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# ANTIMICROBIAL DRUGS – BURDEN OF ANTIMICROBIAL RESISTANCE

# FINAL

*SUBMITTED TO:*
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# DISCLAIMER

# LIST OF ACRONYMS

| | |
|---|---|
| ABSSSI | Acute bacterial skin and skin structure infection |
| AMR | Antimicrobial resistance |
| ARIMA | Autoregressive integrated moving average |
| ASPE | HHS Office of the Assistant Secretary for Planning and Evaluation |
| AST | Antimicrobial susceptibility test |
| BICU | Burn intensive care unit |
| BSI | Bloodstream infection |
| CAESAR | Central Asian and European Surveillance of Antimicrobial Resistance |
| CAP | Community-acquired pneumonia |
| CDC | Centers for Disease Control and Prevention |
| CDF | Cumulative distribution function |
| CLIA | Clinical Laboratory Improvement Amendment |
| CLSI | Clinical and Laboratory Standards Institute |
| CMS | Centers for Medicare and Medicaid Services |
| COVID | Coronavirus disease |
| CPI | Consumer Price Index |
| CPO | Carbapenemase-producing organism |
| CRAB | Carbapenem-resistant *Acinetobacter baumannii* |
| CRE | Carbapenem-resistant *Enterobacterales* |
| CRKP | Carbapenem-Resistant *Klebsiella pneumoniae* |
| CRPA | Carbapenem-resistant *Pseudomonas aeruginosa* |
| CSKP | Carbapenem-susceptible *Klebsiella pneumoniae* |
| DTR | Difficult-to-treat |
| EARS-Net | European Antimicrobial Resistance Surveillance Network |
| ERG | Eastern Research Group, Inc. |
| ESBL | Extended spectrum beta-lactamase |
| EUCAST | European Committee on Antimicrobial Susceptibility Testing |
| FDA | Food and Drug Administration |
| FRKP | Fluoroquinolone-resistant *Klebsiella pneumoniae* |
| GDP | Gross Domestic Product |
| GLASS | Global Antimicrobial Resistance and Use Surveillance System |
| GNI | Gram-negative infection |
| HAI | Healthcare-acquired infection |
| HAP | Healthcare-acquired pneumonia |
| HHS | U.S. Department of Health and Human Services |
| ICU | Intensive care unit |
| IDSA | Infectious Diseases Society of America |
| LOS | Length of stay |
| LRTI | Lower respiratory tract infection |
| MDR | Multi-drug resistant |
| MIC | Minimum inhibitory concentration |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| NARMS | National Antimicrobial Resistance Monitoring System |
| NHS | U.K. National Health Service |
| NHSN | CDC National Healthcare Safety Network |
| PDR | Pan-resistant infection |
| PNE | Pneumonia |
| PPI | Producer-based index |

| | |
|---|---|
| PPL | Priority pathogen list |
| SSI | Surgical site infection |
| UTI | Urinary tract infection |
| VAP | Ventilator-associated pneumonia |
| WHO | World Health Organization |
| XDR | Extensively drug-resistant |

# EXECUTIVE SUMMARY

It is well known that antimicrobial resistance (AMR) creates a substantial and ongoing public health and economic burden and understanding the size and nature of this burden is important for the ability to respond to the threat of AMR. However, estimating or projecting that burden within the U.S. is a difficult task that prompts a variety of assumptions and produces conflicting results, making it challenging for researchers and policymakers to interpret and act upon that data.[1] To better understand the issues that complicate efforts to model the current and future AMR burden in the U.S., we conducted a systematic literature review of the 15 combinations of pathogen and drug resistance (shown in Table ES - 1), nearly all of which were designated serious or urgent threats by CDC in its report *Antibiotic Resistance Threats in the United States, 2019* (CDC, 2019). The pathogens spanned *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*), *Enterobacter aerogenes/Enterobacter cloacae* (*E. aerogenes/E. cloacae*)[2], *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* (*P. aeruginosa*).[3] The drug resistance phenotypes included multi-drug resistance, carbapenem resistance, third-generation cephalosporin resistance, and fluoroquinolone resistance. Table ES - 1 presents the fifteen pathogen-drug combinations we studied and the number of studies we included, categorized by region (U.S., Europe, and Other).

**Table ES - 1. Number of Studies from Each Region, by Pathogen-Drug Combination**

| Drug Resistance | Pathogen | U.S. | Europe | Other |
|---|---|---|---|---|
| Carbapenem | *A. baumannii* | 3 | 2 | 23 |
| Multi-Drug Resistant (MDR) | *A. baumannii* | 4 | 1 | 11 |
| Carbapenem | *E. coli* | 2 | 0 | 6 |
| Third-Generation Cephalosporin | *E. coli* | 2 | 3 | 7 |
| Fluoroquinolone | *E. coli* | 4 | 2 | 0 |
| MDR | *E. coli* | 1 | 6 | 5 |
| Carbapenem | *E. aerogenes/E. cloacae* | 0 | 1 | 3 |
| MDR | *E. aerogenes/E. cloacae* | 0 | 0 | 1 |
| Carbapenem | *K. pneumoniae* | 11 | 10 | 9 |
| Third-Generation Cephalosporin | *K. pneumoniae* | 3 | 1 | 8 |
| Fluoroquinolone-Resistant | *K. pneumoniae* | 3 | 0 | 0 |
| MDR | *K. pneumoniae* | 0 | 1 | 8 |
| Carbapenem-Resistant | *P. aeruginosa* | 2 | 6 | 13 |
| Third-Generation Cephalosporin | *P. aeruginosa* | 1 | 1 | 3 |
| MDR | *P. aeruginosa* | 1 | 9 | 4 |

Our primary objective was to assess the availability and quality of published studies on the 15 selected pathogen-drug combinations that could support models of the AMR burden in the U.S. In so doing, we defined the key model parameters as mortality, length of stay (LOS), and healthcare costs for resistant and susceptible infections of interest and characterized the current state of the literature on those parameters. We also identified research gaps with respect to estimating those

[1] In this report, we use "estimate" to refer to calculations of the current burden and "projection" to refer to calculations of future burden. "Model" refers to the calculations, underlying assumptions, input data, and output predictions.

[2] As of 2020, *E. aerogenes* is now classified as *K. aerogenes*. However, in this report, we use the previous term *E. aerogenes* for consistency with CDC's *Antibiotic Resistance Threats in the United States, 2019* and literature published prior to 2020.

[3] When very little literature was available, we broadened our search scope (e.g., including all fluoroquinolone-resistant Enterobacteriaceae when searching for fluoroquinolone-resistant *K. pneumoniae*). These instances are described in Section 4.1.

model parameters, and we compared pathogen-drug combinations on their capacity for AMR burden modeling. We reviewed 2,926 studies, 167 of which were included for analysis. Table ES - 2 shows, for each pathogen and drug, the number of available published estimates of resistant-strain mortality and resistant-strain LOS in the included literature. Cost data were far less common than mortality or LOS data, so costs were analyzed separately (see Section 5.1.9) and are excluded from the counts in Table ES - 2. The values in Table ES - 2 include both U.S. and non-U.S. studies. Comparing with Table ES - 1 shows there are more estimates than publications; this is because many publications provide multiple estimates for more than one infection site, such as bloodstream infections (BSIs), urinary tract infections (UTIs), pneumonia infections, or surgical site infections (SSIs).

**Table ES - 2. Number of Resistant-Strain Mortality and LOS Estimates Available, by Pathogen-Drug Combination**

| Pathogen-Drug Combination | Number of Resistant-Strain Mortality Estimates | Number of Resistant-Strain LOS Estimates |
|---|---|---|
| Carbapenem-Resistant *A. baumannii* | 45 | 14 |
| Carbapenem-Resistant *K. pneumoniae* | 33 | 8 |
| Carbapenem-Resistant *P. aeruginosa* | 24 | 14 |
| MDR *P. aeruginosa* | 20 | 11 |
| MDR *A. baumannii* | 16 | 9 |
| Carbapenem-Resistant *E. aerogenes/E. cloacae* | 12 | 12 |
| 3rd Gen. Cephalosporin-Resistant *E. coli* | 13 | 8 |
| 3rd Gen. Cephalosporin-Resistant *K. pneumoniae* | 12 | 7 |
| Carbapenem-Resistant *E. coli* | 11 | 4 |
| MDR *E. coli* | 10 | 5 |
| MDR *K. pneumoniae* | 8 | 3 |
| Fluoroquinolone-Resistant *E. coli* | 6 | 2 |
| 3rd Gen. Cephalosporin-Resistant *P. aeruginosa* | 5 | 2 |
| Fluoroquinolone-Resistant *K. pneumoniae* | 3 | 1 |
| MDR *E. aerogenes/E. cloacae* | 1 | 0 |

Note: the total number of estimates may exceed the number of studies, as some studies contain multiple estimates.

All of the publications[4] we included are relevant to AMR in general. However, the extent to which published estimates are suitable for modeling the current or future national AMR burden in the U.S. depends on several factors that relate to generalizability. We developed a scoring algorithm that accounts for the following four factors: the region where the study was conducted, the precision of the study's estimate, the study design (cohort, case-control, or other), and the recency of data, as measured by the year when the study stopped enrolling participants. Each study was rated on each of these factors using a three-point scale, presented in Table ES - 3.

By aggregating these four components, we assigned each study an overall relevance score and categorized the studies as having low, medium, or high relevance. Throughout this report, we refer to the score as measuring a study's overall relevance rather than overall quality because we acknowledge that we are attempting to use these studies for a task (national AMR burden modeling) that the studies were not originally designed for.

[4] In this report, we use "publication" and "study" interchangeably, as each publication constituted a different study. In the context of these publications, the "estimates" refer to a published value of mortality, LOS, or cost.

**Table ES - 3. Scoring Methodology for Four Components**

| Feature of Study | 1 point | 2 points | 3 points |
|---|---|---|---|
| Final year when participants were enrolled | 1999-2006 | 2007-2013 | 2014-2020 |
| Region where study was conducted | Other | Europe | U.S. |
| Precision of resistant-strain estimate [a] | Bottom tercile | Middle tercile | Top tercile |
| Study design | Other | Case-control study | Cohort study |

[a] Precision refers to either the standard error of a resistant-strain mortality estimate, or the sample size associated with a resistant-strain LOS estimate.

Initial searching suggested that there would be too few U.S. publications to produce all required estimates, which was later confirmed through our literature review.[5] We therefore included studies from other countries and did not restrict our search just to U.S. publications. We found that the region where a study was conducted often introduces the most variation into estimates of resistant-strain mortality and LOS. Whereas most of the components of the scoring algorithm attempt to capture data quality, region likely captures more fundamental differences. Because the underlying AMR-attributable mortality rates can vary substantially by region, studies conducted in different countries may be attempting to measure altogether different targets.

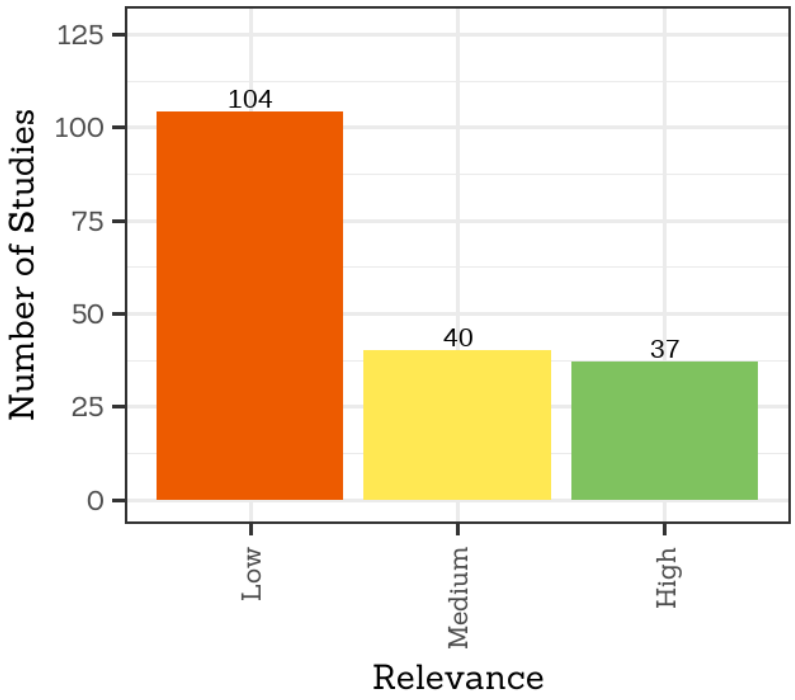
The presence of a large number of studies does not necessarily indicate that they are all highly relevant/suitable for the task of modeling national AMR burden in the U.S. Using a 1-3 scale (1 = low relevance, 2 = medium relevance, and 3 = high relevance), we found that only 20 percent of published studies achieve overall scores indicating high relevance to U.S. AMR burden modeling. Two features are primarily responsible for the small number of studies earning high scores: a vast majority of the studies were conducted in countries where AR mortality rates tended to differ from U.S. rates, and of the U.S. studies we identified, only three had enrollment periods extending past 2013. Of the included studies, those conducted in the U.S. tended to have slightly better precision (as measured by standard error or sample size) and made more frequent use of cohort designs but utilized slightly older data. Overall, resistant-strain mortality estimates were far more common than resistant-strain LOS estimates. Figure ES - 1 presents the distribution of studies based on relevance to AMR burden modeling. In this graph, studies with distinct estimates for different pathogen-drug combinations were counted multiple times.

In general, we found insufficient data in the literature to support infection-site-specific AMR burden modeling. This poses a major obstacle, as mortality and LOS vary widely across infection sites. For example, BSIs make up the vast majority of included studies yet are associated with substantially higher mortality rates than other infection types. Accordingly, building a burden model exclusively on these relatively abundant studies would lead to overestimation. However, even differentiating between just four infection sites (BSIs, UTIs, SSIs, and pneumonia) is not feasible based on the studies we included.

When comparing the 15 pathogen-drug combinations, we found that *E. aerogenes/E. cloacae* was the least-studied and *A. baumannii* and *K. pneumoniae* were the most-studied. Among the drug resistances, fluoroquinolones were the least studied and carbapenems were the most studied. However, simply because a pathogen-drug combination had a large number of studies did not imply that the studies all achieved high relevance scores, and this was especially true for *A. baumannii*.

[5] Of the 167 distinct publications we included, 29 were conducted in the U.S. When aggregating counts of studies across study-pathogen combinations, 37 of 181 studies were conducted in the U.S. The second tabulation method gives greater weight to larger studies that reported outcomes for multiple pathogen-drug combinations, counting them multiple times.

**Figure ES - 1. Distribution of Studies, by Relevance (Low, Medium, High)**




Note: the designations (low, medium, and high) relate to a study's relevance to modeling national AMR burden in the U.S. These designations are based on a composite score that considers (a) the region in which the study was performed, (b) the recency of data (as indicated by the final year of participant enrollment), (c) the precision of the estimates (as indicated by standard error or sample size), and (d) the type of design (e.g., cohort, case-control, or other).

One strategy for modeling overall AMR burden is to generate separate estimates or projections of the attributable mortality and LOS for specific infection sites, and then aggregate across all infection sites to acquire total attributable mortality and LOS, for a given pathogen-drug combination. The motivation for this type of granular approach is that mortality and LOS vary widely by infection site, for example, with BSIs tending to have higher mortality than UTIs. We found that none of the 15 pathogen-drug combinations had sufficient literature to support infection-site-specific mortality and LOS parameters. In the absence of infection-site-specific data, the alternative modeling approach is to use studies that were not focused on just a single infection. However, these studies similarly were too scarce, and they raise concerns of generalizability, as the distribution of infection sites in the study groups may not broadly represent the distribution in the full U.S. population. Accordingly, there is insufficient literature either for infection-site-specific modeling or non-infection-site-specific modeling.

