NA	Yes	Yes	LOW-RISK
Seligman et al (2013) (*65*)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	LOW-RISK
Tuon et al (2012) (*66*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Valderrama et al (2016) (*67*)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	NA	NA	No	FAIR
Zavascki et al (2006) (*68*)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	Yes	Yes	LOW-RISK

*CD, cannot be determined; NA, not applicable; NR, not reported. Assessment questions 1–14 appear below.

1. Was the study question or research objective clearly specified?

2. Was the study population clearly specified and defined?

3. Did at least 50% of eligible subjects take part?

4. Were all subjects screened or recruited from the same population or from similar populations (including the same period of time)? Were inclusion and exclusion criteria to take part in the study pre-specified and applied consistently to all participants?

5. Was rationale for sample size, power description or variance and effect estimations provided?

6. For analysis of this study, were the exposures of interest measured before results?

7. Was the follow-up period enough for one to reasonably expect to observe an association between exposure and result, if any?

8. For exposures that may var.y in terms of amount or level, did the study examine different levels of exposure relative to the result (e.g., categories of exposure or exposure measured as a continuous variable)?

9. Were measures of exposure (independent variables) clearly defined, valid, reliable and consistently implemented for all study participants?

10. Were exposures evaluated more than once over time?

11. Were measures of results (dependent variables) clearly defined, valid, reliable and consistently implemented for all study participants?

12. Were results raters blinded to participants' exposure?

13. Were lost to follow-up 20% or less after the study startup?

14. Were potential confounding variables key due to their impact on the exposure(s)-result(s) ratio measured and statistically adjusted?

Appendix Table 8. Risk of Bias Assessment for Case-Control studies

	Evaluation*												
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Final**
Araya et al (2019) (*69*)	Yes	Yes	No	Yes	Yes	No	NA	NA	Yes	Yes	CD	No	POOR
de Oliveira Conterno et al (2002) (*70*)	Yes	Yes	No	Yes	Yes	Yes	CD	CD	Yes	Yes	No	Yes	LOW-RISK

*CD. cannot be determined; NA, not applicable; NR, not reported. Assessment questions 1–12 appear below.

1. Was the research question or objective in this paper clearly stated and appropriate?

2. Was the study population clearly specified and defined?

3. Did the authors include a sample size justification?

4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?

5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?

6. Were the cases clearly defined and differentiated from controls?

7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?

8. Was there use of concurrent controls?

9. Were the investigators able to confirm that the exposure/risk occurred before the development of the condition or event that defined a participant as a case?

10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?

11. Were the assessors of exposure/risk blinded to the case or control status of participants?

12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Appendix Table 9. Additional characteristics of included studies*

Study	Site of infection	Charlson Comorbidity Index	Severity Score	Empiric treatment appropriateness	Length of hospital stay (days) R	Length of hospital stay (days) S
Bravo et al (2017) (*25*)	CLABSI: 17 (23.9%); BSI: 14 (19.7%); SSTI: 9 (12.7%); SSI: 5 (7%); Cardiac: 3 (4.2%)	NR	NR	all: 61 (86%)	NR	NR
de Vedia et al (2017) (*39*)	SSTI: 37 (46.8%); Pneumonia: 62 (78.5%)†	NR	NR	NR	NR	NR
Ducanteizelier et al (2017) (*40*)	UTI: 35 (32.7%); P-IAI: 25 (23.4%); Pneumonia: 14 (13.1%); BSI: 12 (11.2%); SSTI: 10 (9.3%)	NR	NR	R: 4 (10.5%); S: 54 (79%)	NR	NR
Gañete et al (2021) (*42*)	BSI: 71 (71%); CLABSI: 18 (18%); SSTI: (9%); B&J: (4%); Cardiac: (1.1%)†	NR	NR	NR	NR	NR
Gentile et al (2018) (*43*)	NR	NR	NR	NR	NR	NR
Herrera et al (2021) (*47*)	CLABSI: 358 (28%); P-IAI: 214 (16.8%); Pneumonia: 118 (9.2%); Other infections: 916 (71.7%)†	NR	NR	NR	NR	NR
Lipari et al (2021) (*52*)	NR	NR	NR	NR	NR	NR
Michelud et al (2021) (*9*)	UTI: 263 (54%); P-IAI: 111 (22.8%)	NR	NR	all: 345 (70.8%); R: 19 (24.6%)	12 (16.2)‡	8 (9)‡
Arnoni et al (2007) (*20*)	BSI: 92 (100%)	NR	NR	NR	NR	NR
Bellísimo-Rodrigues et al (2006) (*21*)	BSI: 33 (31.7%); Pneu: 31 (29.8%); SSTI: 23 (22.1%); P-IAI: 7 (6.7%); UTI: 5 (4.8%)	NR	NR	NR	25.1‡	23.7‡
Quillici et al (2021) (*23*)	BSI: 270 (100%)	≥3: 86 (31.8%)	NR	all: 79 (29.3%); R: 27 (15.1%)	NR	NR
Carneiro et al (2012) (*27*)	BSI: 132 (100%)	NR	NR	NR	NR	NR
Cassettari et al (2005) (*28*)	BSI: 41 (25.2%); CLABSI: 33 (20.2%); Pneumonia: 26 (16%); SSI: 20 (12.3%); SSTI: 10 (6.1%)	NR	NR	all: 149 (91.4%)	NR	NR
Correa et al (2013) (*33*)	NR	≥3: 23 (38%)	APACHE II: R: 22.1‡; S: 16.4‡	NR	20‡	32‡
da Silva et al (2021) (*34*)	BSI: 257 (72%); CLABSI: 123 (34.5%); Unknown: 63 (17.6%); P-IAI: 23 (6.4%); Other infections: 16 (4.5%)†	4.48 (0–15)§	Pitt Score ≥4: 112 (31.4%)	all: 225 (63.2%)	NR	NR
Oliveira da Silva et al (2021) (*35*)	NR	2.5 (1–3)§	SAPS III: R: 53 (46–61)§ S: 52 (47–59)§	NR	63 (27–145)§	34.5 (18–74)§
Castro-Lima et al (2019) (*36*)	CLABSI: 42 (55.3%); VAP: 34 (44.7%); CAUTI: 8 (10.5%)†	NR	SOFA: 6 (3–10.8)§	NR	24‡	NR
Matos et al (2016) (*37*)	BSI: 25 (46.3%); Pneumonia: 24 (44.4%); UTI: 5 (9.3%)	0–2: 28 (52%)	McCabe (Potentially fatal): R: 13 (65%); S: 11 (32.3%)	R: 0 (0%); S: 15 (44.2%)	≥30 d: 18 (90%)	≥30 d: 25 (73.5%)

Study	Site of infection	Charlson Comorbidity Index	Severity Score	Empiric treatment appropriateness	Length of hospital stay (days) R	Length of hospital stay (days) S
de Oliveira Conterno et al (2002) (*70*)	CLABSI: 55 (21.9%); Pneumonia: 45 (17.9%); Other infections: 42 (16.7%); Unknown: 90 (35.9%)	NR	NR	(1991–92) all: 94 (69%) (1995–96) all: 102 (89%)	NR	NR
Costa et al (2015) (*38*)	NR	NR	NR	R:12 (25.5%); S: 34 (63%)	8§	2§
Gomes et al (2006) (*44*)	UTI: 55 (38.5%); SSI: 27 (18.9%); BSI: 23 (16.1%); Pneumonia: 18 (12.6%); P-IAI: 14 (9.8%)	NR	NR	all: 70 (49%)	NR	NR
Guilarde et al (2006) (*46*)	CLABSI: 22 (19.8%); BSI: 18 (16.2%)	NR	NR	all: 67 (60%)	NR	NR
Karve et al (2018) (*50*)	UTI: 80 (100%)	2.4 (2.3)‡	NR	all: 21 (25.6%)	NR	NR
Marra et al (2006) (*53*)	Pneumonia: 41 (38%); P-IAI: 28 (25.9%); CLABSI:15 (13.9%); UTI: 12 (11.1%); Other infections: 6 (5.6%)	NR	McCabe (Potentially fatal): R: 21 (37.5%); S: 32 (62.5%)	R: 27 (47.8%); S: 27 (52.2%)	NR	NR
Moreira et al (2008) (*54*)	VAP: 61 (100%)	NR	NR	all: 37 (60.6%); R: 14 (48.7%); S: 16 (51.3%)	NR	NR
Nassar et al (2021) (*55*)	NR	NR	SAPS III: R: 62.3 (17.6)†; S: 56.7 (16.3)‡	NR	23.9 (14.9)‡	16.6 (11.4)‡
Naves et al (2012) (*56*)	BSI: 51 (100%)	NR	NR	all: 34 (66.6%); R: 19 (65.5%); S: 15 (68.2%)	NR	NR
Neves et al (2017) (*57*)	NR	NR	NR	NR	NR	NR
Patermina-de la Ossa et al (2018) (*58*)	SSTI: 161 (57.7%); BSI: 52 (18.6%); B&J: 35 (12.5%); Pneumonia: 26 (9.3%); CNS: 23 (8.2%)†	NR	NR	NR	29.3 (12.6–60.3)§	14 (7–31)§
Pinhati et al (2016) (*71*)	BSI: 40 (100%)	NR	APACHE II: R: 14 (3–29)§; S: 16 (3–30)§	NR	NR	NR
Porto et al (2013) (*60*)	BSI: 230 (100%)	NR	NR	NR	NR	NR
Prata-Rocha et al (2012) (*61*)	Pneumonia: 37 (50.7%); BSI: 33 (45.2%); UTI: 15 (20.5%)†	NR	NR	all: 43 (58.9%) R: 29 (59.2%); S: 14 (58.3%)	NR	NR
Rossi Gonçalves et al (2017) (*62*)	BSI: 98 (62.4%); CLABSI 21 (13.4%); Pneumonia: 27 (17.2%); UTI: 6 (3.8%)	NR	ASIS Score ≥4: all: 69 (51.6%); R: 35 (50.7%); S: 33 (50.7%)	all: 92 (69%); R: 37 (54%); S: 57 (88%)	60.01 (48.97)‡	68.86 (110.4)‡
da Silva et al (2014) (*63*)	BSI: 304 (100%)	NR	NR	NR	36 (22.5)‡	NR
Seligman et al (2013) (*65*)	HAP: 140 (100%)	NR	NR	NR	NR	NR
Tuon et al (2012) (*66*)	BSI: 77 (100%)	NR	NR	all: 77 (40.3%); R: 8 (28%); S: 23 (48%)	43 (31.7)‡	43.1 (31.2)‡