For each pathogen-drug combination, we also assessed the extent to which comparable estimates agreed by evaluating the standard deviation (SD) of medium- or high-scoring estimates of the same pathogen, drug, and infection site. Then, for a given pathogen and drug, we averaged these metrics across the available infection sites. In general, we found that multi-drug resistance (MDR) tended to have less internal agreement, possibly due to conflicting definitions of MDR, and that fluoroquinolone resistance tended to have more agreement. For example, comparable estimates of fluoroquinolone-resistant *K. pneumoniae* had a mean SD of 0.5 percent, whereas comparable estimates of MDR *A. baumannii* had a mean SD of 21.6 percent.

In total, we evaluated each pathogen-drug combination on five components, which spanned the number of available studies, the relevance of the best available studies, the availability of data that could potentially represent all infection sites, and the extent of agreement within comparable estimates. Each criterion was converted into a three-point scale, as shown in Table ES - 4.

**Table ES - 4. Components for Final Score of Each Pathogen-Drug Combination**

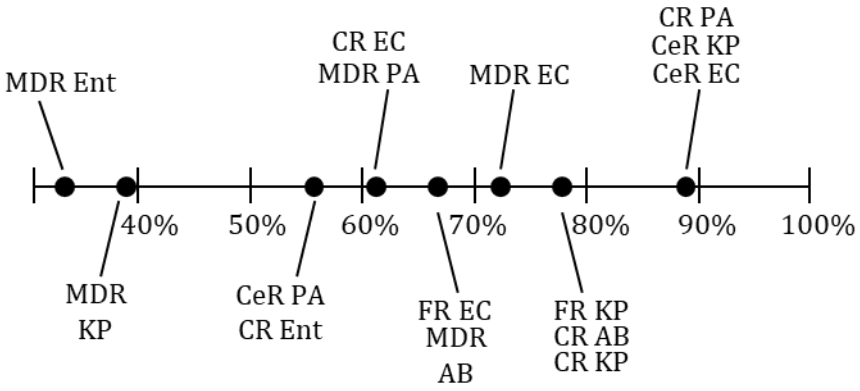
| Component | 1 point | 2 points | 3 points |
|---|---|---|---|
| Number of studies with a resistant-strain mortality or LOS estimate | 1-10 | 11-20 | 21-30 |
| Mean score of the top-scoring resistant-strain mortality studies | 3-8 | 9-15 | 16-27 |
| Mean score of the top-scoring resistant-strain mortality studies, limiting to "any infection" studies [a] | 3-8 | 9-15 | 16-27 |
| Mean score of the top-scoring resistant-strain LOS studies | 3-8 | 9-15 | 16-27 |
| Mean score of the top-scoring resistant-strain LOS studies, limiting to "any infection" studies | 3-8 | 9-15 | 16-27 |
| Mean SD between comparable medium- or high-scoring estimates | >15% | 10-15% | <10% |

[a] We define an "any infection" study as one that was not limited to just a single infection site and encompassed at least three infection sites.

Figure ES - 2 presents a final line plot of the relative strength of literature for national burden modeling of the 15 pathogen-drug combinations. The percentages in this figure combine the five components of Table ES - 4.[6] Overall, we found that carbapenem-resistant pathogens tended to have the highest capacity for AMR burden modeling (including *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*), as did third-generation cephalosporin-resistant pathogens. MDR *E. aerogenes/E. cloacae* and MDR *K. pneumoniae* had the lowest capacity for burden modeling.

[6] As discussed in Section 5.2.7, the final percentage is acquired by summing the five component scores and dividing by the possible points. This final percentage accounts for the number of available publications, the relevance score of the publications, and the availability of data that is not limited to a single infection site.

**Figure ES - 2. Line Plot of Overall Scores for Each Pathogen-Drug Combination**




Legend for Drugs
CR = carbapenem-resistant
MDR = multi-drug-resistant
CeR = 3rd gen. cephalosporin-resistant
FR = fluoroquinolone-resistant

Legend for Pathogens
Ent = *E. aerogenes/E. cloacae*
KP = *K. pneumoniae*
AB = *A. baumannii*
EC = *E. coli*
PA = *P. aeruginosa*

# 1 INTRODUCTION

Since the discovery of penicillin in 1928, antimicrobial (AM) agents have been used to treat first bacterial and then fungal infections in humans and animals (Aslam, et al., 2018). Resistance to these agents can begin to develop immediately upon release of a new drug, and in some cases even before a drug's release in U.S. markets (e.g., fluconazole was FDA approved in 1990, two years after fluconazole-resistant *Candida* was first identified) (CDC, 2019). Antimicrobial resistance (AMR) makes infections more difficult or impossible to treat, can require use of more expensive treatments or treatments with more side effects, and poses an economic burden. AMR also jeopardizes the use of healthcare procedures that carry higher risk of infection in general (e.g., organ transplants, some surgeries), as the possibility that an associated infection may be resistant increases the associated risk (CDC, 2019). AMR is a concern not only for bacterial infections, but also for fungal infections, as only three classes of antifungal drugs are available for *Candida* and *Aspergillus* infections (CDC, 2019).

Although the development of resistance to AM drugs in microorganisms is a natural process, the overuse of AM drugs in humans and animals has caused AMR to grow. Because the development and spread of AMR is driven by exposure to AM drugs, inappropriate uses—such as use with a target that is already resistant, use of the wrong dose or duration, and overuse (in healthcare and in agriculture)—can contribute to the development of AMR. Based on limited data from nursing homes, the CDC reported in 2017 that over half of all nursing home residents receive antibiotics each year, and "up to 75 percent of antibiotics prescribed in nursing homes are prescribed incorrectly," including use of an antibiotic when none is needed, as well as incorrect antibiotic choice, dose, or duration (CDC, 2017). In hospitals, over half of patients receive antibiotics for at least one day (CDC, 2017).

AM treatments for infections are grouped into classes based on the drug's mechanism of action. AM treatments are also designated as first-line treatments, second-line treatments, etc., depending on when they are typically used, although these designations can vary by facility, region, infection type, and patient characteristics. First-line antibiotics are recommended as the first treatment against an infection due to high effectiveness with minimal side effects or other harms. Second- and third- line treatments are less preferred either due to lower efficacy, worse side effects, greater propensity to contribute to AMR, or other harms (CDC, 2019). Chemicals in the same class have similar chemical structures and act on target organisms in the same way, so organisms that develop resistance to one drug in a class usually also gain resistance to other drugs in that class. The strength of resistance is often classified using the following categories.

- Multi-drug resistant (MDR): resistant to at least one agent in more than two available class of AM treatments (Kadri, et al., 2018).
- Extensively-drug resistant (XDR): only susceptible to a maximum of two AM classes and resistant to all other classes (CDC, 2019) (Kadri, et al., 2018).
- Pan-resistant infections (PDR): resistant to all available AM treatments (CDC, 2019).

The categorizations of MDR, XDR, and PDR indicate increasing resistance to more types of AM agents. In addition, infections might also be described as difficult-to-treat (DTR), denoting resistance to all first-line AM agent classes (Kadri, et al., 2018). Infections that can be treated effectively by the recommended dosage and standard AM regimen are called susceptible (CDC, 2019). Infections that are MDR, XDR, or DTR can have negative impacts on patient outcomes and costs. For example, Kadri et al. found DTR gram-negative BSIs had 40 percent higher adjusted mortality risk than patients with susceptible gram-negative BSIs (Kadri, et al., 2018).

In the U.S., AMR threats are prioritized by CDC (CDC, 2019). Global threats requiring more research, discovery, and development of AM drugs are listed by the World Health Organization (WHO). Table 1 compares WHO's global priority pathogen list (PPL) to CDC's threats list. The CDC and WHO AR threat designations are shown below, in descending order from most serious:

- CDC AR threat designations: Urgent, Serious, Concerning, and Watch List
- WHO AR threat designations: Critical, High, and Medium

There is reasonable correspondence between the criteria for establishing threats. Urgent and Critical indicate the highest levels of threat, and Concerning and Medium indicate important but less urgent levels of threat. While there is much overlap in the criteria for identifying AR threat designations, WHO's PPL was designed to guide research, discovery, and development of new AM drugs for top pathogens of concern, whereas CDC's threat list categorizes pathogens based on human health concerns and projected incidence. For example, WHO's AR threat designations account for whether there is a lack of new antibiotics in the R&D pipeline, while CDC's designations are based on 10-year projections of incidence. Some pathogens of serious concern in the U.S., including two categorized as "urgent," are not included in WHO's top priorities for research globally, and all but two of the WHO PPL pathogens are included as pathogens of concern on CDC's threat list.[7] Note that CDC also lists three fungi not considered by WHO, and *Clostridioides difficile* (*C. difficile*) as pathogens of concern.

[7] As shown in Table 1, *H. pylori* and *H. influenzae* are not included in CDC's list but are classified by WHO as high and medium threats, respectively.

**Table 1. Comparison of CDC's 2019 Antibiotic Resistance Threats List and WHO's 2017 Global Priority Pathogen List (PPL)**

| Pathogen | Resistance | CDC Threat Level [a] | WHO Threat Level [b] |
|---|---|---|---|
| *Acinetobacter* | Carbapenem | Urgent | Critical |
| *Candida auris* (fungus) | - | Urgent | NA [c] |
| *C. difficile* [d] | - | Urgent | NA |
| Enterobacteriaceae | Carbapenem | Urgent | Critical |
| *Neisseria gonorrhoeae* | Any | Urgent | High (cephalosporin resistance, fluoroquinolone resistance) |
| *Campylobacter* | Any | Serious | High (fluoroquinolone resistance) |
| *Candida* (fungus) | Any | Serious | NA |
| ESBL-producing Enterobacteriaciae | Beta-lactams | Serious | Critical |
| *Enterococci* | Vancomycin | Serious | High (specifically, *Enterococcus faecium*) |
| *P. aeruginosa* | MDR | Serious | Critical (carbapenem resistance) |
| Nontyphoidal *Salmonella* | Any | Serious | High (fluoroquinolone-resistant *Salmonellae*) |
| *Salmonella* serotype Typhi | Any | Serious | High (fluoroquinolone-resistant *Salmonellae*) |
| *Shigella* | Any | Serious | Medium (fluoroquinolone resistance) |
| *Staphylococcus aureus* | Methicillin | Serious | High (Methicillin-resistant, vancomycin intermediate and resistant) |
| *Streptococcus pneumoniae* | Any | Serious | Medium (penicillin non-susceptible) |
| *Mycobacterium tuberculosis* | Any | Serious | Considered an established priority |
| Group A *Streptococcus* | Erythromycin | Serious | NA |
| Group B *Streptococcus* | Clindamycin | Serious | NA |
| *Aspergillus fumigatus* (fungus) | Azole | Watch List | NA |
| *Mycoplasma genitalium* | Any | Watch List | NA |
| *Bordetella pertussis* | Any | Watch List | NA |
| *Helicobacter pylori* | Clarithromycin | NA | High |
| *Haemophilus influenzae* | Ampicillin | NA | Medium |

[a] CDC uses the following AR threat designations: Urgent, Serious, Concerning, and Watch List.

[b] WHO uses the following designations: Critical, High, and Medium.

[c] NA = Not applicable and is used when the agency did not include a given pathogen on its list. WHO did not consider fungal infections.

[d] *C. difficile* is a species of bacteria that can cause disease when patients take broad-spectrum antibiotics. Many people may be colonized with *C. difficile* and then become infected when antibiotics kill off competing susceptible bacteria. *C. difficile* is not considered a drug-resistant pathogen but can thrive when competing bacteria are killed. Some patients get better by terminating broad-spectrum antibiotics, while others need to be treated with another antibiotic (CDC, 2021).

## 1.1 ESTIMATES OF NUMBER OF AMR INFECTIONS

Countries including the U.S. have developed surveillance systems to monitor, track, and identify trends in infections and AMR. Surveillance systems may be designed to identify emerging threats (such as new AMR infections), to track trends in existing infections, or to prevent infections (e.g., by identifying contaminated food products or identifying hospital patients requiring stronger containment measures). Surveillance systems are discussed in greater detail in Appendix A.

No surveillance networks collect universal data on a full population for all potentially relevant variables. As a result, estimates must be generated based on samples from surveillance systems and other data collections, and these estimates can vary based on input data, assumptions made, and estimation methods. A 2018 review article found that different burden calculation methodologies sometimes resulted in large differences in burden estimates (Naylor, et al., 2018). The underlying data sources are prone to measurement difficulties, such as the possibility of asymptomatic carriage (colonization), which can lead to false positives in patients who have been colonized but do not have an infection. Different protocols are used to test different organisms, which can limit laboratories' ability to test for all drug-resistant organisms (Dunachie, et al., 2020), potentially skewing certain datasets toward specific pathogens.

Some of the key factors that contribute to this variation in reported AMR infections include differences in:

- Definition of resistance.
- Estimation techniques and underlying data sources.
- Healthcare-associated versus community-acquired infections.
- The extent to which time-dependent biases are accounted for.

***Definition of Resistance.*** Differences in the definition of resistance can cause differences in estimates of AMR. Microbiological tests include measurement of minimum inhibitory concentration (MIC), which is the minimum concentration of a drug needed to inhibit an organism's growth, or antibiotic disk diffusion susceptibility testing, in which the size of the zone of inhibition around the disk is an indirect measure of antimicrobial susceptibility. MICs and disk diffusion zone values are interpreted against breakpoints to determine whether an organism is considered resistant or susceptible.[8] Breakpoints are organism-specific but can be updated over time, and different organizations sometimes publish different breakpoints given, for example, different definitions of the susceptibility categories.[9] This can result in the same organism being characterized as resistant when using one set of breakpoints or characterized as intermediate or susceptible if using different breakpoints (Humphries, et al., 2017).

***Estimation Techniques and Underlying Data.*** The impacts of different estimation techniques and data sources are illustrated in the example of CDC's 2013 and 2019 Antibiotic Resistance Threats Reports (CDC, 2019). In the 2019 report, CDC updated certain estimation methods and recalculated its 2013 estimates using new data sources that were not available in 2013. This resulted in an almost two-fold increase in the original death estimate of the 2013 report, illustrating the impact of the underlying data sources on the final estimates. CDC's burden estimate for drug-resistant *Campylobacter* provides an illustrative example of the number and type of assumptions required to estimate infections and deaths. As detailed in its 2019 report, CDC's estimate is based on an estimate of total *Campylobacter* infections and deaths multiplied by average

[8] Other methods are available, such as using molecular methods to identify resistance genes.
[9] For further discussion of the types of considerations organizations use when determining breakpoints, see https://www.eucast.org/clinical_breakpoints.

resistance prevalence for *Campylobacter*. The average resistance prevalence was based on the National Antimicrobial Resistance Monitoring System (NARMS) isolate data, which classified resistance by applying the European Committee on Antimicrobial Susceptibility Testing (EUCAST) cutoff values to MIC data. For *Campylobacter*, cutoff values are available for two species which constitute approximately 98 percent of *Campylobacter* infections tested by NARMS, but cutoffs were not available for other species, so those were assumed to have the same resistance rate as the two available species. For some pathogens, case counts are based on surveillance covering a portion of the U.S. population. For example, surveillance for Group A *Streptococcus* is performed through a network of 10 sites covering approximately 34 million people (CDC, 2019). This is just one example of the many different data sources, estimates, and assumptions required to estimate the number of one type of AMR case.

***Healthcare-associated versus Community-acquired Cases.*** There may be significant differences in true community-acquired cases compared to healthcare-associated cases. For example, in healthcare facilities, AM drug use is common and applies a constant selective pressure for resistance. In the community, these pressures are lower, so resistant bacteria must be able to compete with susceptible bacteria, presumably preventing spread of resistance genes that have a fitness cost to the bacteria. Therefore, resistance profiles in communities may be very different than resistance profiles in healthcare settings, complicating efforts to extrapolate trends measured in healthcare settings. Typically, more data are available on healthcare-associated infections (HAIs) and infections requiring hospitalization than on community-acquired infections. However, it can be difficult to accurately assess whether a case is community-acquired or healthcare-associated. Community-acquired cases are sometimes misclassified as HAI due to delays in symptom onset or testing. Alternatively, cases may be classified as community-acquired instead of healthcare-associated in cases where a patient was exposed and colonized with an organism in a healthcare setting with significant delay prior to onset of infection (van Duin & Paterson, 2016).

***Accounting for Time-Dependent Biases.*** With community-acquired infections, attributable LOS is simply the total length of the hospital stay, which occurs in its entirety after infection by the resistant strain. With hospital-associated infections, only a portion of the hospital stay is attributable to the infection, and this is true for both the resistant group and the comparison group. Literature has shown that treating infection as a time-fixed variable, and comparing total LOS between the resistant group and the comparison group, is an insufficient approach that tends to lead to upwardly biased estimates of the excess LOS attributable to the resistant strain (Nelson, et al., 2015; Pouwels, et al., 2020; de Kraker & Lipsitch, 2021). Several methods exist for modeling LOS more suitably. These include matching members of the resistant group with members of the comparison group based on uninfected patient-days (de Kraker & Lipsitch, 2021), performing weighted Kaplan-Meier survival analysis based on inverse probabilities (Pouwels, et al., 2020), and applying multistate models with infection status as a time-varying quantity (Nelson, et al., 2015). The validity of AMR-attributable LOS estimates depends on the extent to which studies adjust for these time-dependent biases.

## 1.2 TEMPORAL AMR TRENDS

Recent trends in AMR in the U.S. can be examined by comparing CDC's 2019 AR Threats Report to their 2013 report (CDC, 2019). Overall, the 2019 report emphasizes that the burden of AMR is higher than previously thought. Nonetheless, the 2019 report shows that deaths have declined since 2013. CDC lists most AMR threats at the same urgency level in the 2013 and 2019 AR Threats Reports. However, there are some notable changes.

In the 2019 report, CDC identified five urgent threats, 11 serious threats, two concerning threats, and three watch list organisms. Of these, one urgent threat, one serious threat, and one

watch list organism are fungi; the other 18 threats are bacteria (CDC, 2019). The fungus *C. auris* was added as an urgent threat (the highest threat level). Some strains of *C. auris* have been identified that are resistant to all three available antifungal treatments. Carbapenem-resistant *Acinetobacter* was upgraded from a serious threat to an urgent threat due to the lack of AM treatments and the emergence of easily-spread genetic material that allows resistance in *Acinetobacter* to be transferred to other bacteria. Vancomycin-resistant *Staphylococcus aureus*, listed as a concerning threat in 2013, was removed from the list because only isolated cases have been identified, and spread between patients has not been documented.

The 2019 urgent threats are: carbapenem-resistant *Acinetobacter*, *Candida auris, C. difficile,* carbapenem-resistant Enterobacteriaceae, and drug-resistant *Neisseria gonorrhoeae*. Cases of carbapenem-resistant *Acinetobacter* and *C. difficile* decreased from 2013 to 2017. Cases of drug-resistant *C. auris* have increased, and resistance to many antibiotics has increased in *N. gonorrhoeae*. Cases of carbapenem-resistant Enterobacteriaceae have increased, though containment strategies have prevented further spread of some CRE strains (CDC, 2019).

Globally, there tends to be broad variation in AMR trends. Gelband et al. (2015) reviewed trends in AMR across many countries and found that trends were organism- and country-specific. For example, methicillin resistance in *Staphylococcus aureus* has recently declined in the U.S., Canada, and European countries, but is rising in India and Latin America. Regional differences in healthcare, spread, at-risk populations, and background health all impact the attributable mortality rates and attributable LOS.

## 1.3 PROJECTIONS OF AMR

There have been several attempts to model AMR infections into the future using different modeling strategies. Autoregressive integrated moving average (ARIMA) and regression models, among other frameworks, have all been used to project AMR trends into the future.

Several studies employed regression models to predict future resistance trends (Soucy, et al., 2019; Durham, et al., 2010; Alvarez-Uria, et al., 2018). These studies use percent resistance of a pathogen-drug combination as the response variable as it represents the proportion of pathogen isolates that are resistant to the AM drug. Two studies used data from the large-scale surveillance networks, EARS-Net and ResistanceMap (Durham, et al., 2010; Alvarez-Uria, et al., 2018). The third study used data from three hospitals in Quebec, Canada, between 2010 and 2017 (Soucy, et al., 2019), though this study did not explicitly predict future trends. Durham et al. (2010) modeled future trends in fluoroquinolone-resistant *E. coli* from 2001 to 2013 using data from EARS-Net between 2001 and 2007. Durham et al. modeled trends in 18 different countries in the European Union as well as in the U.S. Predicted trends increased until 2013 in every country. Alvarez-Uria et al. (2018) modeled the trends of *E. coli* and *K. pneumoniae* globally to 2030 based on data collected from 2005 to 2015. While *E. coli* resistance to third-generation cephalosporins and carbapenems increased over the study period, they projected *K. pneumoniae* resistance to third-generation cephalosporins to decrease, despite resistance increasing to carbapenems.

Other studies used time-series analysis methods to project future trends using ARIMA models (Monnet, et al., 2001; Lopez-Lozano, et al., 2000; Willmann, et al., 2013). All three of these studies used resistance data from a single healthcare facility over 8.5 years on average (range: 7.5-10 years). Willmann et al. (2013) used quarterly resistance data to predict how past multi-drug and extensively-drug resistant *P. aeruginosa* would change with the introduction of a stewardship intervention that decreased drug use (Willmann, et al., 2013). Monnet et al. (2001) used AM drug use to model *P. aeruginosa* resistance, while Lopez-Lozani (2000) used a similar method to use the current resistance level while predicting the following year of resistance data. The key aspect of these models is that resistance is stochastic over short intervals of time.

There were several other methods employed to predict future resistance levels. One study, prompted by rising resistance levels of *Neisseria gonorrhoeae*, used stochastic methods to generate simulations of transmission to estimate the impact of a vaccine on prevalence (Craig, et al., 2015). Alawieh et al. (2015) created a computational framework that utilizes the EARS-Net data to predict resistance rates one or two years into the future. Blanquart et al. (2017) created a mathematical framework to measure the seasonal fluctuations of AMR as well as the lag in resistance following AM drug use. Nikolaou et al. (2006) created a framework that models the dynamics of a heterogenous bacterial population with distributed AMR and the influence of AM drug use on this dynamic.

Increasing emphasis on and adoption of strategies for combatting AMR, such as stewardship, infection control, and development of new AM drugs, could greatly impact the trajectory of future AMR cases and resulting burden. This is a complicating factor, particularly for long-term projections, as burden models must either rely on the current state of AMR prevention measures or predict future interventions and their degree of success. Systematic evaluations of the accuracy of previous AMR burden models are rare. Difficulties in estimating the current burden contribute to the challenge of evaluating historical models, and to the extent that present-day estimates of cases and deaths differ from the projected values, it may not be possible to remove the impact of, for example, new resistant strains that emerged during the projection period but were not accounted for in the model.

# 2 CHARACTERIZING LITERATURE ON PARAMETERS FOR AMR BURDEN MODELING

Issues arise when attempting to define and estimate model parameters; impacts with broad scope can be challenging to estimate accurately. Current literature has explored some of these difficulties, which are presented below.

## 2.1 MORTALITY AND MORBIDITY RATES

Many of the issues discussed in Section 1 apply to estimates and projections of attributable mortality and morbidity, including differences in underlying data and in estimation methodologies. In general, many burden models aim to use information from multiple published sources, aggregating across pathogens, AM drugs, geographies, etc. For national estimates or projections, this type of aggregation may be essential, as many studies only estimate mortality or morbidity associated with resistance to a single AM drug, a single organism, or a certain infection site. However, certain challenges, discussed below, can lead modelers to (a) rely more heavily on a smaller number of sources or (b) narrow their focus, for example, limiting burden estimates or projections to specific regions, pathogens, or drug resistances.

Modeling AMR mortality requires estimating the number of resistant infections. Several data sources are available for this purpose, but each has limitations. For example, Burnham et al. (2019) used death certificates to estimate deaths attributable to multi-drug resistance. As the authors were aware, death certificates do not always correctly identify the cause of death, particularly when there are multiple conditions at the time of death. Moreover, death certificates are often completed by an individual who was not involved in the patient's care (Direk Limmathurotsakul, et al., 2019). Burnham et al. (2019) addressed this issue by introducing and justifying additional assumptions, for example, about resistance rates and the proportion of death certificates that are incorrectly or incompletely indexed.

Efforts to aggregate AMR-attributable mortality and morbidity across multiple studies are complicated by overlap in resistance classes. Rossi et al. (2019) investigated carbapenem-resistant *A. baumannii* infections in a teaching hospital in Brazil and found most of the infections were also

multidrug resistant (94 percent) or extensively drug resistant (42 percent). It is difficult to define mortality rates consistently across studies when multiple researchers could potentially assign an infection to more than one resistance class. This calls into question the validity of pooling estimates from multiple studies and may lead to reliance on fewer sources when modeling current or future AMR burden. Overlapping resistance classes also make it challenging to aggregate estimates of mortality and morbidity from different pathogen-drug combinations (e.g., summing deaths due to MDR *K. pneumoniae* and due to carbapenem-resistant *K. pneumoniae*) or evaluate trends over time for specific pathogen-drug combinations. The more publications a model relies on, the greater the possible risk of counting the same infection multiple times in resistance classes that are intended to be non-overlapping.

Another challenge with generating national estimates of attributable mortality and morbidity is that study populations are not always generalizable to the broader U.S. population. Research has found that attributable mortality depends heavily on age, sex, and healthcare setting (Cassini, et al., 2019). Discrepancies in demographics between the study population and the broader U.S. population introduce bias into burden estimates. This may be particularly relevant for models that rely on smaller studies that were not designed to be nationally representative. A study sponsored by Becton Dickinson and Tetraphase Pharmaceuticals[10] determined that hospital characteristics (size, urban vs. rural, medical school affiliation) and geographic region were associated with significant differences in resistance prevalence in Enterobacteriaceae and *Acinetobacter* spp. isolates. These differences may explain some discrepancies between published resistance and burden estimates, especially among studies that are limited in geographic coverage or hospital types (Gupta, et al., 2019).

Morbidity rates are prone to many of the same challenges as mortality rates. Studies can be biased toward higher estimates of morbidity if they contain a disproportionately large number of male participants or adults over the age of 65 (Cassini, et al., 2019) (Goldstein, et al., 2019). Different assumptions and methodologies raise issues when attempting to make comparisons or aggregate findings from multiple studies into a single burden model with consistent assumptions and interpretable findings.

## 2.2 LENGTH OF STAY AND TREATMENT DURATION

There is general agreement that resistant infections lengthen patients' LOS and treatment duration relative to susceptible infections. However, the impact of these extended stays on burden is an area of debate. The burden due to extended and costly hospital stays is, at times, difficult to quantify and may have less research than exists on attributable mortality. As seen previously, the landscape of pathogens, AM drugs, etc. tends to introduce substantial variation into estimates of the LOS attributable to AMR.

Naylor et al. (2019) found that hospital LOS was only greater by 0.8 days in *E. coli* infections resistant to at least one AM drug, compared to susceptible infections. However, the authors also found that the attributable LOS depends on the AM drug(s) to which the infection is resistant. Results from a meta-review by Serra-Burriel et al. (2020) agreed with these findings, showing that, overall, LOS was significantly longer in MDR healthcare-associated infections compared to non-MDR healthcare-associated infections. Roberts et al. (2009) found significantly increased hospital LOS (as well as costs) for patients with resistant infections compared to those without a resistant infection.

Despite these findings, some researchers have taken the position that the extended stays do not create additional burden. Taheri et al. (2000) argue that reducing LOS for hospitalized patients

[10] The study used data from a BD database of 375 hospitals.

produces minimal savings in direct costs because costs are concentrated at the beginning of patient stays, and much of hospitals' costs are overhead costs that remain fixed regardless of a patient's LOS. Nonetheless, while the extended stays may not generate substantial additional costs to hospitals, LOS can still create additional costs for patients or insurers, who often pay several times the actual cost per day.

## 2.3 DIRECT COSTS OF RESISTANT AND SUSCEPTIBLE INFECTIONS

Resistant infections increase hospital costs to patients and insurers through several mechanisms, the most notable of which is increased LOS (discussed in Section 2.2). Costs also increase due to inpatient services such as additional drugs, laboratory tests, and imaging (Filice, et al., 2010), as well as patient isolation measures (Engler-Hüsch, et al., 2018). Of these direct costs, extended LOS is generally the most straightforward to quantify when estimating burden, as illustrated by Naylor et al. (2018), which used reference costs for National Health Service (NHS) hospitals in the UK to estimate the burden of resistant strains of *E. coli* bacteremia.

Wozniak et al. (2019) reviewed estimates of economic burden of AMR from 14 studies in multiple countries and found estimates varied widely across the studies and across organisms.[11] The authors noted that appropriate study design and analysis were available for just three types of BSIs; they were unable to generate robust estimates of societal costs, as only two studies provided this information (Wozniak, et al., 2019). This points to a relative lack of literature on attributable costs compared to attributable mortality or attributable LOS.

Thorpe et al. (2018) conducted a very wide-ranging study on costs in the U.S. based on a nationally representative sample that spanned annual data from 2002 through 2014. They estimated that resistance added $1,383 to the cost of treatment of an infection, amounting to $2.2 billion in the U.S. annually. For infections other than UTIs (which tend to be less severe than many other infection sites), the incremental cost of a resistant infection is $2,656. Further, costs may depend on the type of resistance. Morales et al. (2012) studied hospital costs associated with *P. aeruginosa* infections and found that resistant and MDR infections were significantly more expensive than susceptible infections (Morales, et al., 2012).

## 2.4 INDIRECT COSTS OF SECONDARY BURDEN

In addition to direct hospital costs, there are additional, indirect costs associated with AR pathogens, which are referred to collectively as the secondary burden of AMR. Smith and Coast (2012) argue that much of the cost of AMR is due to these secondary effects, especially in the case of multi-drug and extensively drug-resistant infections. Shrestha et al. (2018) estimated that, in the U.S., indirect costs were more than ten times the direct costs.[12] Although more difficult to capture and quantify, we discuss several sources of secondary burden below.

Many medical procedures, particularly surgeries and cancer treatments, prescribe AM drugs prophylactically to prevent infection. AMR threatens these procedures by reducing the efficacy of such preventative measures and elevating the risk of serious infection. Teillant et al. (2015) calculated that a reduction in AM prophylaxis efficacy of 30 percent would result in 6,367 additional infection-related deaths annually in the U.S. This projection only accounted for seven

[11] This same result was also found by Nelson et al. (2021), a very large study of inpatient stays in the Department of Veterans Affairs healthcare system, conducted between January 2007 and October 2015. Nelson et al. also found that costs vary between healthcare-associated infections and community-associated infections.

[12] Shrestha et al. (2018) studied five resistant infections in the U.S. and Thailand. The authors found that cumulative costs of treatment varied by infecting organism and by drug class.

procedures (including cancer chemotherapy but excluding Caesarean sections) for which prophylactic AM drugs are established to be effective.

Another secondary effect of AMR is the economic impact of reduced productivity due to worker death, disability, time away from work, and increased care responsibilities upon the labor supply. Assuming a resistance rate of 40 percent, Taylor et al. (2014) calculated that 40 years of accumulated loss of workers would lower global GDP by 0.51 percent, equivalent to annual losses of $1.65 trillion in 2011 USD.[13] This model only considered three infectious diseases (HIV, tuberculosis, and malaria) and hospital-acquired infections from three bacteria (*E. coli, K. pneumoniae,* and *S. aureus*) (Taylor, et al., 2014).