Study	Site of infection	Charlson Comorbidity Index	Severity Score	Empiric treatment appropriateness	Length of hospital stay (days) R	Length of hospital stay (days) S
Zavascki et al (2006) (*68*)	Pneumonia: 150 (50.3%); UTI: 61 (20.5%); SSTI: 47 (15.8%); P-IAI: 25 (8.4%); CLABSI: 23 (7.7%)†	3.4 (1.3–5.4)§	NR	R: 39 (45%)	NR	NR
Caceres et al (2020) (*26*)	BSI: 90 (100%)	NR	NR	NR	NR	NR
Castillo et al (2012) (*29*)	CLABSI: 139 (37.4%); Pneumonia: 56 (15.1%); SSTI: 22 (5.9%); SSI: 12 (3.2%); Unknown: 113 (30.4%)	>3: 188 (50.5%)	APACHE II: all: 15 (11–21)§; R: 15 (11–22)§; S: 15 (10–20)§	all: 247 (66.3%)	30‡	21‡
Echeverri-Toro et al (2012) (*41*)	UTI: 104 (42.8%); BSI: 54 (22.2%); Pneumonia: 33 (13.6%); B&J: 19 (7.8%); P-IAI: 17 (7%)	NR	NR	NR	>30 d: 43 51.2%)	>30 d: 50 (31.4%)
González et al (2014) (*45*)	Pneumonia: 87 (40.1%); CLABSI: 67 (30.9%); SSTI: 29 (13.4%); P-IAI: 27 (12.4%)	3 (5)‡	APACHE II: all: 14 (10)§	all: 122 (56.3%)	NR	NR
Lemos et al (2014) (*51*)	Pneumonia: 57 (34.5%); SSI: 24 (24.2%); BSI: 24 (14.5%); CLABSI: 20 (12.1%); UTI: 7 (4.2%)	NR	APACHE II: R: 12.8 (5.4)‡; S: 10.1 (4.6)‡	R: 64 (61.5%); S: 51 (83.6%)	13.2 (13.8)‡	10.1 (8.7)‡
Valderrama et al (2016) (*67*)	Pneumonia: 51 (30.4%); P-IAI: 44 (26.2%); BSI: 23 (13.7%); UTI: 17 (10.1%); CLABSI: 7 (4.2%)	NR	APACHE II: R: 14.5 (0–29)§; S: 11.5 (0–33)§	R: 22 (52.4%); S: 95 (75.4%)	General ward: 26 (3–115)§; ICU: 12.5 (0–106)§	General ward: 16 (1–161)§ ICU: 8 (0–161)§
Kallel et al (2020) (*49*)	BSI: 98 (43.9%); CLABSI: 37 (16.6%); VAP: 27 (12.1%); UTI: 15 (6.7%); SSTI: 5 (2.2%)	NR	SAPS: all: 50 (40–64)‡; R: 57 (42–75)§; S: 50 (39–63)§	all: 223 (65.1%); R: 24 (61.5%); S: 127 (69%)	37 (18–57)§	24 (15–48)§
Blot et al (2019) (*24*)	P-IAI: 364 (100%)	NR	NR	NR	NR	NR
Seas et al (2018) (*64*)	CLABSI: 378 (41.3%); BSI: 180 (19.7%); SSTI: 80 (8.7%); Pneumonia: 77 (8.4%); B&J: 60 (6.6%)	2 (1–3)‡	APACHE II: R: 0 (1–14)§; S: 0 (0–12)§	R: 232 (74.5%); S: 188 (51.9%)	ICU: 17.2 (16.6)‡; Site not specified: 39.1 (37.6)‡	ICU: 13.6 (14.8)†; Site not specified: 28.6 (31.2)‡
Bello-Chavolla et al (2018) (*22*)	CLABSI: 254 (56.4%); CAP: 34 (7.6%); HCAP: 33 (7.3%); SSTI: 28 (6.2%); P-IAI: 27 (6%)	4 (2–6)‡	NR	all: 308 (68.4%)	NR	NR
Cornejo-Juarez et al (2016) (*31*)	VAP: 34 (53.1%); CAUTI: 22 (34.4%); SSI: 13 (20.3%); CLABSI: 4 (6.2%); P-IAI: 3 (4.7%)†	NR	APACHE II: 18.9 (6.4)‡	NR	NR	NR
Cornejo-Juarez et al (2015) (*32*)	VAP: 72 (53.7%); CAUTI: 41 (30.6%); SSI: 21 (15.7%); P-IAI: 20 (14.9%); CLABSI: 5 (3.7%)†	NR	SOFA: 8.4 (3.3)†	all: 135 (56%)	16 (10)‡	12 (6)‡
Islas-Muñoz et al (2018) (*48*)	CLABSI: 156 (31.5%); UTI: 93 (18.8%); P-IAI: 82 (16.5%); BSI: 75 (15.1%); SSTI: 34 (6.9%)	>2: 245 (49.5%)	NR	all: 448 (90.3%)	NR	NR
Lopez Luis et al (2019) (*3*)	BSI: 192 (100%)	NR	NR	NR	NR	NR
Ponce de León et al (2010) (*59*)	CLABSI: 70 (40.7%); Pneumonia: 45 (26.2%); SSTI: 28 (16.3%); B&J: 10 (5.8%); Cardiac: 8 (4.7%)	NR	NR	all: 172 (82%); R: 57 (72.1%); S: 86 (90.3%)	31§	21§

Study	Site of infection	Charlson Comorbidity Index	Severity Score	Empiric treatment appropriateness	Length of hospital stay (days) R	Length of hospital stay (days) S
Araya et al (2019) (*69*)	BSI: 50 (46.7%); CAP: 50 (46.7%); B&J: 30 (28%); Cardiac: 4 (3.7%)†	NR	NR	NR	NR	NR
Copaja-Corzo et al (2021) (*30*)	VAP: 37 (29.8%); CLABSI: 10 (8.1%); CAUTI: 3 (2.4%)	NR	NR	NR	NR	NR

*Values are no. (%). B&J: Infections of bone, joints, and related organs; BSI: Bloodstream infection; CAP: Community-acquired pneumonia; Cardiac: Endocarditis and other cardiac infections; CAUTI: Catheter-associated urinary tract infection; CLASBI: Central line-associated bloodstream infections; CNS: Meningitis and other bacterial central nervous system infections; HAP: Hospital-acquired pneumonia; HCAP: Healthcare-associated pneumonia; LOS: length of stay; NR: not reported; P-IAI: Peritoneal and intra-abdominal infections; R: resistant group; S: susceptible group; SSI: Surgical site infection; SSTI: Skin and soft tissue infections; UTI: Urinary tract infection; VAP: Ventilator-associated pneumonia.
†More than one site of infection per patient.
‡Reported as mean (SD).
§Reported as median (interquartile range or range).