*C. difficile*, while not itself an AM pathogen, contributes to the secondary burden of AMR. Colonization with *C. difficile* is common across the population, but normally only causes infection when other gut microbes are killed by AM drugs. As such, overuse of AM drugs has increased incidence of *C. difficile*, leading to an estimated 29,300 deaths (Lessa, et al., 2015) and 476,400 cases (Guh, et al., 2020) in the U.S. in 2011 and an estimated 12,800 deaths (CDC, 2019) and 462,100 cases (Guh, et al., 2020) in the U.S. in 2017.

Michaelidis et al. (2016) estimated the aggregated downstream societal cost of AMR on a per-prescription basis for ambulatory antibiotics. These costs accounted for hospital costs, as well as first- and second-line outpatient AM drug costs. The authors estimated downstream societal costs to be $13 per AM prescription, with a range of $3-$95 (Michaelidis, et al., 2016). The wide range for these costs shows how sensitive such cost estimates can be to the model assumptions.

The secondary burden associated with these and other indirect costs is difficult to quantify in aggregate and has large associated uncertainties. Omitting secondary burden underestimates the true cost associated with AMR; however, including secondary burden leads to estimates with wide ranges and may require assumptions for which evidence is lacking.

## 2.5 SELECTING A COUNTERFACTUAL

A crucial distinction between different estimates of the burden of AMR is the counterfactual—that is, whether to compare the impact of an AMR infection to a susceptible strain of the disease or to a case with no infection (Dunachie, et al., 2020). The "no-infection" counterfactual estimates the total harm of resistant infections, whereas the "susceptible infection" counterfactual estimates the incremental harm due to an infection being resistant (de Kraker & Lipsitch, 2021). As a result, no-infection counterfactuals produce substantially larger burden estimates. Research is mixed on which is more appropriate, but as the selection of counterfactual is highly consequential for burden estimates, we discuss the two choices in detail, below.

As de Kraker & Lipsitch (2021) explain, both counterfactuals have been utilized and supported through evidence. Studies that select the susceptible-infection counterfactual do so on the assumption that resistant strains and susceptible strains compete with one another, such that successful suppression of a resistant strain would lead to an increase in the susceptible strain. In contrast, the no-infection counterfactual assumes that resistant strains add altogether new instances of infection rather than replacing the existing susceptible infections. In most cases, the question of whether the resistant and susceptible strains compete cannot be answered through the available medical or microbiological evidence. Instead, researchers compare time-series trends in the number of susceptible and resistant infections to show whether increasing prevalence of the

[13] This finding is similar to that of Smith et al. (2006), who modeled macroeconomic effects of MRSA and estimated that changes in labor supply and productivity would cause real GDP to fall by 0.79 percent and unemployment to increase by 8.59 percent.

resistant strain is met by decreasing prevalence of the susceptible strain. For example, Thorpe et al. (2018) conducted a nationally representative study with data from 2002 through 2014 and concluded that the number of bacterial infections in the U.S. remained roughly constant despite resistant infections increasing from 5 percent in 2002 to 11 percent in 2014 (Thorpe, et al., 2018). This is support for using the susceptible counterfactual; in order for the overall infection count to have remained constant, the number of susceptible infections must have decreased.

de Kraker & Lipsitch (2021) argue that the correct choice of counterfactual is dependent on the intervention being considered. When evaluating new antibiotics, "the potential impact is most clearly related to the question of how much worse the outcome of [a resistant] infection is than the outcome of [a susceptible] infection." This supports the use of a susceptible counterfactual. On the other hand, when considering prophylactic antibiotic use during surgery, the no-infection counterfactual is more relevant, since an antibiotic that is successful against the resistant strain would prevent susceptible infections.

Whereas many studies treat the counterfactual as a single, dichotomous choice, de Kraker & Lipsitch (2021) advocate for generating estimates using both counterfactuals. The susceptible infection counterfactual generally produces lower burden estimates, since the harm from the resistant strain is measured against the harm produced by the susceptible strain. Accordingly, the susceptible counterfactual and no-infection counterfactual can provide lower and upper bounds, respectively, on the estimated burden.

### 2.6 BIAS IN PUBLISHED ESTIMATES

A literature review by Serra-Burriel et al. (2020) found evidence of publication bias in mortality estimates of multi-drug resistance. In general, the effect of higher standard error is to cause estimates to become more widely dispersed around a common mean. When publication bias exists, less precise studies are selectively published only when they achieve higher effect sizes. This produces an asymmetric funnel plot. Serra-Burriel et al. performed a funnel plot analysis and found that studies with higher standard error tended to have higher estimated mortality rates. This asymmetry in the funnel plot was statistically significant and suggests that, among less precise studies, higher mortality rates may lead to higher rates of publication. No bias was found for cost or LOS (Serra-Burriel, et al., 2020).

## 3 STUDY OBJECTIVE

Understanding the impact of AMR on the health and economy of the U.S. is critical to create effective policy. This understanding must be based on estimates or projections of AMR burden in the U.S. that are accurate and, when possible, supported by the scientific literature. Our primary objective for this study is to assess the availability and quality of published estimates of mortality, LOS, and healthcare costs associated with selected bacterial infections with resistance to one or more AM drugs. These variables are key for modeling the economic burden of AMR in the U.S. and depend heavily on pathogen, AM drug resistance, and infection site. We selected a total of 15 pathogen-drug combinations (Table 2) and four primary infection sites—BSIs, UTIs, pneumonia, and SSIs[14]—to focus on based on discussions with CDC and ASPE.

Table 2. Included Pathogen-Drug Combinations

| Pathogen | Antimicrobial Drug Class | CDC Threats Report Designation | WHO Pathogen Priority List |
|---|---|---|---|
| *A. baumannii* | Carbapenems | urgent | critical |
| *A. baumannii* | MDR [a] | urgent | |

[14] While bacterial infections are possible at other body sites, such as bone, peritoneal cavity, etc., we did not find any published studies that reported mortality, LOS, or healthcare costs for these types of infections.

| Pathogen | Antimicrobial Drug Class | CDC Threats Report Designation | WHO Pathogen Priority List |
|---|---|---|---|
| *E coli* | Carbapenems | urgent | critical |
| *E coli* | Cephalosporins | | |
| *E coli* | Fluoroquinolones | serious | critical |
| *E coli* | MDR | urgent | |
| *K. pneumoniae* | Carbapenems | urgent | critical |
| *K. pneumoniae* | Cephalosporins | | |
| *K. pneumoniae* | Fluoroquinolones | serious | critical |
| *K. pneumoniae* | MDR | urgent | |
| *P. aeruginosa* | Carbapenems | serious | critical |
| *P. aeruginosa* | Ceftazidime | serious | |
| *P. aeruginosa* | MDR | serious | |
| *E. aerogenes/E. cloacae* | Carbapenems | urgent | critical |
| *E. aerogenes/E. cloacae* | MDR | urgent | |

[a] As discussed below, in Section 4, we defined multi-drug resistant as resistance to all three classes (carbapenems, cephalosporins, and fluoroquinolones).

# 4 METHODOLOGY

For each of the 15 pathogen-drug combinations, we first conducted a systematic review of published literature to:

- Characterize the current state of knowledge with respect to mortality, LOS, and healthcare costs, and
- Identify data gaps both across and within pathogen-drug combinations.

Then we evaluated studies using several metrics of relevance to the task of AMR burden modeling in the U.S. One important metric was the precision of the study estimates, which impact the uncertainty of current estimates and future projections of AMR burden. We also compared estimates across region[15] to identify the extent to which U.S. estimates and projections could rely on data from other countries where AMR rates may differ. We analyzed studies' enrollment periods to assess the recency of data. We considered the epidemiological design on which studies were based. By aggregating these metrics, we developed a scoring methodology that quantifies each study's relevance to the task of AMR burden modeling in the U.S. This metric served as the basis for comparisons across and between pathogen-drug combinations.

Our analysis focused primarily on study estimates of resistant-strain parameters—specifically, mortality and LOS.[16] However, we also considered susceptible-strain estimates, which were tended to have better precision but was investigated at a lower frequency. We evaluated the capacity for infection-specific modeling and addressed additional modeling considerations, such as publication bias, representativeness of the study populations, disease prevalence, and healthcare setting.

## 4.1 SYSTEMATIC LITERATURE REVIEW

For each pathogen-drug combination, we searched PubMed and Web of Science using Medical Subject Headings (MeSH) terms, as well as terms used to index medical journal articles or books. For example, for carbapenem-resistant *K. pneumoniae* (CRKP), our search string for

[15] Countries outside of North America were aggregated by continent or geopolitical region.

[16] Studies investigating cost were far less common than those investigating mortality or even LOS. For this reason, studies containing cost information are analyzed separately in Section 5.1.9.

PubMed included the following terms where "mortality" was specified both as a MeSH term and a MeSH subheading term that encompassed a range of mortality related entry terms such as "death rate" or "crude morality rate:"

> *( ("Klebsiella-pneumoniae") ) AND ( ("Carbapenems") ) AND ( ("Drug Resistance, Bacterial"[MeSH]) ) AND ( ("Length of Stay"[MeSH]) OR ("Mortality"[MeSH]) OR ("Mortality"[MeSH subheading]) OR ("Outcome Assessment, Health Care"[MeSH]) OR ("Risk factors"[MeSH]) )*

For Web of Science searches, we made slight modifications to the search string as needed, such as:

> *Klebsiella pneumoniae AND Fluoroquinolones AND Bacterial Drug Resistance AND (Length of Stay OR Mortality OR Health Care Outcome Assessment OR Risk factors)*

Our search included all types of publications (e.g., books and documents, meta-analysis) and covered the period from 2007 through 2021. The search string was adapted to the other pathogen-drug combinations by replacing the pathogen and drug class terms. After retrieving all studies for each pathogen-drug combination, we uploaded them to Rayyan, a systematic literature review platform, to remove duplicates and to screen them efficiently. After removing duplicates, we used the following step-wise approach to review studies for inclusion/exclusion:

- Title and abstract review, and
- Full-text review.

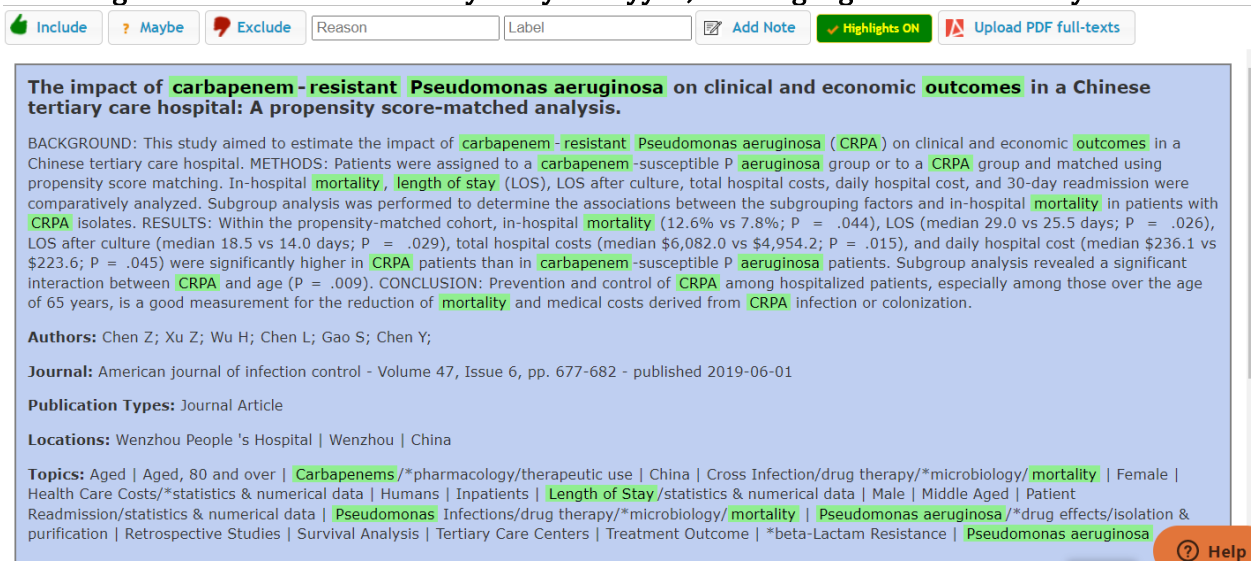
The *title and abstract review* involved defining "keywords to exclude" that allowed us to identify and exclude out-of-scope studies (e.g., studies involving pediatric patients only) and then "keywords to include" to target in-scope studies. The "keywords to include" consisted of the pathogen name and drug class along with any abbreviations and a variety of outcomes. Table 3 presents these keywords to include and to exclude, using carbapenem-resistant *K. pneumoniae* as an example.

**Table 3. Keywords to Include and to Exclude in Rayyan, for Carbapenem-Resistant *K. pneumoniae***

| Keywords to Include | Keywords to Exclude |
|---|---|
| *Klebsiella pneumoniae*<br>carbapenem, pneumonia, CRKP, CSKP<br>resistant, susceptible<br>outcomes<br>mortality, death, deaths, died<br>stay, length of stay, hospital stay | children<br>neonatal<br>pediatric |

Filtering by these keywords categorized the literature into topic-specific groups. Rayyan highlighted the exclusion and inclusion terms which allowed us to screen studies efficiently (see Figure 1 for a sample study entry). The title and abstract review concluded by migrating all non-excluded studies into a "maybe" folder, thereby triggering a full-text review.

**Figure 1. Screenshot of a Study Entry in Rayyan, with Highlighted Inclusion Keywords**




For the *full-text review*, we retrieved the full-text PDFs of the studies where possible from Google Scholar.[17] We then uploaded the full-text PDFs to Rayyan and reviewed each study to determine if it included data on the mortality and/or LOS of adult patients infected with the pathogen of interest and resistant to the AM drug of interest. We also screened studies for counterfactual data, reporting the same outcomes for patients infected with the pathogen of interest but susceptible to the AM drug of interest. Next, we moved all studies with the relevant data to the "include" folder in Rayyan. Further, we verified that all listed studies in the systematic review studies identified were among the "include" folder. When we found a study that was listed in the systematic review study but had not been identified in our search, we added that study to our "include" folder. When a study did not report any of the variables of interest for the pathogen-drug combination of interest or met an exclusion criterion, we removed the study from our sample, noting the reason(s) for exclusion.

A complete list of exclusion reasons is provided below.

- **Data are not specific** to the target "bug-drug" combination.
- **Out-of-scope outcome variables**. The study reports prevalence rates only and no mortality or LOS information.
- **Out-of-scope population**. The study reports data for paediatric/neonatal patients (mostly excluded in the title abstract screen).
- **Out-of-scope study design**. The study investigated isolates from fewer than three patients; or the study compares two patient groups based on the AM therapy they were treated with or the type of procedure (e.g., transplant) that caused the infection.
- **Systematic review**. While we evaluated information in systematic reviews (and used those reviews to retrieve additional studies), data in the systematic review itself were excluded.

We then extracted information on the study design, enrollment period, country, setting (single vs. multicenter), site of infection (e.g., BSI, UTI), the sample size of the resistant and

[17] Studies for which we were unable to obtain full texts were labeled "not available."

susceptible infection groups of patients, the LOS for the resistant and susceptible infection groups, and the mortality for the resistant and susceptible infection groups in each of the studies in our final "Include" folder. For those pathogen-drug combinations that lacked data on one or more of these variables, we consulted with an epidemiologist and implemented the following strategies to broaden the scope and fill in the data gaps:

- For fluoroquinolone-resistant *K. pneumoniae* (FRKP), we included data on mortality, hospital LOS, or healthcare costs from studies on all fluoroquinolone-resistant Enterobacteriaceae.[18]
- For *K. pneumoniae*, we included data on mortality, hospital LOS, or healthcare costs from studies on *K. pneumoniae* or both *K. pneumoniae* and *E. coli* or all gram-negative bacteria.
- For *E. coli*, we included data on mortality, hospital LOS, or healthcare costs from studies of *E. coli*, studies of both *K. pneumoniae* and *E. coli,* or studies of all gram-negative bacteria.
- For third-generation cephalosporin-resistant bacteria, we included data on mortality, hospital LOS, or healthcare costs from studies on all ESBL-producing bacteria.
- For carbapenem-resistant *E. aerogenes/E. cloacae*, we included data on mortality, hospital LOS, or healthcare costs from studies on all carbapenem-resistant Enterobacteriaceae.
- For third-generation cephalosporin-resistant *P. aeruginosa*, we included data on mortality, hospital LOS, or healthcare costs from studies on *P. aeruginosa* and cefepime.