Appendix Table 10. Meta-regression analysis of adjusted measures*

Variable	No. studies	No. patients (No. of R-bacteria/No. of S-bacteria)	Coefficient	95% CI	p-value from meta regression
Year	14	4472 (1877/2595)	−0.006	−0.027–0.015	0.568
Population risk	14	4472 (1877/2595)	−0.072	−0.619–0.473	0.794
Appropriate antimicrobial therapy†	8	2789 (1155/1634)	0.1072	−0.369–0.583	0.583
Resistance mechanism‡	14	4472 (1877/2595)	..	..	0.726
Multidrug resistant bacteria	4	1009 (398/611)	Ref.	..	..
Carbapenem-resistant	3	1234 (498/736)	−0.038	−0.515–0.437	0.872
Extended spectrum β-lactamase	2	236 (113/123)	0.287	−0.271–0.845	0.313
Methicillin-resistant	5	1993 (868/1125)	0.021	−0.364–0.405	0.917

*We converted all non-RR point estimates into RRs for meta-regression analysis as previously published (*72*,*73*). The table shows the meta-regression results for study and patient characteristics of an aRR for the association between resistance and lethality.
†We consider an appropriate therapy if at least one group (resistant, susceptible, or both) has more than 70% of patients who have received early appropriate empirical therapy.
‡For the analysis we considered different types of resistance mechanism as a categorical feature: multidrug resistant bacteria (as reference), Carbapenem-resistant, Extended spectrum β-lactamase and Methicillin-resistant.

Appendix Table 11. Sensitivity analysis in the association between resistance and lethality with Knapp-Hartung adjustments

Type of adjustment	Type of association	Random effects model effect estimate (95% CI)
Without Knapp-Hartung adjustment	aOR	1.93 (1.58–2.37)
With Knapp-Hartung adjustment	aOR	1.93 (1.55–2.41)
Without Knapp-Hartung adjustment	aHR	1.31 (0.93–1.83)
With Knapp-Hartung adjustment	aHR	1.31 (0.81–2.12)

*aOR, adjusted odds ratio; aHR, adjusted hazard ratio.

Appendix Table 12. Characteristics of included studies*

Study	Country	Inclusion period	Study design	Sample size	Population risk	Age group	Site of admission	Resistant germs	Quality assessment
Bravo et al (2017)	Argentina	2016–17	RC	71	Unknown	Adults	NR	MRSA	Poor
de Vedia et al (2017)	Argentina	2002–17	RC	79	High	Adults	ICU	MRSA	Poor
Ducanteizelier et al (2017)	Argentina	2016–17	RC	107	Unknown	Adults	NR	CRE	Poor
Gañete et al (2021)	Argentina	2017–18	PC	100	High	Adults	NR	MRSA	Fair
Gentile et al (2018)	Argentina	2012–14	CS	1141	Average	Pediatric	NR	MRSA	Fair
Herrera et al (2021)	Argentina	2014–20	PC	1277†	High	Adults	ICU and non-ICU	CR-GNB	Low-Risk
Lipari et al (2021)	Argentina	2015–21	RC	186	Unknown	Adults	NR	CRE	Poor
Michelud et al (2021)	Argentina	2014–18	RC	487	High	Elderly	ICU and non-ICU	ESBL-E	Poor
Arnoni et al (2007)	Brazil	2001–03	RC	85	High	Neo/Pediatric	ICU and non-ICU	MDR-GNB	Poor
Bellísimo-Rodrigues et al (2006)	Brazil	2002–03	PC	104	High	Adults	NR	ESBL-E	Fair
Quillici et al (2021)	Brazil	2012–18	RC	270	High	Adults	ICU	MDR-GNB	Fair
Carneiro et al (2012)	Brazil	2007–11	RC	132	High	Neonatal	ICU	ESBL-E	Fair
Cassettari et al (2005)	Brazil	1999	PC	163	Average	All ages	ICU and non-ICU	MRSA	Fair
Correa et al (2013)	Brazil	2006–08	RC	60	High	Adults	ICU and non-ICU	CRE	Fair
da Silva et al (2021)	Brazil	2013–15	PC	357	High	Adults	NR	MDRO	Low-Risk
Oliveira da Silva et al (2021)	Brazil	2019	RC	331	High	Adults	ICU	MDRO	Poor
Castro-Lima et al (2019)	Brazil	2013–17	RC	76	High	Adults	ICU	MDRO	Low-Risk
Matos et al (2016)	Brazil	2010–12	RC	54	High	All ages	ICU	CR-PA	Fair
de Oliveira Conterno et al (2002)	Brazil	1991–96	CC	251	High	Adults	NR	MRSA	Low-Risk
Costa et al (2015)	Brazil	2009–12	RC	76	High	Pediatric	ICU	MDR-GNB	Fair
Gomes et al (2006)	Brazil	1998	RC	143	High	Adults	ICU and non-ICU	ESBL-E	Low-Risk
Guilarde et al (2006)	Brazil	2000–01	RC	111	High	All ages	ICU and non-ICU	MRSA	Fair
Karve et al (2018)	Brazil	2013–14	RC	80	High	Adults	NR	MDR-GNB	Fair
Marra et al (2006)	Brazil	1996–01	RC	108	High	All ages	ICU and non-ICU	ESBL-E	Low-Risk
Moreira et al (2008)	Brazil	2005–07	RC	61	High	Adults	ICU	MRSA	Fair
Nassar et al (2021)	Brazil	2019–20	PC	307	High	Adults	ICU	MDRO	Fair
Naves et al (2012)	Brazil	2007–08	RC	39	Average	All ages	General ward	MRSA	Fair
Neves et al (2017)	Brazil	2011–14	RC	1261	Average	Adults	ICU and non-ICU	CRE	Fair
Patermina-de la Ossa et al (2018)	Brazil	2012–16	RC	279	Average	Pediatric	Emergency department	MRSA	Fair
Pinhati et al (2016)	Brazil	2011–12	CS	40	High	Adults	ICU	AZC	Fair
Porto et al (2013)	Brazil	2010	RC	230	High	Adults	NR	MRSA	Poor
Prata-Rocha et al (2012)	Brazil	2009–10	PC	73	High	All ages	ICU and non-ICU	CR-AB	Poor
Rossi Gonçalves et al (2017)	Brazil	2009–12	RC	157	High	All ages	ICU and non-ICU	CR-PA	Poor
Santos da Silva et al (2014)	Brazil	1998–08	RC	304	Average	All ages	ICU and non-ICU	VRE	Fair
Seligman et al (2013)	Brazil	2007–09	RC	140	High	Adults	General ward	MDR-GNB	Low-Risk
Tuon et al (2012)	Brazil	2006–09	RC	77	High	Adults	ICU and non-ICU	CR-PA	Fair
Zavascki et al (2006)	Brazil	2004–05	PC	298	High	Adults	NR	CR-PA	Low-Risk
Caceres et al (2020)	Colombia	2015–16	RC	90	High	All ages	ICU	AZC	Poor
Castillo et al (2012)	Colombia	2005–06	RC	372	High	Adults	ICU and non-ICU	MRSA	Low-Risk
Echeverri-Toro et al (2012)	Colombia	2009–10	PC	243	High	Adults	ICU and non-ICU	ESBL-E	Low-Risk
González et al (2014)	Colombia	2005–08	RC	217	High	Adults	ICU	CR-PA	Low-Risk
Lemos et al (2014)	Colombia	2006–10	PC	165	High	Adults	ICU	CR-AB	Low-Risk
Valderrama et al (2016)	Colombia	2008–14	RC	168	High	Adults	ICU and non-ICU	CR-PA	Fair
Kallel et al (2020)	French Guiana	2013–19	RC	223	High	Adults	ICU	ESBL-E	Low-Risk

Appendix Table 12. Characteristics of included studies*

Study	Country	Inclusion period	Study design	Sample size	Population risk	Age group	Site of admission	Resistant germs	Quality assessment
Blot et al (2019)	LAC‡	2016	PC	364	High	Adults	ICU	MDRO	Low-Risk
Seas et al (2018)§	LAC¶	2011–14	PC	915§	High	Adults	ICU and non-ICU	MRSA	Low-Risk
Bello-Chavolla et al (2018)	Mexico	2006–14	RC	450	High	Adults	ICU and non-ICU	MRSA	Low-Risk
Cornejo-Juarez et al (2016)	Mexico	2003–04	PC	64	High	Adults	ICU	MDRO	Fair
Cornejo-Juarez et al (2015)	Mexico	2007–11	RC	134	High	Adults	ICU	MDRO	Fair
Islas-Muñoz et al (2018)	Mexico	2016–17	PC	496	High	Adults	NR	MDRO	Low-Risk
Lopez Luis et al (2019)	Mexico	2007–17	RC	192	Unknown	NR	NR	VRE	Fair
Ponce de León et al (2010)	Mexico	2003–07	RC	172	High	Adults	ICU and non-ICU	MRSA	Fair
Araya et al (2019)	Paraguay	2010–14	CC	107	Average	Pediatric	ICU and non-ICU	MRSA	Poor
Copaja-Corzo et al (2021)	Peru	2020–21	RC	124	High	Adults	ICU	XDRO	Low-Risk

*ARC, Azol-resistant Candida spp.; CC, case-control; CR-AB, Carbapenem-resistant Acinetobacter baumannii; CRE, Carbapenem-resistant Enterobacterales; CR-GNB, Carbapenem-resistant Gram-negative bacilli; CR-PA, Carbapenem-resistant Pseudomonas aeruginosa; CS, cross-sectional; ESBL-E, extended spectrum β-lactamase producing Enterobacterales; ICU, intensive care unit; MDR-GNB, Multidrug resistant Gram-negative bacilli; MDRO, Multidrug resistant organisms; MRSA, methicilin-resistant Staphylococcus aureus; NR, not reported; PC, prospective cohort; RC, retrospective cohort; VRE, Vancomycin-resistant Enterococcus spp.; XDRO, Extremely drug-resistant organisms.
†771 out of 1277 patients were included in the final analysis.
‡The following countries were included: Argentina, Chile, Colombia, Ecuador, Jamaica, Mexico, Paraguay, Peru.
§675 out of 915 patients were included in the final analysis.
¶The following countries were included: Argentina, Chile, Brazil, Colombia, Ecuador, Guatemala, Mexico, Perú, Venezuela.

Appendix Table 13. Outcome and association measures of included studies*

Study	In-hospital lethality R (n/N)	In-hospital lethality S (n/N)	15-d lethality R (n/N)	15-d lethality S (n/N)	30-d lethality R (n/N)	30-d lethality S (n/N)	Unadjusted OR/RR/HR (95% CI)	Adjusted OR/RR/HR (95% CI)	Type of adjustment
Methicilin-resistant *Staphylococcus aureus* (MRSA)	..	..	..	..	..	..	..	..	..
Araya et al (2019)	6/42	10/65	NR	NR	NR	NR	OR: 0.91 (0.30–2.74)	NR	..
Bello-Chavolla et al (2018)	NR	NR	NR	NR	30/95	45/355	OR: 3.18 (1.86–5.42)†	HR: 2.69 (1.52–4.76)	Charlson Comorbidity Index
Blot et al (2019	NR	NR	NR	NR	2/3	0/1	..	..	..
Bravo et al (2017)	11/22	25/49	NR	NR	11/22	25/49	OR: 0.96 (0.35–2.63)†	NR	..
Cassettari et al (2005)	43/96	20/67	32/96	18/67	NR	NR	OR: 1.91 (0.99–3.69)	NR	..
Castillo et al (2012)	106/186	86/186	NR	NR	106/186	86/186	HR: 1.31 (0.96–1.79)	HR: 0.90 (0.62–1.30)	NR
da Silva et al (2021)	NR	NR	NR	NR	13/38	15/35	OR: 0.69 (0.27–1.79)†	NR	..
de Oliveira Conterno et al (2002) (Total)	NR	NR	73/159	19/92	NR	NR	OR: 3.3 (1.8–5.9)	OR: 1.80 (1.27–2.54)	Treatment received
de Oliveira Conterno et al (2002) (1991–1992)	NR	NR	44/90	9/46	NR	NR	OR: 3.93 (1.7–9.09)	NR	..
de Oliveira Conterno et al (2002) (1995–1996)	NR	NR	29/69	10/46	NR	NR	OR: 2.61 (1.12–6.10)	NR	..

Study	In-hospital lethality R (n/N)	In-hospital lethality S (n/N)	15-d lethality R (n/N)	15-d lethality S (n/N)	30-d lethality R (n/N)	30-d lethality S (n/N)	Unadjusted OR/RR/HR (95% CI)	Adjusted OR/RR/HR (95% CI)	Type of adjustment
de Vedia et al (2017)	19/50	2/29	NR	NR	NR	NR	OR: 8.27 (1.76–38.8)†	NR	..
Gañete et al (2021)‡	4/38	14/65	NR	NR	NR	NR	OR: 0.43 (0.13–1.41)†	NR	..
Gentile et al (2018)	20/904	4/237	NR	NR	NR	NR	OR: 1.32 (0.45–3.89)	NR	..
Guilarde et al (2006)	29/61	10/50	NR	NR	33/61	12/50	HR: 3.94 (1.70–9.10)	HR: 2.52 (0.96–6.60)	Age, sex and severity of underlying disease
Islas-Muñoz et al (2018)§	0	1	NR	NR	2/6	4/43	OR: 4.88 (0.67–35.48)	NR	..
Moreira et al (2008)	11/29	8/32	NR	NR	NR	NR	OR: 1.83 (0.54–6.34)	NR	..
Naves et al (2012)‡	17/29	7/22	NR	NR	NR	NR	OR: 3.0 (0.95–9.71)	OR: 0.5 (0.11–2.24)	¶
Patermina-de la Ossa et al (2018)‡	8/120	5/159	NR	NR	NR	NR	OR: 2.20 (0.70–6.90)	NR	..
Ponce de León et al (2010)	29/79	32/93	NR	NR	17/79	20/93	In-hospital mortality: OR: 0.41 (0.14–1.22) 30 d mortality: OR: 1.00 (0.48–2.07)	NR	..
Porto et al (2013)	10/61	20/169	NR	NR	NR	NR	OR: 1.46 (0.64–3.33)	NR	..
Seas et al (2018)#	NR	NR	NR	NR	132/367	123/442	RR: 1.28 (1.06–1.55)	RR: 1.09 (0.96–1.22)	Age, Charlson comorbidity score, Pittsbirgh bacteraemia score, severity of sepsis, hospital clustering, previous surgery
Seligman et al (2013)	23/38	7/14	NR	NR	NR	NR	OR: 1.53 (0.45–5.26)†	NR	..
Vancomycin-resistant *Enterococcus* spp. (VRE)	..	..	..	..	..	..	..	..	..
Blot et al (2019)	NR	NR	NR	NR	5/11	6/28	OR: 3.06 (0.69–13.57)†	NR	..
da Silva et al (2021)	NR	NR	NR	NR	3/5	7/19	OR: 2.57 (0.34–19.33)†	NR	..
Lopez Luis et al (2019)	NR	NR	NR	NR	64/107	20/85	OR: 4.84 (2.57–9-11)	NR	..
Santos da Silva et al (2014)	23/30	NR/274	NR	NR	NR	NR	OR: 2.73 (1.09–7.78)	NR	..

Study	In-hospital lethality R (n/N)	In-hospital lethality S (n/N)	15-d lethality R (n/N)	15-d lethality S (n/N)	30-d lethality R (n/N)	30-d lethality S (n/N)	Unadjusted OR/RR/HR (95% CI)	Adjusted OR/RR/HR (95% CI)	Type of adjustment
Extended spectrum β-lactamase producing Enterobacterales (ESBL-E)	..	..	..	..	..	..	..	..	..
Bellísimo-Rodrigues et al (2006)	26/47	21/57	16/47	11/57	NR	NR	OR: 2.12 (0.97–4.67)†	OR: 2.3 (0.7–7.5)	**
Blot et al (2019)	NR	NR	NR	NR	24/59	25/81	OR: 1.54 (0.76–3.10)†	NR	..
Carneiro et al (2012)	27/66	16/66	NR	NR	25/66	8/66	OR: 2.16 (1.03–4.57)	OR: 3.47	NR
da Silva et al (2021)	NR	NR	NR	NR	15/54	53/138	OR: 0.62 (0.31–1.23)†	NR	..
Echeverri-Toro et al (2012)	NR	NR	NR	NR	12/84	30/161	OR: 0.72 (0.35–1.49)	NR	..
Gomes et al (2006)	NR	NR	NR	NR	14/68††	16/75††	RR: 0.97 (0.51–1.83)	NR	..
Islas-Muñoz et al (2018)	13	12	NR	NR	37/123	35/148	OR: 1.39 (0.81–2.39)	NR	..
Kallel et al (2020)	NR	NR	NR	NR	12/39‡‡	45/184‡‡	OR: 1.37 (0.64–2.93)	NR	..
Marra et al (2006)	NR	NR	18/56	8/52	NR	NR	OR: 2.61 (1.02–6.66)	NR	..
Michelud et al (2021)	17/77	76/410	NR	NR	NR	NR	RR: 1.19 (0.74–1.89)	NR	..
Carbapenem-resistant Enterobacterales (CRE)	..	..	..	..	..	..	..	..	..
Blot et al (2019)	NR	NR	NR	NR	8/20	41/120	OR: 1.28 (0.49–3.39)†	NR	..
Correa et al (2013)	10/20	11/40	NR	NR	NR	NR	OR: 2.64 (0.86–8.07)	NR	..
da Silva et al (2021)	NR	NR	NR	NR	16/25	53/138	OR: 2.85 (1.18–6.91)†	NR	..
Ducanteizelier et al (2017)	8/40	8/68	NR	NR	NR	NR	OR: 1.88 (0.64–5.47)†	NR	..
Lipari et al (2021)	NR	NR	NR	NR	34/93	14/93	OR: 3.3 (1.6–6.6)	NR	..
Neves et al (2017)	49/97	268/1164	NR	NR	NR	NR	OR: 3.41 (2.24–5.20)†	NR	..
Carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA)	..	..	..	..	..	..	..	..	..
Blot et al (2019)	NR	NR	NR	NR	2/3	3/12	OR: 6.00 (0.39–92.28)†	NR	..
da Silva et al (2021)	NR	NR	NR	NR	13/19	3/21	OR: 10.83 (2.25–52.2)†	NR	..
González et al (2014)	NR	NR	NR	NR	43/70	70/147	OR: 2.35 (1.1–5.1)	NR	..
Islas- Muñoz et al (2018)§§	4	2	NR	NR	6/9	5/34	OR: 11.6 (2.16–62.22)	NR	..