We also conducted a supplementary literature review using the expanded definitions (e.g., mortality of patients with fluoroquinolone-resistant Enterobacteriaceae), where necessary, when there were fewer than 5 studies a given pathogen-drug combination.

Finally, we made the following additional assumptions based on data quality and availability:[19]

- Crude mortality was sufficient when attributable mortality was not available.
- We included 30-day, 60-day mortality, and all-time hospital mortality.
- "Multi-drug resistant[20]" was equivalent to "resistant to all three classes."
- Total LOS was acceptable when LOS after isolating the pathogen was unavailable.

## 4.2 STUDY QUALITY SCORING

Using the data extracted from the studies, we compared the available literature across pathogen-drug combinations on relative strength for supporting AMR burden models. When

[18] For example, if there were very few studies that investigated patients infected with *Klebsiella pneumonia* resistant to fluoroquinolones (FRKP), then we expanded the FRKP definition to also include patients infected with any Enterobacteriaceae resistant to fluoroquinolones, assuming that the outcomes of these infections would be applicable to FRKP.

[19] Any attempt to model AMR burden must address the issue of how mortality is defined and the implication this has on interpreting the model's results. For our purposes of the systematic review, all three definitions of mortality were included to capture and characterize the literature broadly, without making modeling assumptions about how to define mortality.

[20] Multi-drug resistance is commonly defined as "resistance to at least one drug in at least three antimicrobial classes." We used "multi-drug resistant" or "MDR" in our search logic for these pathogen-drug combinations.

modeling AMR burden, the two most critical parameters are attributable mortality and attributable LOS.[21] These parameters can vary widely by pathogen, drug, and site of infection—whether it be BSI, UTI, pneumonia, SSI, or another. For mortality and LOS, the relevant metric is the excess amount that can be attributed to the resistant strain. In an unadjusted analysis, this excess is computed by taking the difference between estimates for the resistant-strain group and the susceptible-strain group. While these excess values are the primary focus for modeling AMR burden, the analysis of Section 5 focuses instead on the resistant strain, because many studies did not analyze a susceptible group and thus could not present excess values.

Using four basic components, we developed a scoring metric that conveys the strength of evidence and emphasizes relative differences between the various pathogen-drug combinations. The score for a given study is based on four study components, presented in Table 4.

**Table 4. Scoring Methodology for Four Components**

| Feature of Study | 1 point | 2 points | 3 points |
|---|---|---|---|
| Final year when participants were enrolled | 1999-2006 | 2007-2013 | 2014-2020 |
| Region where study was conducted | Other | Europe | U.S. |
| Precision of resistant-strain estimate [a] | Bottom tercile | Middle tercile | Top tercile |
| Study design | Other | Case-control study | Cohort study |

[a] Precision refers to either the standard error of a resistant-strain mortality estimate, or the sample size associated with a resistant-strain LOS estimate.

In instances where a study's feature was not determined, we assigned a score of 1. Using these four components, we computed a score for every resistant-strain mortality and resistant-strain LOS estimate that a study contained:

$$\text{score} = \text{region score} \times (\text{enrollment year score} + \text{precision score} + \text{design score}) \qquad (1)$$

In some cases, a study received multiple scores because it presented more than one estimate (e.g., a study might present mortality for resistant-strain BSI infections, mortality for resistant-strain UTI infections, and LOS for any susceptible-strain infection). When making comparisons at the study level, we averaged multiple scores to acquire a single score per study. However, through the search process, 11 studies (out of 167 unique studies) were identified multiple times for different drug-pathogen combinations. Because these studies were associated with multiple pathogen-drug combinations, they were included multiple times when generating comparisons across pathogen-drug combinations. For consistency, these studies were also included multiple times when analyzing data at the study level (e.g., when calculating the distributions of Figure 4, below). Hence, while it was rare to find a study that generated distinct estimates for multiple pathogen-drug combinations, our analytical approach gives greater weight to such studies that achieved the equivalent research outcomes of several smaller studies.

In the scoring algorithm of Equation 1 above, the region score serves as a multiplicative factor rather than an additive term. This was done for several reasons, the most important being that studies conducted in different regions are often attempting to measure fundamentally different quantities. This is different from many of the other components on which the score was based. For example, the fact that a study might have very high standard error does not change the expected mortality rate; such a study can still attempt to measure the same value as a study with very low standard error. However, even two perfectly conducted studies with ideal precision may nonetheless measure different rates if they were performed in different countries, simply because

[21] While not included in our analysis, another useful metric would be whether studies used appropriate statistical methods to adjust estimates for time-dependent biases.

they are not measuring the same underlying quantity and attributable AMR mortality rates can vary substantially across countries and regions (Murray, 2022).

In addition, when comparing mortality estimates for a single pathogen-drug combination and infection site, we found that the study region introduced more variation than any other variable. This large effect due to region was observed in exploratory regression modeling and is visible in Table 5, which displays the mean mortality rates for the resistant strain by country, for three illustrative combinations of pathogen, drug, and infection site:

**Table 5. Illustrative Examples of Regional Disagreement among Mortality Estimates**

| Pathogen, Drug, and Infection Site | Mean Resistant-Strain Mortality | | | | |
|---|---|---|---|---|---|
| | U.S. | Europe | Asia [a] | South America | Middle East |
| Third-Generation Cephalosporin-Resistant *P. aeruginosa*, Any Infection | 20.2% | 17.9% | 37.8% | 48.5% | NA |
| Carbapenem-Resistant *A. baumannii*, Any Infection | 45.2% | 39.5% | 50.3% | 66.7% | 54.7% |
| Carbapenem-Resistant *P. aeruginosa*, BSI Infection | 33.3% | 35.5% | 68.3% | 57.0% | 66.7% |

[a] None of the included studies were conducted in Japan.
[b] NA = not applicable

As Table 5 shows, the mortality estimates are somewhat similar for U.S. studies and European studies, but estimates are substantially higher in Asian studies, South American studies, and Middle Eastern studies.

The design score is based on accepted levels of evidence for epidemiological studies (Ascension Wisconsin Library, 2022). Because resistant pathogens tend to afflict older populations with comorbidities, controlling for factors like age and concomitant illness is critical to estimating the excess mortality or excess LOS that is *attributable* to the resistant pathogen. Unadjusted differences between the resistant-strain group and the susceptible-strain group may overestimate the attributable mortality or attributable LOS, as some of the difference between these groups potentially should be attributed to other factors, such as differences between the group members' age, etc. This risk of upward bias in the parameters of interest necessitates reliance on carefully designed studies that account for differences between the resistant and susceptible infection groups. The design score is aimed at capturing (at least partially) this element of an epidemiological study.

In some cases, we found that study estimates were suitable for modeling but limited in usefulness because subjects in the study/case group were not exclusively afflicted with a single resistant pathogen. In these instances, the study was assigned a design score of 1.

The precision score conveys information about the range of an estimate, with the goal of assigning higher scores to more precise estimates (i.e., those with narrower confidence intervals). Precision was determined using the resistant-strain estimate, as not all studies included a susceptible-strain estimate or an estimate of the attributable mortality/LOS. For mortality, the metric of precision is the computed standard error (SE). To acquire comparable SE estimates across the various studies, each study's standard error in the resistant-strain mortality was computed as $\sqrt{r(1-r)/n}$, where $r$ is the mortality rate and $n$ is the sample size.

For LOS estimates, sample size served as the metric of precision because studies did not report LOS range information consistently. Some studies reported LOS quartiles, others reported LOS standard deviation, still others reported LOS maxima and minima, and many did not report any

range information for LOS estimates at all. Sample size of the resistant-strain study group was used as a surrogate for precision, as it was reported much more consistently.

Precision scores were computed for each estimate that a study presented. For example, a study containing three estimates—resistant-strain mortality among BSI participants, resistant-strain mortality among UTI participants, and resistant-strain LOS estimates among any-infection participants—would receive three separate precision scores. To acquire precision scores, we separated mortality estimates from LOS estimates and computed terciles within the two lists. High precision corresponds to a small SE and large sample size.

The scoring algorithm presented in this section should be interpreted as a relevance score, as it is designed specifically to measure *suitability for supporting AMR burden modeling*. It is highly likely that few, if any, of the studies were conducted with this purpose in mind. It is our belief that the scores presented and discussed in this report have narrow application to analysis of models of the AMR burden in the U.S., for which these scores have been designed. The scores do not provide an accurate assessment of the studies in general, their usefulness in broader epidemiological settings, their contribution to the literature of AMR, or their success relative to the original intended research purposes.

# 5 RESULTS

The literature review resulted in a total of 2,926 reviewed studies and 167 included studies. The number of studies included for a single pathogen-drug combination ranged from 1-30 and is discussed in detail below. The number of included studies represented between 3-15 percent of the total number of studies reviewed for each combination. The total number of studies reviewed, studies included, and the ratio of included over reviewed are presented in Table 6.

In most cases, 50 to 80 percent of the total studies identified for a pathogen-drug combination were excluded in the title and abstract review. Of the remaining studies, approximately 50 percent were typically excluded during the full-text review. Table 6 presents the number of studies that were reviewed and included, for each of the selected pathogen-drug combinations.

**Table 6. Results on Number of Studies Reviewed and Included for All Pathogen-Drug Combinations**

| Pathogen | Antimicrobial Drug Class | CDC Threats Report Designation | WHO Pathogen Priority List | Number of PubMed Results | Number of WoS Results | Additional Studies [a] | Number of Included Studies | Percentage of Studies Included |
|---|---|---|---|---|---|---|---|---|
| *A. baumannii* | Carbapenems | urgent | Critical | 206 | 78 | 5 | 28 | 10% |
| *A. baumannii* | Resistant to all three classes | urgent | | 297 | 119 | | 16 | 4% |
| *E. coli* | Carbapenems | urgent | critical | 106 | 62 | 1 | 8 | 5% |
| *E. coli* | Fluoroquinolones | | | 137 | 30 | | 6 | 4% |
| *E. coli* | Third-generation Cephalosporins | serious | critical | 147 | 34 | | 12 | 7% |
| *E. coli* | Resistant to all three classes | urgent | | 181 | 196 | | 12 | 3% |
| *K. pneumoniae* | Carbapenems | urgent | critical | 291 | NA [b] | | 30 | 10% |
| *K. pneumoniae* | Fluoroquinolones | | | 43 | 15 | 3 | 3 | 5% |
| *K.pneumoniae* | Third-generation Cephalosporins | serious | critical | 90 | 16 | 1 | 12 | 11% |
| *K.pneumoniae* | Resistant to all three classes | urgent | | 178 | 130 | | 9 | 3% |
| *P. aeruginosa* | Carbapenems | serious | critical | 148 | 40 | 3 | 21 | 11% |
| *P. aeruginosa* | Ceftazidime | serious | | 63 | 53 | | 5 | 4% |
| *P. aeruginosa* | Resistant to all three classes | serious | | 288 | 195 | | 14 | 3% |
| *E. aerogenes/E. cloacae* | Carbapenems | urgent | critical | 21 | 6 | | 4 | 15% |
| *E. aerogenes/E. cloacae* | Resistant to all three classes | urgent | | 19 | 12 | | 1 | 3% |

[a] Additional studies may include studies reviewed for a different pathogen-drug combination and deemed relevant, studies from a supplementary Google search, studies mentioned in additional systematic reviews identified through our search, or studies identified using the reference list of another study.

[b] NA = Not applicable. We did not perform a WoS search for carbapenem-resistant *K. pneumoniae* (CRKP) because it served as a test case for refining the search criteria. For CRKP, exhaustive searches using a variety of terms were performed on several platforms, resulting in 30 included studies. Then, CRKP searches were performed in PubMed, and the search terms were refined until all 30 CRKP studies were retrieved.

## 5.1 FINDINGS ON AMR LITERATURE, ACROSS ALL PATHOGEN-DRUG COMBINATIONS

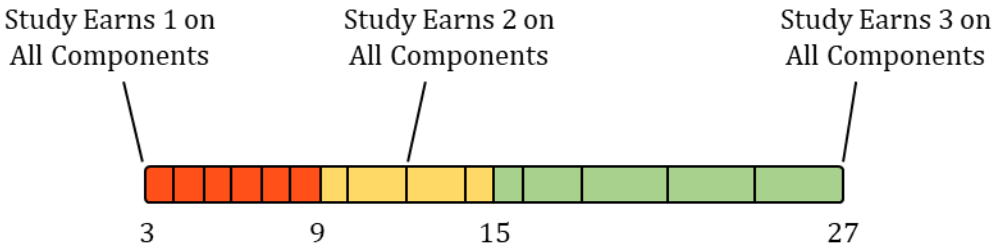
In this section, we present study-level statistics in order to characterize the current state of AMR literature in general, across all pathogen-drug combinations. Section 5.1.1 introduces a methodology for scoring studies to assess their relevance and generalizability for modeling the national burden of AMR in the U.S. This score is based on four components, which are discussed in detail in Sections 5.1.2 through 5.1.5—final enrollment year, region, study design, and precision. We analyzed the availability of mortality and LOS data (Section 5.1.6), including the availability of studies specific to a particular infection site (Section 5.1.7). While mortality estimates tend to be more abundant, they are also more consistently reported; in Section 5.1.8, we discuss some of the issues associated with inconsistent reporting of LOS. Finally, in Section 5.1.9, we assess the available data on healthcare costs, which was far sparser and thus analyzed separately from the mortality and LOS publications.

The analysis of 5.1 does not compare the availability or quality of literature across pathogen-drug combinations. Rather, it provides an overall evaluation of the included literature. In the next section (5.2), we make comparisons between specific pathogen-drug combinations and discuss specific pathogen-drug combinations with greater capacity for burden modeling.

### 5.1.1 Overall Study Scores

Figure 2 displays a scale of possible study scores using the algorithm of Equation 1.[22] The scale ranges from 3 (a 1 in all components) to 27 (a 3 in all components), with a central value of 12 (equivalent to a 2 in all components). The three shaded regions represent low scores (<9), middle scores (9-15), and high scores (>15).

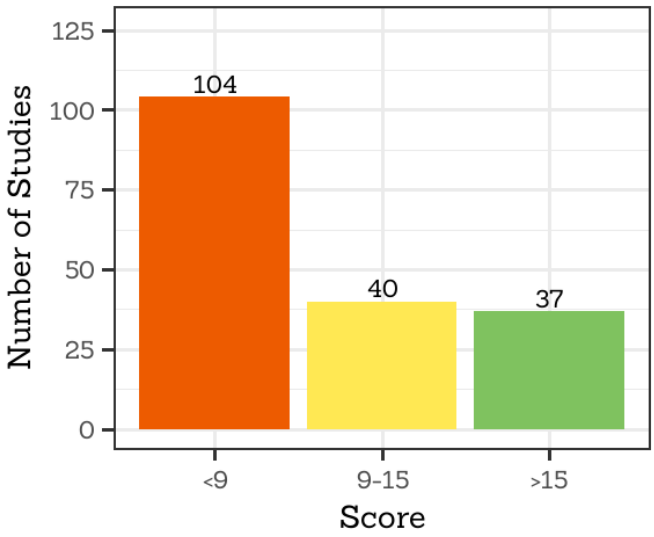
**Figure 2. Scale of Possible Study Scores**




Far more studies fall into the low score range (colored red in Figure 2) than the middle or high score ranges. Below, Figure 3 displays the distribution of studies in these three score ranges. The lowest scoring group is more than twice the size of either of the other two groups.