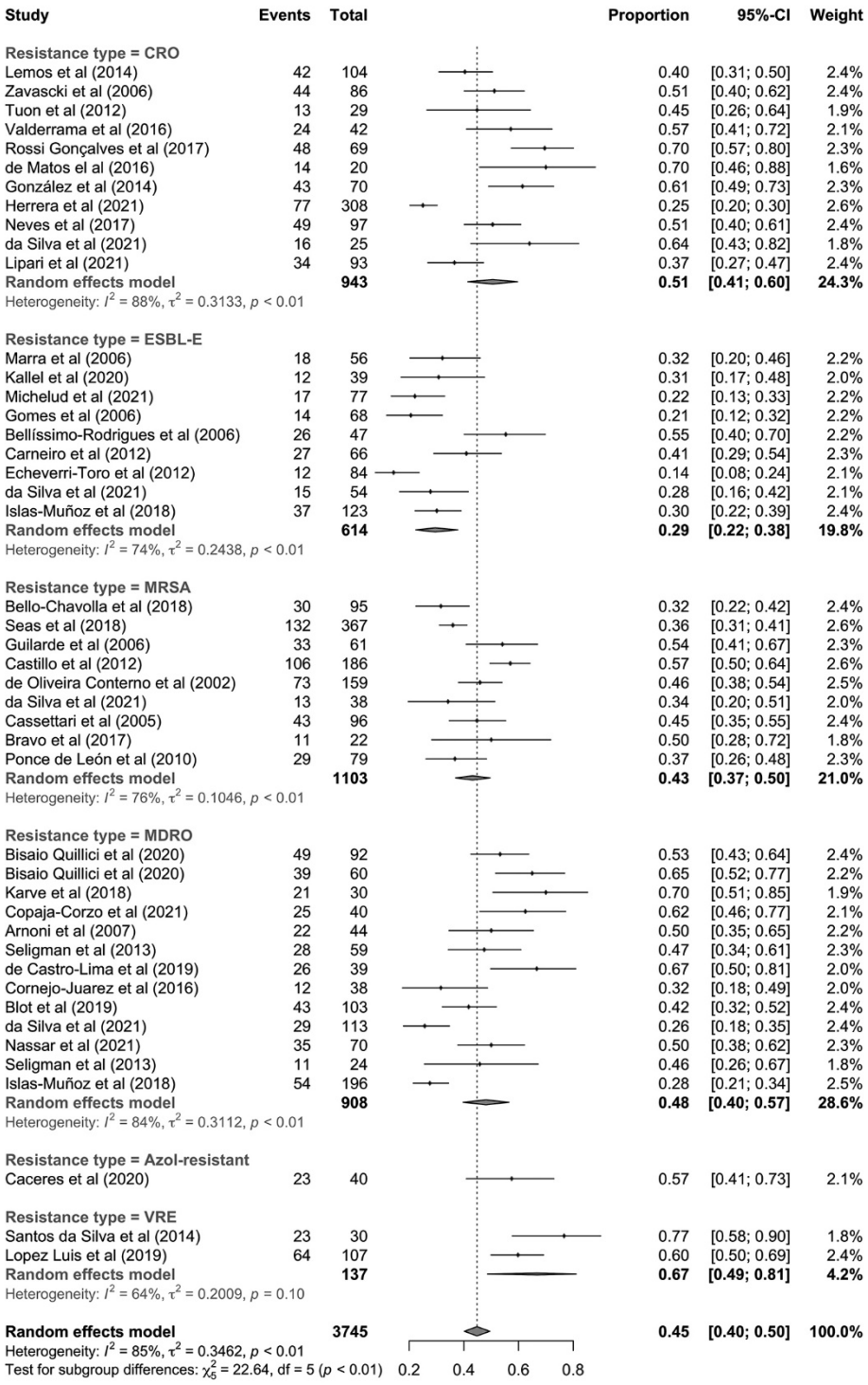
Study	In-hospital lethality R (n/N)	In-hospital lethality S (n/N)	15-d lethality R (n/N)	15-d lethality S (n/N)	30-d lethality R (n/N)	30-d lethality S (n/N)	Unadjusted OR/RR/HR (95% CI)	Adjusted OR/RR/HR (95% CI)	Type of adjustment
Rossi Gonçalves et al (2017)	48/69	32/65	NR	NR	NR	NR	OR: 2.35 (1.16–4.78)	NR	..
Tuon et al (2012)	NR	NR	NR	NR	13/29	26/48	OR: 0.68 (0.27–1.73)	NR	..
Valderrama et al (2016)	24/42	45/126	NR	NR	NR	NR	OR: 2.40 (1.18–4.89)†	NR	..
Zavascki et al (2006)	44/86	68/212	NR	NR	NR	NR	RR: 1.60 (1.20–2-12); HR: 1.55 (1.06–2.27)	HR: 1.07 (0.72–1.60)	Age, severe sepsis or septic shock, appropriate therapy, surgical procedure
Carbapenem-resistant *Acinetobacter baumannii* (CR-AB)	..	..	..	..	..	..	..	..	..
Blot et al (2019)	NR	NR	NR	NR	2/7	0/4	..	..	..
da Silva et al (2021)	NR	NR	NR	NR	30/50	3/11	OR: 4 (0.95–16.9)†	NR	..
Lemos et al (2014)	NR	NR	NR	NR	42/104	13/61	HR: 2.12 (1.14–3.95)	HR: 1.45 (0.74–2.87)	Age, gender, APACHE II score, number of diagnoses, and inappropriate empirical treatment
Azol-resistant *Candida* spp.	..	..	..	..	..	..	..	..	..
Caceres et al (2020)	23/40	26/50	NR	NR	17/40	20/50	In-hospital mortality: OR: 1.41 (0.59–3.34) 30 d mortality: OR: 1.25 (0.52–3.01)	NR	..
Pinhati et al (2016)	NR	NR	NR	NR	9/21	9/19	OR: 0.90 (0.30–2.75)	NR	..
Multidrug-resistant organisms (MDRO)	..	..	..	..	..	..	..	..	..
Arnoni et al (2007)‡	NR	NR	NR	NR	22/44	12/48	OR: 3.00 (1.24–7.24)†	NR	..
Quillici et al (2021) (Total)	NR	NR	NR	NR	99/180	46/90	OR: 1.17 (0.70–1.94)†	NR	..
Quillici et al (2021)¶¶	NR	NR	NR	NR	39/60	12/28	OR: 2.48 (0.99–6.20)	OR: 1.7 (0.8–3.5)	NR
Blot et al (2019) (Total)##	NR	NR	NR	NR	43/103	75/246	OR: 1.63 (1.01–2.63)†	OR: 1.51 (0.85–2.69)	Intra-abdominal infection with or without anatomic barrier disruption, age, liver disease, CHF, source