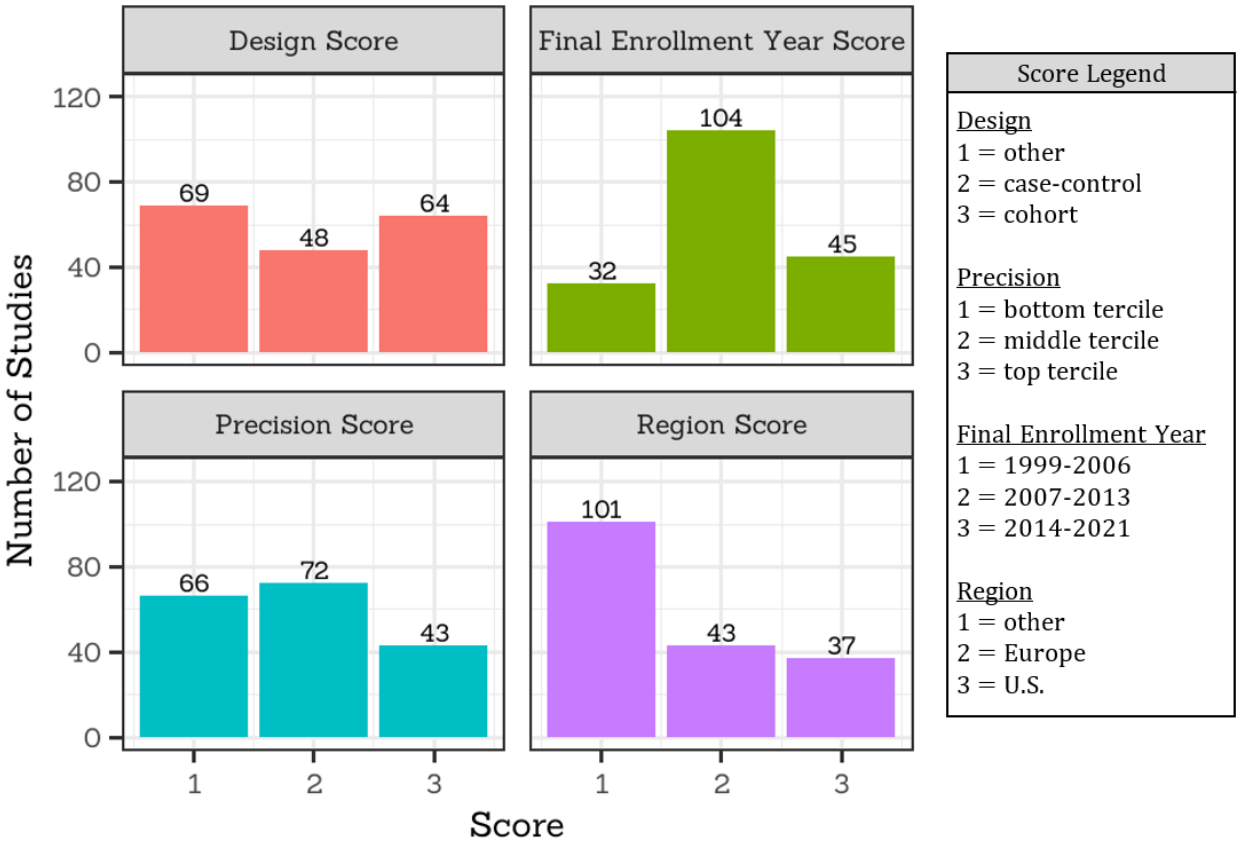
[22] Studies with multiple estimates were assigned multiple scores, which were subsequently averaged. This led to some studies having scores lying between the displayed tick marks. The thresholds between low scores, middle scores, and high scores are based on integer-rounded values.

**Figure 3. Distribution of Low, Middle, and High Scores**




The discrepancy in study scores is largely attributable to imbalances in region. Figure 4 presents distributions for each component score. One hundred four of the 181 studies, or 57 percent, were conducted in a region other than the U.S. or Europe. Figure 4 also shows that a second area of relative imbalance is the final enrollment year, with many studies closing their enrollment period between 2007 and 2013.

**Figure 4. Distribution of the Four Component Scores, Among All Studies**



### 5.1.2 Enrollment Year

Figure 4 shows that there is not equal distribution of studies with regard to the final year participants were enrolled.[23] Only 45 studies, or 25 percent, had enrollment periods that extended beyond 2013. The remaining 75 percent were based on enrollment periods that were at least eight years in the past when the literature review was conducted in 2021. Across all studies, the final year of enrollment was 2012 on average, and the latest enrollment year of any study was 2019. Figure 5 shows that, among the included studies, the annual number of publications per year varies widely but does not display a clear trend.

**Figure 5. Annual Number of Studies Published and Annual Number of Studies Closing Enrollment**

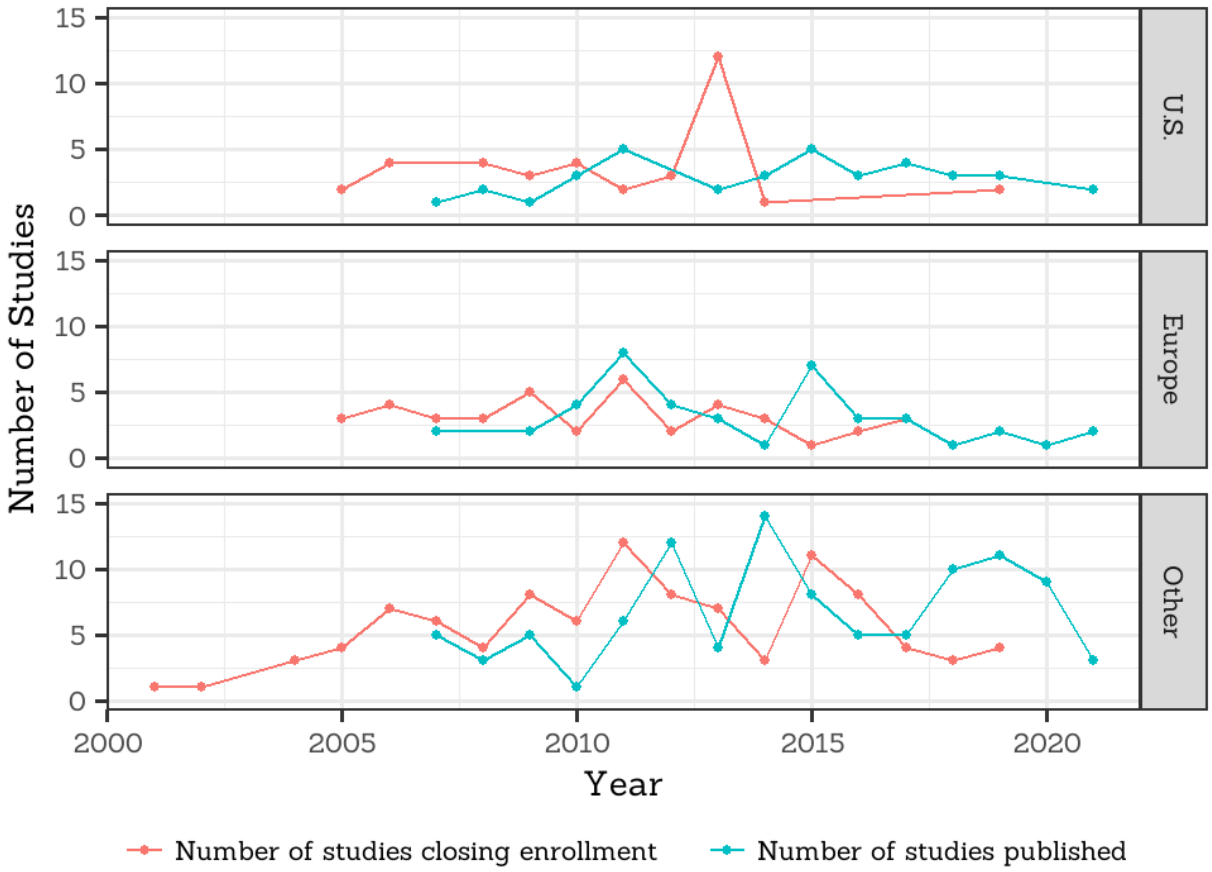



Figure 5 also shows a lack of trend in final enrollment year. Notably, U.S. studies have older enrollment closure dates; only three U.S. studies enrolled participants after 2013, suggesting that the included U.S. studies represent older data.

### 5.1.3 Region of Study

The region where a study was conducted was found to introduce substantial variation across estimates, and this effect is not surprising given differences in healthcare systems. Table 7 presents the average deviation of non-U.S. regions' resistant-strain mortality estimate from U.S. studies' corresponding estimate. The values of Table 7 are averaged across the unique combinations of pathogen, drug, and infection site (BSI, UTI, etc.) for which comparison with U.S.

[23] When developing the scoring algorithm, the final enrollment year was used rather than the midpoint of the enrollment period to avoid penalizing long-running studies that collected recent data but also used longer enrollment periods to improve sample size and, likely, representativeness.

estimate(s) was possible. For example, 12 different pathogen-drug-infection combinations existed with at least one European study and at least one U.S. study. The difference between these two regions' mean estimates—across all 12 combinations—was 6.2 percent.

**Table 7. Deviation from U.S. Estimates of Resistant-Strain Mortality**

| Region/Country | Mean Difference from U.S. Estimate of Resistant-Strain Mortality [a] | Number of Pathogen-Drug-Infections where Comparison with U.S. Estimate was Possible |
|---|---|---|
| Europe | 6.2% | 12 |
| Australia | -8.9% [b] | 1 |
| Mexico | 15.2% | 2 |
| Asia [c] | 17.0% | 15 |
| Middle East | 18.4% | 5 |
| South America | 26.6% | 11 |
| Africa | 30.3% | 3 |

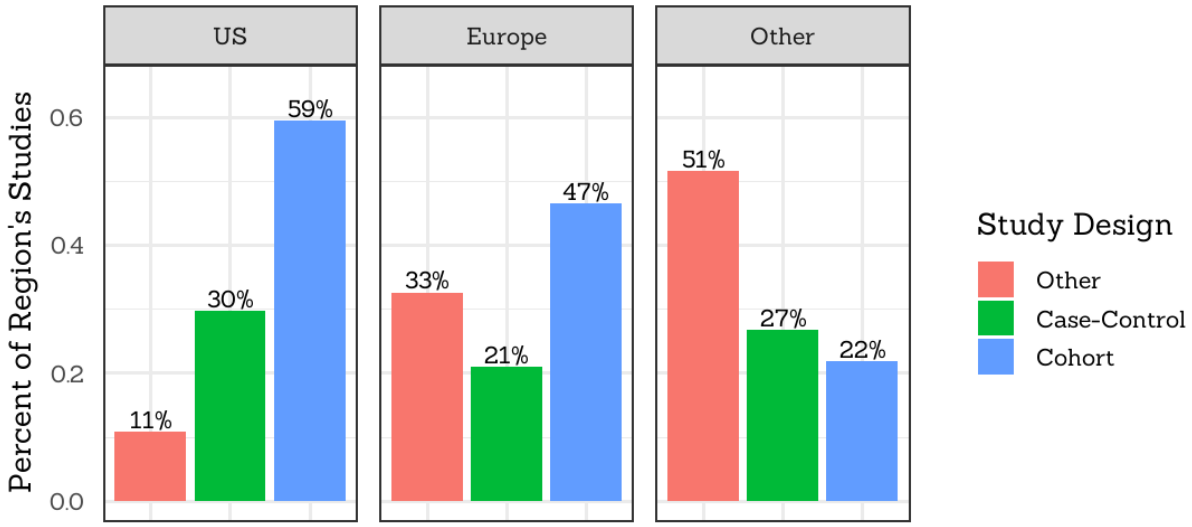
[a] Each region/country's deviation from the mean U.S. estimate was computed for every unique pathogen-drug-infection combination. Values presented here represent averages across all pathogen-drug-infection combinations for which comparison with a mean U.S. estimate was possible.
[b] A negative value indicates that Australia had lower resistant-strain mortality estimates than the U.S.
[c] None of the included studies were conducted in Japan.

Notably, studies from Europe are the most similar to U.S. studies on average, and this relative similarity (compared to other regions) between U.S. mortality and European mortality rates is part of the justification for assigning a region score of 2 for European study estimates.

### 5.1.4 Study Design

We categorized the study design into three categories: cohort, case-control, and other. Figure 6 shows the proportion of studies with each type of design, by region.

**Figure 6. Distribution of Study Design, by Region**




The U.S. has the highest proportion of cohort studies, at nearly 60 percent. Across all regions, 35 percent of studies used a cohort design, 27 percent used a case-control design, and 38 percent used another design.

### 5.1.5 Precision of Estimates

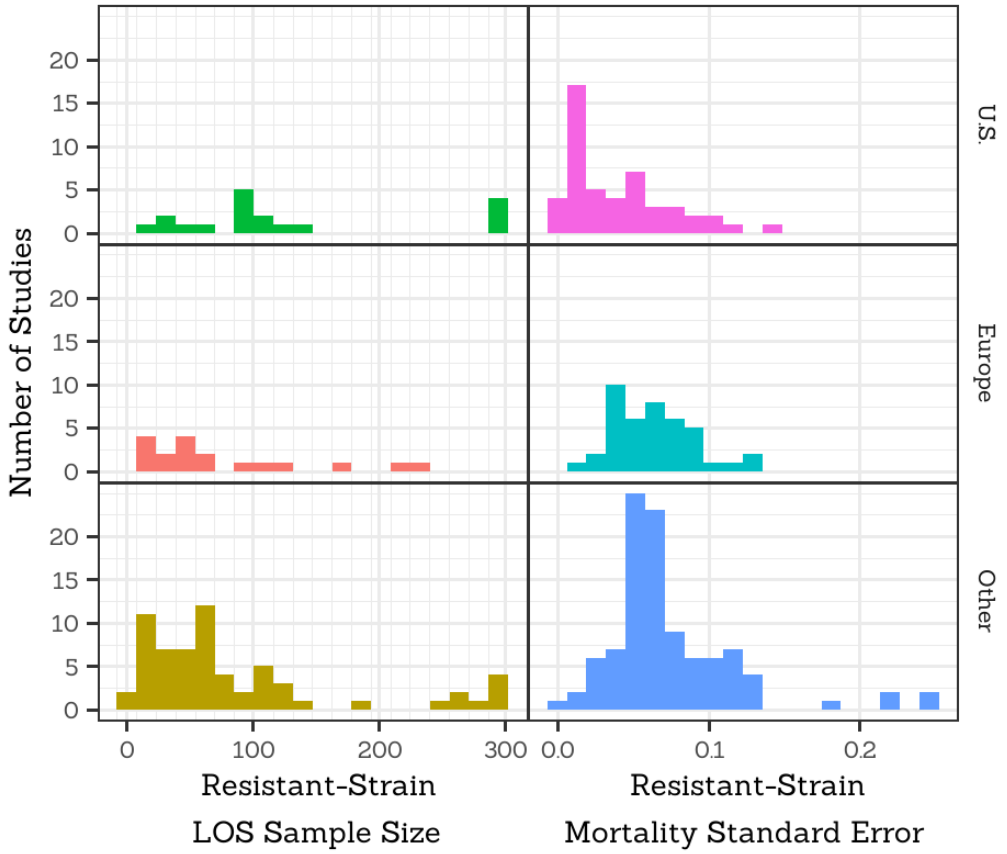
Among all resistant-strain mortality estimates from all studies, the SE ranged from 0.4 percent to 25.0 percent. The mean SE is 6.3%, which would correspond to a margin of error of ±12.4 percentage points, assuming a 95 percent confidence interval and a normal sampling distribution. LOS sample size ranged from 5 to 1,617 participants and was heavily right skewed, with a mean of 126.6 and a median of 66.0. Table 8 presents the terciles—computed across all pathogen-drug combinations—that served as cut points for the precision scores.