Study	In-hospital lethality R (n/N)	In-hospital lethality S (n/N)	15-d lethality R (n/N)	15-d lethality S (n/N)	30-d lethality R (n/N)	30-d lethality S (n/N)	Unadjusted OR/RR/HR (95% CI)	Adjusted OR/RR/HR (95% CI)	Type of adjustment
									control achieved at day 7
Cornejo-Juarez et al (2016)	NR	NR	NR	NR	12/38	13/26	OR: 0.46 (0.16–1.29)†	NR	..
Cornejo-Juarez et al (2015)‡	51/105	7/51	NR	NR	NR	NR	OR: 17.5 (7.49–41.1)†	NR	..
Oliveira da Silva et al (2021)	59/113	89/124	NR	NR	NR	NR	OR: 1.52 (0.96, 2.41)†	NR	..
Castro-Lima et al (2019)	NR	NR	NR	NR	26/39	15/37	OR: 2.89 (1.11–7.52)	OR: 2.59 (0.85–7.9)	Age, diabetes mellitus, SOFA score on the day of the first HAI and MDROS infection
Matos et al (2016) (Total)	14/20	20/34	NR	NR	NR	NR	OR: 1.63 (0.50–5.29)	NR	..
Matos et al (2016) (Pediatric)	1/4	11/20	NR	NR	NR	NR	OR: 0.28 (0.02–3.09)	NR	..
Matos et al (2016) (Adult)	13/16	10/14	NR	NR	NR	NR	OR: 1.73 (0.31–9.57)	NR	..
Costa et al (2015)‡	NR	NR	NR	NR	12/47	9/54	OR: 1.71 (0.65–4.52)†	NR	..
Islas-Muñoz et al (2018) (Total)	NR	NR	NR	NR	54/196	55/300	OR: 1.69 (1.07–2.65)	OR: 1.59 (0.99–2.65)	..
Karve et al (2018)	21/30	16/50	NR	NR	NR	NR	OR: 4.96 (1.86–13.23)	NR	..
Nassar et al (2021)	35/70	115/237	NR	NR	NR	NR	OR: 1.06 (0.62–1.81)†	NR	..
Prata-Rocha et al (2012)	NR	NR	NR	NR	21/49	8/24	OR: 1.50 (0.48–4.72)	NR	..
Seligman et al (2013) (Total)	28/59	34/81	NR	NR	NR	NR	OR: 1.25 (0.64–2.25)	NR	..
Carbapenem-resistant Gram-negative bacilli (CR-GNB)	..	..	..	..	..	..	..	..	..
Herrera et al (2021)***	61/308	34/463	NR	NR	77/308	44/463	HR: 3.9 (2.9–5.2)	HR: 1.89 (1.1–3.1)	***
Extremely drug-resistant organisms (XDRO)	..	..	..	..	..	..	..	..	..
Copaja-Corzo et al (2020)	25/40	16/84	NR	NR	NR	NR	OR: 7.08 (3.06–16.41)†	NR	..
Multidrug resistant Gram-negative bacilli (MDR-GNB)	..	..	..	..	..	..	..	..	..
Quillici et al (2021)	NR	NR	NR	NR	49/92	28/45	OR: 0.69 (0.33–1.43)	NR	..
Seligman et al (2013)	11/24	23/60	NR	NR	NR	NR	OR: 1.36 (0.52–3.54)†	NR	..

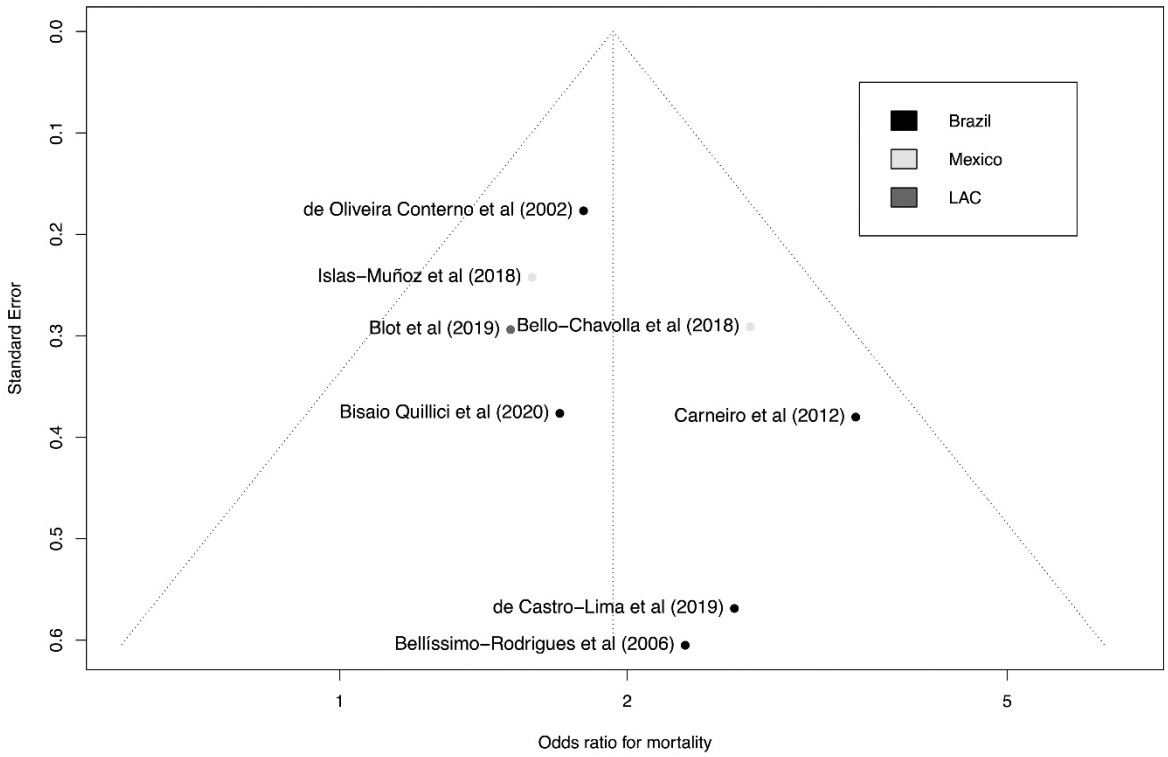
*CHF, congestive heart failure; HAI, hospital-acquired infection; HR, hazard ratio; NR, not reported; OR, odds ratio; R, resistant microorganism; RI, renal insufficiency; RR, risk ratio; S, susceptible microorganism; SOFA, sequential organ failure assessment.

Study	In-hospital lethality R (n/N)	In-hospital lethality S (n/N)	15-d lethality R (n/N)	15-d lethality S (n/N)	30-d lethality R (n/N)	30-d lethality S (n/N)	Unadjusted OR/RR/HR (95% CI)	Adjusted OR/RR/HR (95% CI)	Type of adjustment

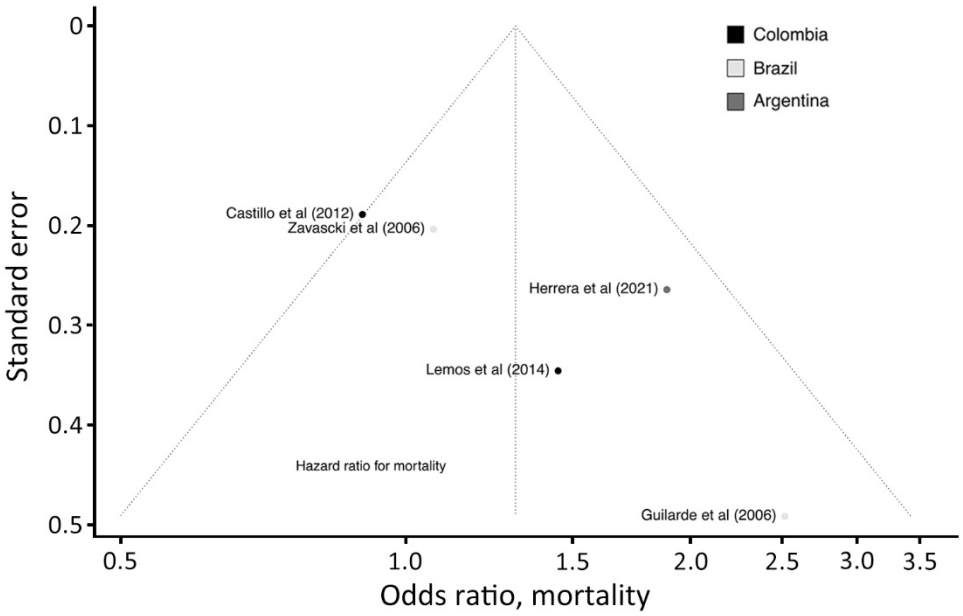
†Comparative measure calculated with reported data.
‡Number of episodes reported (not patients).
§Isolates of MRSA and VRE were included.
¶More than two antimicrobials' agents, cardiopathy, presence of intravascular device, length of hospital stay before bacteraemia >7 d.
#675 out of 915 patients were included in the final analysis.
**Age, gender, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, malignancy, AIDS, Foley catheter, mechanical ventilation, presence of intravascular device, hemodialysis, surgical procedure, use of corticosteroids, bacteraemia, inappropiate empirical treatment (SHOULD BE Bellísimo-Rodrigues et al (2006)
††21-d mortality.
‡‡28-d mortality.
§§Isolates of Carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumanni* were included.
¶¶Isolates of MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were included.(SHOULD BE QUILLICI)
##15 non-fermenting bacteria outside the scope (*Stenotrophomonas maltophilia* and non-specified *Pseudomonas* or *Acinetobacter*) were included in the final analysis.
***771 out of 1277 patients were included in the final analysis.
†††Relapse disease, refractory disease, respiratory source, nosocomial infection, intensive care unit admission, shock, PITT score ≥4, 7-d clinical response.



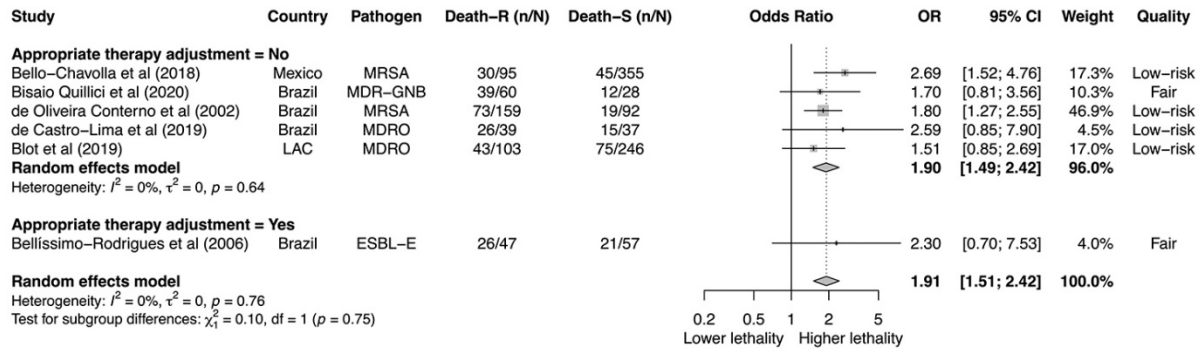
Appendix Figure 1. Crude lethality rate due to different type of antimicrobial resistance. Death-R: death in resistant group; Death-S: death in susceptible group; n: number of death. N: group size; OR: odds ratio; CI: confidence interval; CRO: Carbapenem resistant organisms; ESBL-E: extended spectrum β-lactamase producing Enterobacterales; MRSA: methicillin-resistant *Staphylococcus aureus*; MDRO: multidrug resistant organisms; VRE: Vancomycin-resistant *Enterococcus* spp.



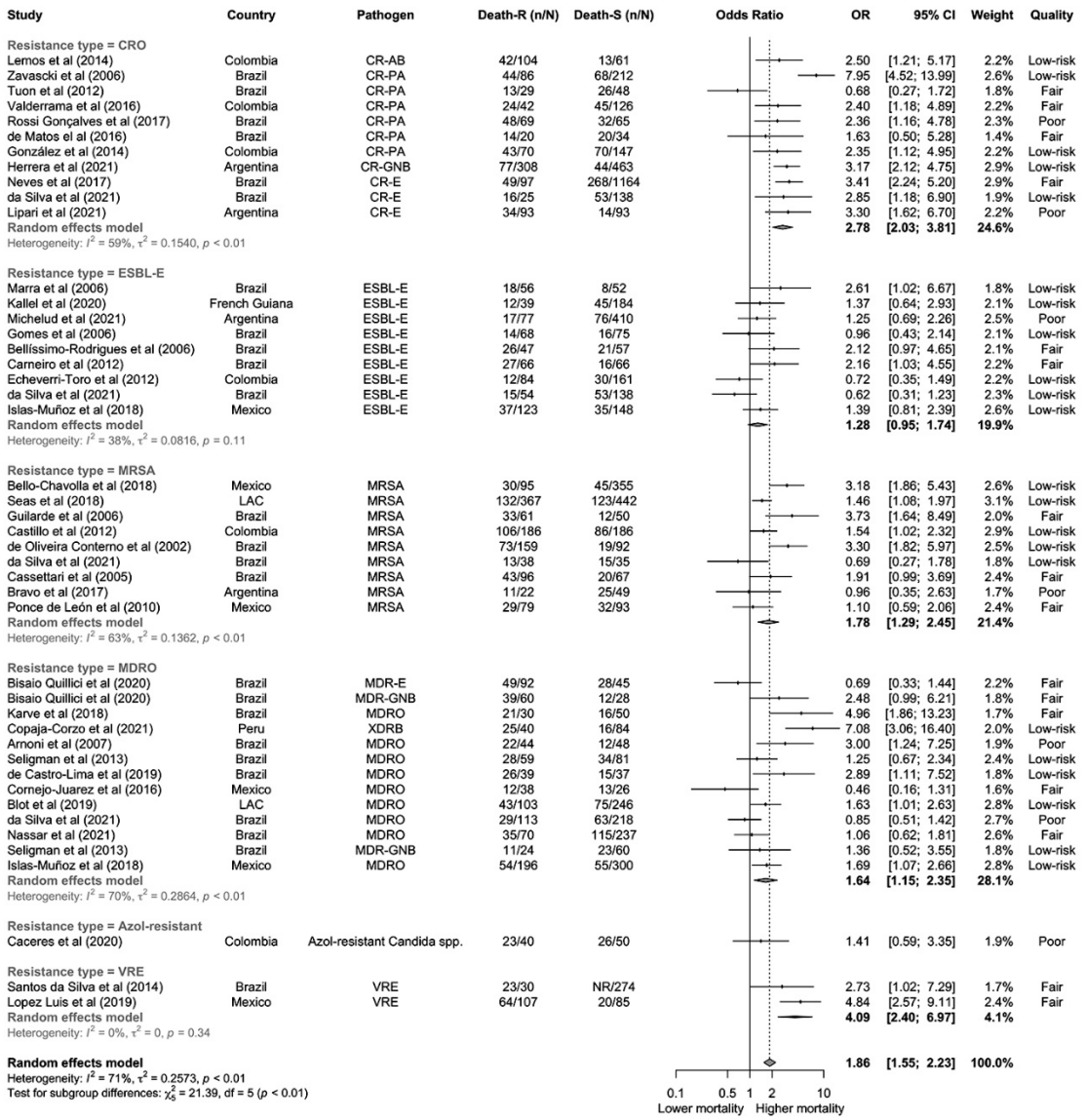
Appendix Figure 2. Funnel plot to assess bias in the studies with adjusted odds ratios for lethality between susceptible and resistant infections. LAC: Latin American and Carribean. Begg's test p-value: = 0.322.



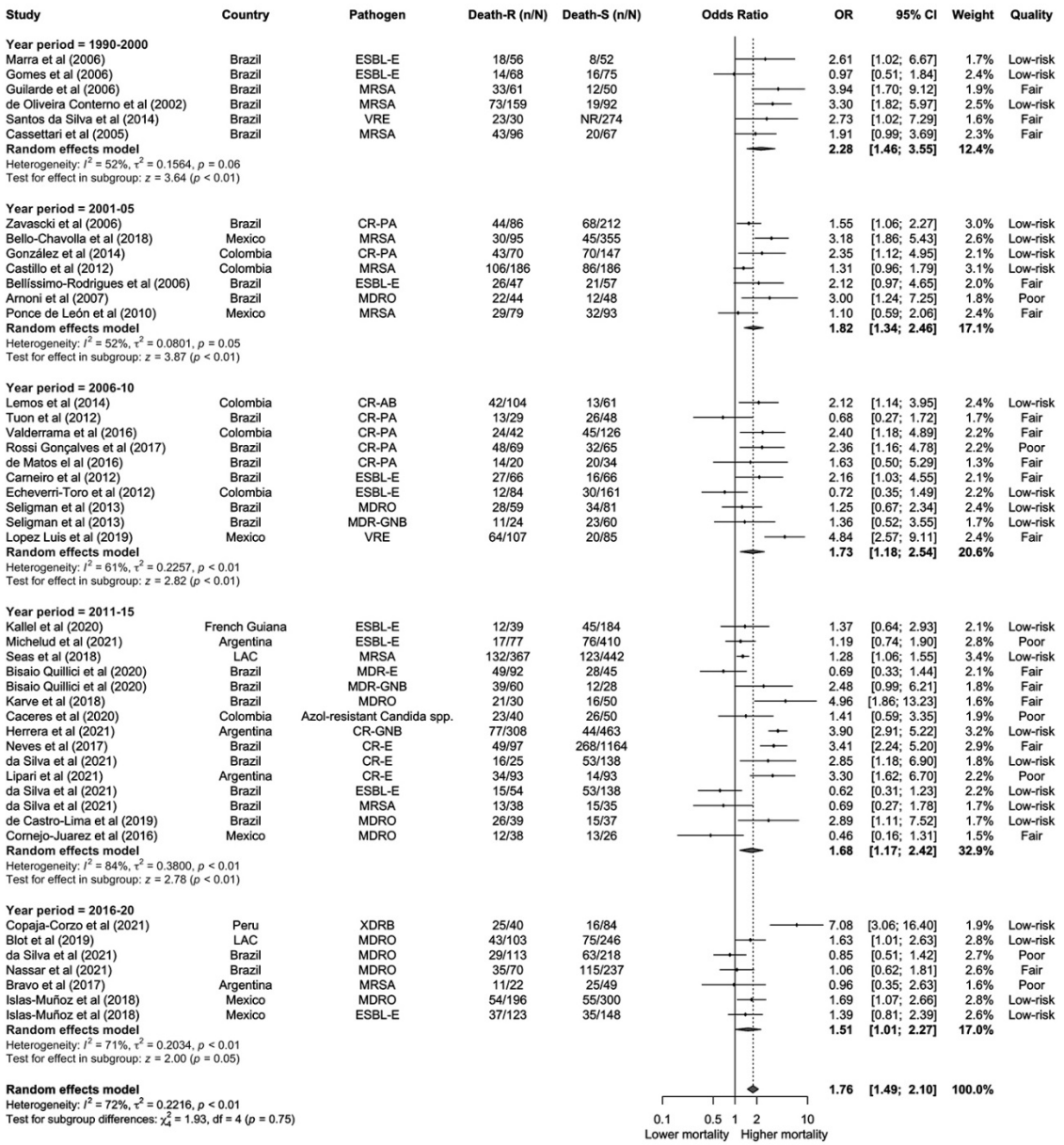
Appendix Figure 3. Funnel plot to assess bias in the studies with adjusted hazard ratios for lethality between susceptible and resistant infections. Begg's test p-value: = 0.141.