**Table 8. Precision Terciles**

| Tercile | Standard Error in Resistant-Strain Mortality | Sample Size of Resistant-Strain LOS |
|---|---|---|
| Bottom Tercile (Precision Score = 1) | <4.6% | <46 |
| Middle Tercile (Precision Score = 2) | 4.6-7.0% | 46-91 |
| Top Tercile (Precision Score = 3) | >7.0% | >91 |

U.S. studies generally had better precision than other regions. Across all U.S. studies, the average resistant-strain mortality SE is 3.9 percent (compared to 6.4 percent in European studies and 7.4 percent in other regions), and the median resistant-strain LOS sample size is 91.5 (compared to 46.5 in European studies and 64.0 in other regions). These differences are evident in Figure 7, which display the distribution of precisions by country and parameter (mortality vs. LOS). Good precision corresponds to high sample size and low SE.

**Figure 7. Comparing Precision of Studies across Regions, by Parameter Type**




[a] For visualization, two studies with sample sizes equal to 809 and 716 are displayed here as having a sample size of only 300.
[b] The left set of plots show LOS sample size, with larger size corresponding to better precision. The right set of plots shown mortality SE, with smaller values corresponding to better precision.

### 5.1.6 Mortality vs. Length of Stay

The preceding sections introduced the overall scoring metric and analyzed the four components of the score. In Section 5.1.6 and 5.1.7, we compare the availability of mortality vs. LOS estimates, and we consider whether the available studies are well-distributed across the various infection sites that contribute to the overall burden.

We found that mortality estimates are available in far greater numbers than LOS estimates. Our literature review identified and included 169 unique studies with resistant-strain mortality

estimates and 88 unique studies with resistant-strain LOS estimates.[24] Some studies contain multiple mortality estimates for different infection sites, leading to 219 different resistant-strain mortality estimates and 100 different resistant-strain LOS estimates (across all pathogen-drug-infection combinations).

On average, for each pathogen-drug combination, we found 14.6 unique studies with resistant-strain mortality estimate(s), compared to only 6.7 unique studies with resistant-strain LOS estimate(s). However, the computed score of study estimates does not vary substantially across LOS and mortality. Resistant-strain mortality estimates produce a study score of 10.7 on average, and LOS estimates produce a study score of 9.9 on average. These scores fall in the middle range of the scale in Figure 2, indicating moderate relevance to modeling AMR burden in the U.S. Among LOS studies, 65.9 percent have a cohort or case-control design, while 60.0 percent of mortality studies have such designs. Across the three regions, no large imbalances exist in the rate at which a study reports mortality vs. LOS data; however, U.S. and European studies report LOS information at a slightly lower rate than the region "Other."

### 5.1.7 Infection Site

A major consideration when modeling AMR burden is the site of infection (BSI, UTI, SSI, pneumonia, etc.). Distinct infection sites can have very different mortality rates and lengths of stay, as the included studies show. To illustrate this difference, Table 9 presents mean mortality rate and mean LOS across carbapenem-resistant *K. pneumoniae* studies, by infection site. The mean mortalities range from 15.6 percent (among other infection sites) to 54.5 percent (among BSIs). The mean LOS values range from 14.0 days (among BSIs) to 99.5 days (among multiple types).

**Table 9. Mean Parameter Estimates for Carbapenem-Resistant *K. pneumoniae*, by Infection Sites**

| Infection Site [a] | Resistant-Strain Mortality | | Resistant-Strain LOS in Days | |
|---|---|---|---|---|
| | Mean Estimate | Number of Estimates | Mean Estimate [b] | Number of Estimates |
| BSI | 54.5 | 9 | 14.0 | 1 |
| Not determined | 38.3 | 7 | 46.0 | 1 |
| Any infection | 38.3 | 7 | 51.6 | 3 |
| Pneumonia | 28.5 | 3 | 19.0 | 1 |
| UTI | 23.4 | 4 | 10.0 | 1 |
| Multiple types | 21.9 | 2 | 99.5 | 1 |
| Other | 15.6 | 1 | NA | 0 |

[a] The designation "multiple types" refers to studies where the sample contained two infection sites. "Any infection" refers to studies that did not screen participants based on infection site or had three or more infection sites. "Other" refers to a study with a single infection site not included in this list (e.g., intra-abdominal).
[b] While mean values are reported, different studies used different metrics to quantify LOS (e.g., means vs. medians). The usefulness of such means across different estimation metrics may be limited.
[c] NA = not applicable

Applying the attributable mortality rate from a BSI study to the full U.S. population (which is inflicted with a variety of infection sites) would likely lead to overestimation. Effective AMR burden modeling must account for these differences across infection sites, particularly given that many studies do not contain representative samples of the infection sites that exist in the U.S. in general.

[24] As before, studies containing separate estimates for distinct pathogen-drug combinations are counted multiple times. The group of 169 mortality studies and 88 LOS studies are overlapping. Of the 88 LOS studies, 76 contain mortality estimates and are included in the count of 169.

The need for infection-site-specific data complicates matters by greatly expanding the number of parameters that must be estimated for effective modeling. Estimating or projecting burden based on attributable mortality and attributable LOS for 15 pathogen-drug combinations and four infection sites (BSI, UTI, SSI, and pneumonia) necessitates 15 combinations × 2 parameters × 4 infection sites = 120 estimates.

Table 10 presents the total number of estimates that were available for each infection site based on our search, as well as the number of high-scoring estimates (i.e., those with an associated total study score of >15). The total number of high-scoring estimates included from the literature review is less than what is required.

**Table 10. Number of Studies by Infection Site and Parameter**

| Infection Site | Resistant-Strain Mortality | | Resistant-Strain LOS | |
|---|---|---|---|---|
| | Total Number of Studies | Number with High Score | Total Number of Studies | Number with High Score |
| Any [a] | 77 | 12 | 42 | 8 |
| BSI | 64 | 17 | 31 | 7 |
| Pneumonia | 25 | 6 | 12 | 1 |
| UTI | 19 | 9 | 6 | 3 |
| Other | 15 | 4 | 4 | 0 |
| Not determined | 15 | 2 | 3 | 0 |
| Multiple | 3 | 2 | 2 | 0 |
| SSI | 1 | 0 | -- | 0 |
| **Total [b]** | **219** | **52** | **100** | **19** |

[a] An "any infection"-study is defined as a study with whose infections encompass three or more infection sites.
[b] Studies with multiple estimates for a single pathogen-drug are counted multiple times (once for each estimate of a distinct pathogen-drug-infection site combination).

Notably, studies on "any infection site"—defined to be a study that did not limit its sample to specific infection sites or had samples composed of three or more different infection sites—make up the majority of publications. Among individual infection sites, estimates for BSI are more than twice as common as for any other infection site. Of the 219 mortality estimates and 100 LOS estimates, only one was for a population whose infection originated from a SSI. As discussed in detail in Section 5.2.3, the lack of research on certain infection sites—particularly with LOS estimates—is a major obstacle to building an AMR burden model that accounts for differences in mortality and LOS across infection sites.

### 5.1.8 Inconsistent Length of Stay Reporting

Overall, studies did not consistently define or report LOS. Some examples of LOS definitions include number of ICU days, total hospital stay, time in hospital after disease onset, and time after a culture was taken. Furthermore, some studies reported mean LOS, while others reported median LOS. Information about the spread or distribution of LOS data was often omitted altogether, but when it was reported, it varied between standard deviation, quartiles, and range. This inconsistency poses a challenge in estimating LOS parameters, but some techniques may be available to extract comparable metrics from studies that report different statistics.

A comprehensive study by Marazzi et al. (1998) evaluated distributional fits for LOS data and analyzed the extent to which studies report LOS range information. They proposed lognormal, Weibull, and Gamma distributions as the primary parametric candidates and found that lognormal models generally had good fits. Based on this finding, we attempted to fit lognormal distributions to studies that reported quartiles and generally were successful. This allowed us to extract mean

LOS and standard deviation in LOS from the reported quartiles, thereby acquiring a consistent metric across all studies.

While it was often possible to achieve good fits to the reported quantiles, this approach relies heavily on the assumption of LOS data being lognormally distributed. We used Mark et al. (2021) as a case study to analyze this assumption, as Mark et al. not only reported LOS quantiles but also median and standard deviation (Mark, et al., 2021). Figure 8 and Figure 9 show the quartiles and the fitted lognormal cumulative distribution function both for the resistant LOS and susceptible LOS distributions of Mark et al. (2021), respectively.

**Figure 8. Reported Resistant LOS Quartiles and Fitted Lognormal CDF for Mark et al.**

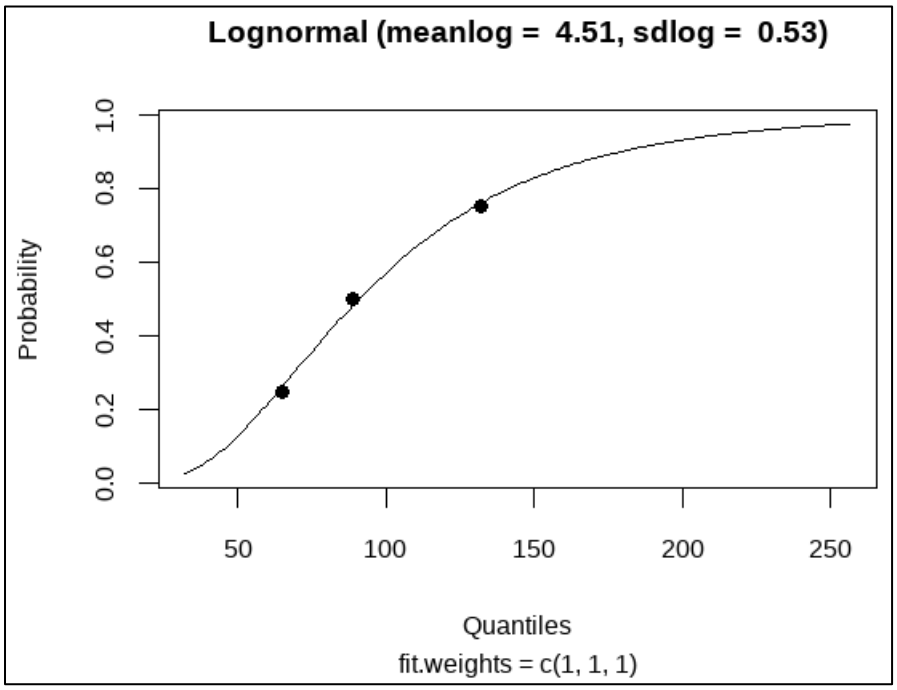
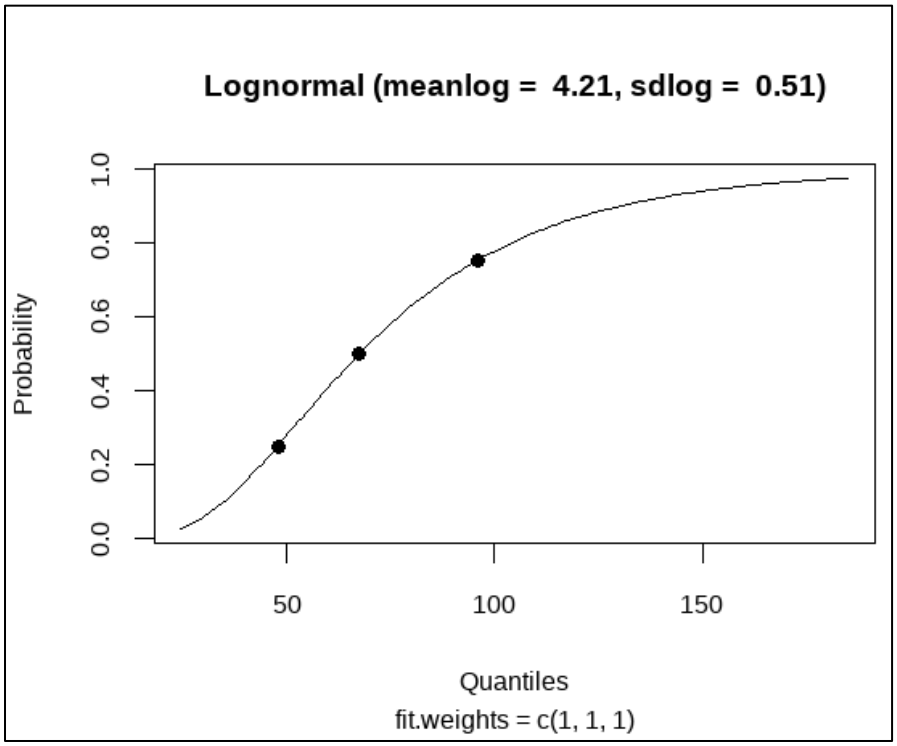


Figure 9. Reported Susceptible LOS Quartiles and Fitted Lognormal CDF for Mark et al.




From the fitted lognormal distributions, we computed the mean and standard deviation and compared them to the reported values in Mark et al. (2021). This comparison is shown in Table 11.

Table 11. Comparing Reported and Fitted Distribution Parameters for LOS in Mark et al. (2021)

| Distributional Parameter | Value Reported in Mark et al. (2021) | Value Calculated from Fitted Lognormal Distribution |
|---|---|---|
| Mean LOS among resistant strain | 115.4 | 104.5 |
| Mean LOS among susceptible strain | 87.1 | 77.1 |
| St. dev. in LOS among resistant strain | 117.8 | 59.5 |
| St. dev. LOS among susceptible strain | 98.6 | 42.4 |

The calculated means are very close to the values reported in Mark et al. (2021) and would likely be suitable for AMR modeling purposes. The computed standard deviations are approximately half the value reported in Mark et al. (2021) and would require an adjustment to correct for the lack of fit. In general, this approach of fitting a lognormal distribution to reported quartiles and calculating the associated mean may provide a way to extract a consistent metric from LOS studies.

### 5.1.9 Excess Healthcare Costs

The preceding sections analyzed studies on mortality and LOS but excluded studies on healthcare costs. In the literature we included, information on the costs associated with AMR was far less common than mortality or LOS data. For this reason, we present a separate analysis of healthcare costs in this section, for all pathogen-drug combinations.

Healthcare costs vary significantly by site of infection. While an UTI may require a course of antibiotics that can be administered in outpatient settings, some UTI cases may need hospitalization (MacVane, et al., 2014). An SSI may require debridement or intravenous antibiotics

(Maruo & Berven, 2014) administered in the hospital. Zimlichman et al. (2013) found that UTIs had the lowest healthcare costs ($1,108 in 2020 $), followed by SSIs ($25,698 in 2020 $). BSIs cost ($45,814 in 2020 $) slightly more than pneumonia cases ($40,144 in 2020 $), much more than the other infection sites. The LOS associated with these infections correlate directly with the estimated healthcare costs; with longer hospital stays resulting in higher healthcare costs, except for BSIs which tend to have shorter hospital stays but higher healthcare costs compared to pneumonia, SSI, and UTI.

The previously described literature review process did not return studies with cost estimates. Through a separate search process, we identified a total of nine studies[25] (U.S. only) that reported excess healthcare costs for different pathogens and infection sites (see Appendix D).[26] Six out of nine studies used the same counterfactual as this study (i.e., susceptible infection). Some of the six studies covered multiple infection sites and/or resistant pathogens yielding a total of 11 excess healthcare cost (i.e., difference between resistant-strain healthcare costs and susceptible-strain healthcare costs in 2020 $) estimates across infection sites (Table 12). Of the six studies, two reported excess healthcare costs for UTIs; MacVane et al. (2014) for ESBL Escherichia coli and Klebsiella spp. and Neidell et al. (2012) for an unspecified resistant pathogen. There was only one study each with reported excess healthcare costs for BSIs and pneumonia and four studies total for an unspecified resistant pathogen. There were no studies that provided estimates specific to SSIs. Table 12 presents the pooled excess healthcare cost estimates across our study sample.