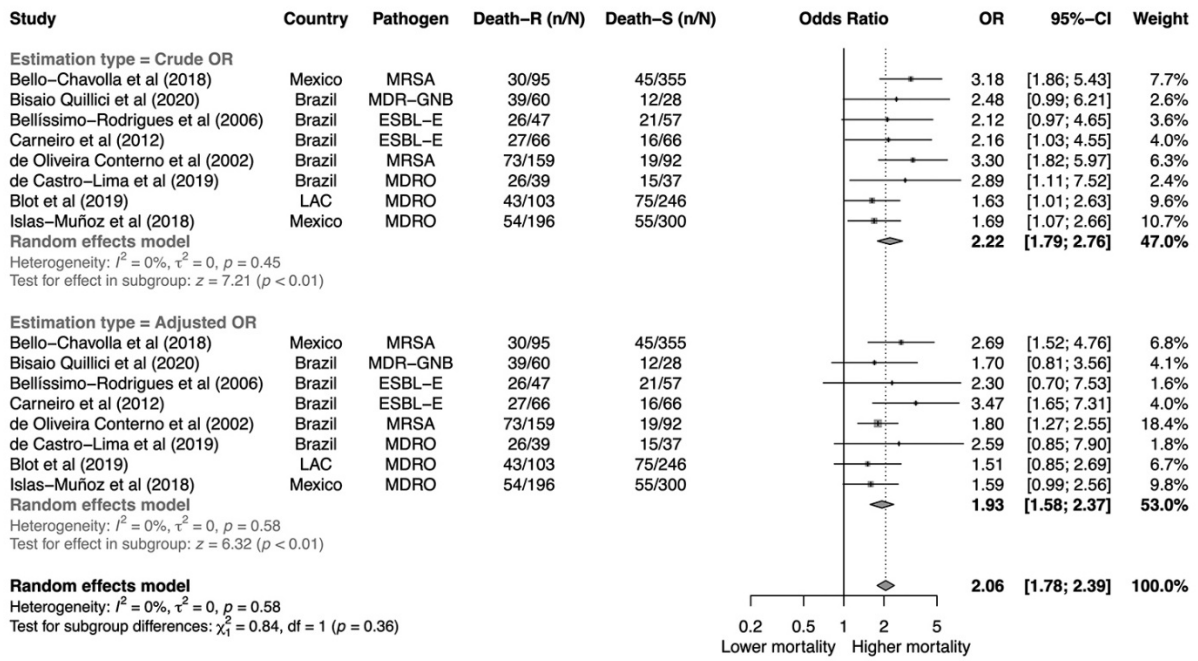
Appendix Figure 4. Association between resistance and mortality by studies that included appropriate empirical antibiotic treatment in the adjusted model. Adjusted odds ratios. We consider the definition of appropriate therapy given by each study author. Only studies that report adjusted odds ratios were included in this analysis. Death-R: death in the resistant group; Death-S: death in the susceptible group; n: number of deaths; N: group size; OR: odds ratio; CI: confidence interval; MRSA: methicillin-resistant Staphylococcus aureus; MDR-GNB: multidrug-resistant Gram-negative bacilli (including ESBL-E: Extended spectrum β-lactamase Enterobacterales, CRE: Carbapenem-resistant Enterobacterales, CRPA: Carbapenem-resistant *Pseudomonas aeruginosa,* CRAB: Carbapenem-resistant *Acinetobacter baumannii*); MDRO: multidrug-resistant organisms (including MRSA, VRE: Vancomycin-resistant *Enterococcus* spp, ESLB-E, CRE, CR-PA, CR-AB); LAC: Latin American and Caribbean countries.



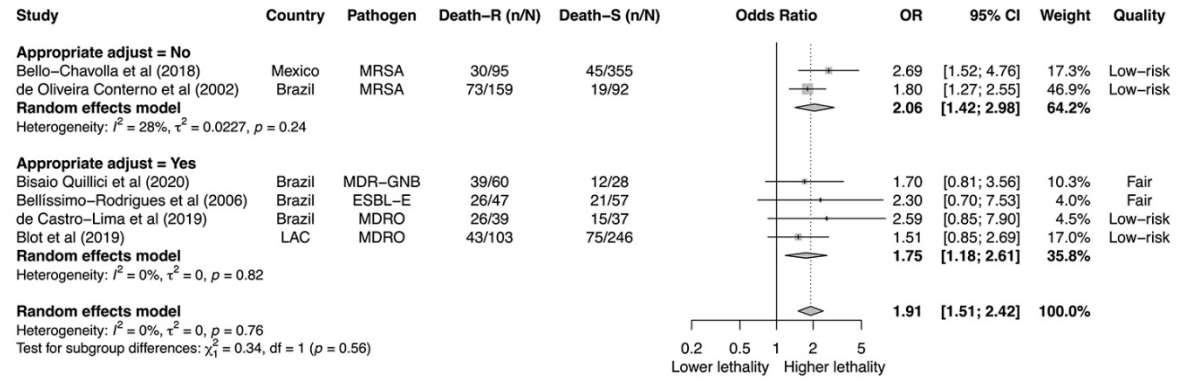
Appendix Figure 5. Forest plot summary of the unadjusted results (OR) for lethality by type of resistance. Death-R: death in resistant group; Death-S: death in susceptible group; n: number of death. N: group size; OR: odds ratio; CI: confidence interval; CR-AB: Carbapenem-resistant *Acinetobacter baumannii*; CR-PA: Carbapenem-resistant *Pseudomonas aeruginosa*; GNB-CR: Gram-negative bacilli carbapenem-resistant; CR-E: Carbapenem-resistant Enterobacterales; CRO: Carbapenen resistant organisms; ;ESBL-E: extended spectrum β-lactamase producing Enterobacterales; MRSA: methicillin-resistant *Staphylococcus aureus*; MDRO: multidrug resistant organisms; MDR-E: multidrug resistant Enterobacterales; MDR-GNB: multidrug resistant Gram-negative bacilli; XDRB: Extremely drug-resistant bacteria (XDRB); VRE: Vancomycin-resistant *Enterococcus* spp.; LAC: Latin American and Caribbean.



Appendix Figure 6. Forest plot summary of the unadjusted results (OR) for lethality by year period of study recruitment. Death-R: death in resistant group; Death-S: death in susceptible group; n: number of death. N: group size; OR: odds ratio; CI: confidence interval; ESBL-E: extended spectrum β-lactamase producing Enterobacterales; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: Vancomycin-resistant *Enterococcus* spp.; CR-PA: Carbapenem-resistant *Pseudomonas aeruginosa*; MDRO: multidrug resistant organisms; CR-AB: Carbapenem-resistant *Acinetobacter baumannii*; MDR-GNB: multidrug resistant Gram-negative bacilli; LAC: Latin American and Caribbean.



Appendix Figure 7. Subgroup analysis for lethality between crude and adjusted ORs. Studies reporting both adjusted and crude odds ratios were included in this analysis. Although no significant difference has been found between the subgroups (p = 0.360), the crude polled estimate tends to overestimate resistance-related lethality. Death-R: death in resistant group; Death-S: death in susceptible group; n: number of death. N: group size; OR: odds ratio; CI: confidence interval; MRSA: methicillin-resistant Staphylococcus aureus; MDR-GNB: multidrug resistant Gram-negative bacilli; ESBL-E: extended spectrum β-lactamase enterobacteriaceae spp.; MDRO: multidrug resistant organism.



Appendix Figure 8. Association between resistance and lethality by appropriate adjustment. OR: odds ratio; CI: confidence interval; MRSA: methicillin-resistant *Staphylococcus aureus*; MDR-GNB: multidrug resistant Gram-negative bacilli; ESBL-E: extended spectrum β-lactamase producing Enterobacterales; MDRO: multidrug resistant organism. We consider appropriate adjustment between lethality and resistance when the study considers in the final model at least one variable in each category: a) variables related to the patients' baseline status, b) variables related to the infection; and c) variables related to the treatment (*68*).

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