**Table 12. Excess Healthcare Costs due to CRKP (in 2020 $), by Infection Site**

| Infection Site | N | Excess Healthcare Costs (in 2020 $) [a] | | |
|---|---|---|---|---|
| | | Mean | Lower Bound [c] | Upper Bound |
| BSI | 1 | $38,191 | $8,456 | $67,927 |
| Pneumonia | 1 | $20,153 | $7,751 | $32,695 |
| UTI | 3 | $5,035 | -$28,608 | $40,587 |
| ABSSSI [b] | 1 | $627 | -$1,011 | $2,277 |
| Unspecified | 5 | $23,492 | -$8,315 | $74,409 |

[a] We used the seasonally adjusted medical care consumer price index (Consumer Price Index for All Urban Consumers: Medical Care in U.S. City Average, Index 1982-1984=100, Annual, Seasonally Adjusted) to scale the figures reported in each study to 2020 dollars. Use of a producer-based index (PPI) rather than a consumer-based index (CPI) would have resulted in slightly lower $ 2020 values.
[b] ABSSSI = Acute bacterial skin and skin structure infection
[c] According to the source study by Neidell et al. (2012), certain types of resistant infections actually had lower healthcare costs than resistant ones resulting in negative "excess" costs.

### 5.1.10 Summary of Study-Level Comparisons

In Section 5.1, we showed that a large majority of included studies have lower scores (<9), indicating less relevance to modeling the AMR burden in the U.S. Only 20.4 percent of studies (n=37) received a high score (>15), which would indicate greater relevance for supporting models of U.S. AMR burden. Much of this imbalance in relevance is due to 56.0 percent of included studies having been conducted in non-U.S. regions where the true mortality rate is more likely to differ from the target rates in the U.S. Even when the study is designed and conducted rigorously, non-U.S. estimates may have limited applicability to U.S. AMR burden modeling, owing to important differences in healthcare systems. The extent to which AMR poses a substantial burden can vary across regions, making it inappropriate to average mortality estimates from countries with

[25] The nine studies with cost estimates are not included in the counts of Table 6, as they were identified through a separate search.
[26] As with mortality and LOS, the ultimate parameter required for modeling burden is excess healthcare cost, which represents the additional cost attributable to AMR.

substantially different AMR mortality rates. We found this to be true when comparing resistant-strain mortality estimates across regions; non-European regions having resistant-strain mortality rates that differ from U.S. estimates by 9 percent to 30 percent on average, whereas European estimates differ by six percent on average. These discrepancies likely reflect underlying differences in the true mortality rates. Within the three region categories (U.S., Europe, Other), the proportion of cohort studies is highest in the U.S., though U.S. studies tend to use older data than studies conducted in Europe or another region. U.S. studies also tend to have higher precision, primarily driven by larger samples sizes. There are approximately twice as many mortality estimates as LOS estimates, which is particularly problematic when attempting to model the AMR burden for less-studied pathogen-drug combinations.

An important element to control for is the site of infection. For example, for carbapenem-resistant *K. pneumoniae*, the mean resistant-strain BSI mortality rate is more than twice the mean resistant-strain UTI mortality rate (54.5 percent and 23.4 percent, respectively). However, infection sites are not studied evenly. We found more resistant-strain BSI estimates (n=64) than all other single-infection sites combined (n=60 for pneumonia, UTI, SSI, and other types).

In summary, more than half of studies have low scores, suggesting limited application to AMR burden modeling. Furthermore, there are substantial gaps in literature. Many infection sites have very little data, and LOS data are much sparser than mortality data. Additionally, the region being studied can introduce large variation in the magnitude of estimates.

## 5.2 COMPARISONS BETWEEN PATHOGEN-DRUG COMBINATIONS

Section 5.1 presented study-level statistics and comparisons. This section discusses differences between the 15 pathogen-drug combinations to highlight gaps in the literature for specific pathogens and drugs that may be of interest for modeling. Section 5.2.1 evaluates the number of studies published on each pathogen-drug combination and shows that carbapenem resistance is generally studied at a more than the other drug resistance phenotypes. In Section 5.2.2, we show that simply because a pathogen-drug combination has a high number of publications does not imply that the publications are all highly relevant to national burden modeling. Section 5.2.3 considers infection sites and shows that, while infection-site-specific data are more abundant for carbapenem resistance, this is primarily due to a single study. No pathogen-drug combination has sufficient data for site-specific modeling. In Sections 5.2.4 and 5.2.5, we compare the mean relevance score for each pathogen-drug combination, when considering mortality data and LOS data.

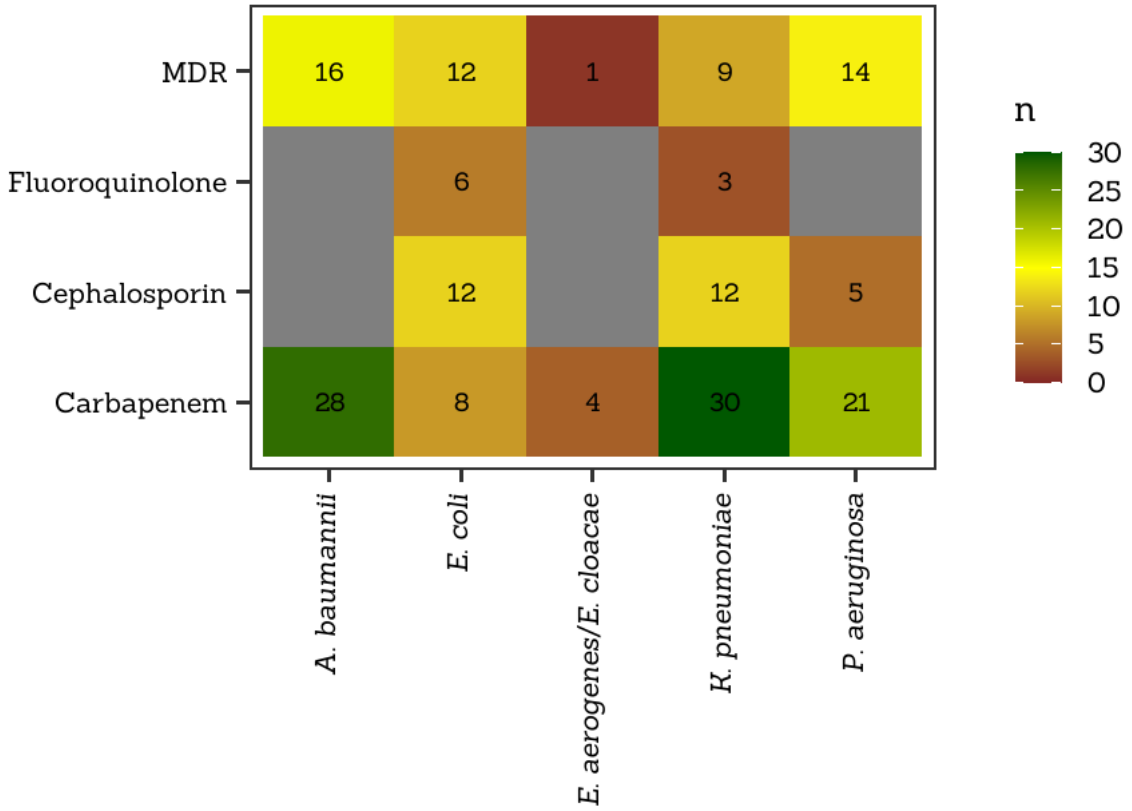
The score metric accounts for some factors that introduce variability, but there are other potential issues, such as whether a study is representative of the broader U.S. population, and the extent to which confounding variables are controlled. Section 5.2.6 captures these potential issues by analyzing the overall variability between comparable estimates. Comparable MDR mortality rates tend to have less internal agreement, and fluoroquinolone-resistant mortality rates tend to have more internal agreement. In Section 5.2.7, we aggregate all of the preceding components into a single percentage score and rank the 15 pathogen-drug combinations by their relative capacity for national burden modeling based on the available literature. Finally, because these analyses focus on resistant-strain mortality and LOS, we address susceptible-strain mortality and LOS in Section 5.2.8.

### 5.2.1 Number of Studies per Pathogen-Drug Combination

The number of AMR studies varies across the five pathogens and four AM drugs we investigated. Counts of publications can provide useful indicators of research interest and available funding. Figure 10 displays a heat map of the number of unique identified studies across the

pathogens and drugs. Gray cells appear for combinations that were excluded from the literature review.

**Figure 10. Heat Map of Number of Studies, by Pathogen-Drug Combination**



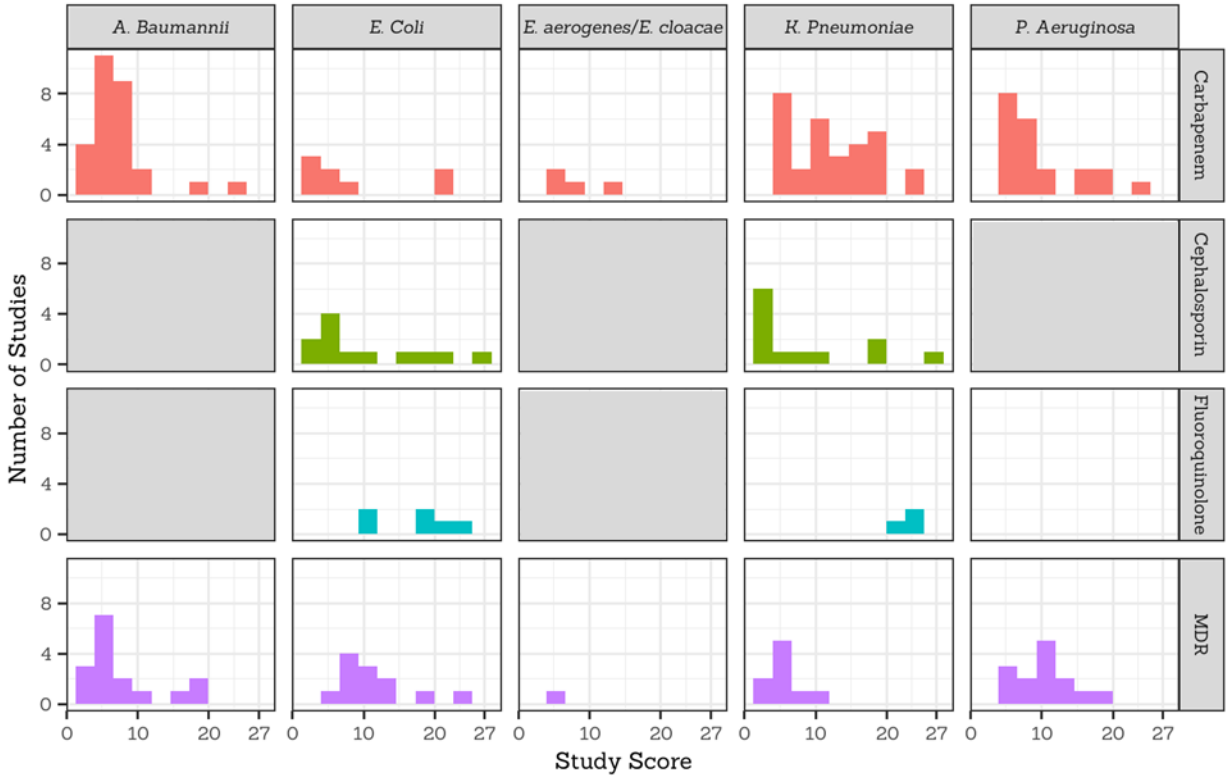

Note: Gray cells correspond to pathogen-drug combinations that were not investigated.

Figure 10 suggests that fluoroquinolone resistance is studied much less frequently than other forms of resistance, with only 4.5 studies per pathogen on average. This may be a consequence of declining fluoroquinolone prescriptions from 2011 to 2018 relative to other classes (CDC, n.d.). In contrast, carbapenem resistance is the most-researched form of resistance and has the highest study count for nearly every type of pathogen. Among the various pathogens, *E. aerogenes/E. cloacae* have been studied least, with only 2.5 studies on average across MDR and carbapenem resistance—substantially below the average of 17.3 in those drug categories among the other pathogens. The most-studied pathogens are *K. pneumoniae*, with 54 total studies across the four drugs, and *A. baumannii*, with 44 total studies across the two most-researched drugs (carbapenem and multi-drug resistance).

### 5.2.2 Strength of Literature across Pathogens and Drugs

The number of studies is an important metric for a pathogen-drug combination, but it does not convey how relevant the studies are to AMR burden modeling in the U.S. To understand relevance, we analyzed the computed study scores presented in Section 5.1.1. Figure 11, below, presents the distribution of study scores for each pathogen-drug combination. The total area of each graph conveys the number of studies, and their placement along the x-axis represents their study scores.

**Figure 11. Distribution of Study Scores by Pathogen and Drug**




[a] The study scores convey the study's relevance to AMR burden modeling by aggregating component scores based on the study's design, precision, final enrollment year, and region.
[b] Gray cells correspond to pathogen-drug combinations that were not investigated.

As the distributions show, having a higher number of studies does not necessarily imply that the studies are highly relevant to the task of modeling U.S. AMR burden. MDR *A. baumannii* has 16 studies, but only three have scores higher than 12. Many of the pathogen-drug combinations with the most studies have at least one high-scoring study (with a score >15), but, as discussed previously, no combination has enough studies for infection-site-specific AMR burden modeling.

Importantly, when modeling AMR burden, a large number of studies per parameter is not always required. For example, a single study with a highly reliable and generalizable estimate for attributable mortality among fluoroquinolone-resistant *E. coli* BSIs obviates the need for additional literature on the same parameter. While having multiple study estimates for the same parameter does confer some benefits (e.g., pooling estimates using meta-analysis techniques), modeling can proceed with even just a single reliable and relevant estimate.

Given that a small number of high-scoring studies can be suitable for developing AMR burden models, we performed additional analysis on a subset of the strongest studies from each pathogen-drug combination. These analyses are presented in Sections 5.2.4 and 5.2.5.

### 5.2.3 Infection Site

As discussed in Section 5.1.7, an effective AMR burden model will account for important differences in attributable mortality and attributable LOS by using separate estimates for each infection site. We analyzed the 15 pathogen-drug combinations for their suitability to support a model with four infection sites: BSI, UTI, pneumonia, and SSI. We found that none of the pathogen-drug combinations met the requirement of possessing at least one estimate for each modeling

parameter. This was true even when we included lower-relevance studies as candidates for estimating parameters. When we examined only studies with high scores (>15), the available studies dropped substantially.

Table 13 presents the infection sites for which estimation is possible, by pathogen-drug combination. The first two columns show the infection sites that can be estimated from literature (using at least one publication). The last two columns show the counts when restricting to high-scoring estimates (>15).

**Table 13. List of Infection Sites with Literature to Support a Resistant-Strain Estimate**

| Pathogen-Drug Combination | Infection Sites with Any Available Estimate | | Infection Sites with a High-Scoring Estimate [a] | |
|---|---|---|---|---|
| | Mortality [b] | LOS | Mortality | LOS |
| Carbapenem, *A. baumannii* | BSI PNE SSI UTI | BSI PNE [c] | BSI PNE UTI | None |
| Carbapenem, *E. coli* | BSI PNE UTI | None | BSI PNE UTI | None |
| Carbapenem, *Enterobacter* | BSI PNE UTI | BSI PNE UTI | None | None |
| Carbapenem, *K. pneumoniae* | BSI PNE UTI | BSI PNE UTI | BSI PNE UTI | BSI PNE UTI |
| Carbapenem, *P. aeruginosa* | BSI PNE UTI | BSI PNE | BSI PNE UTI | None |
| Cephalosporin [d], *E. coli* | BSI UTI | BSI UTI | BSI UTI | BSI UTI |
| Cephalosporin, *K. pneumoniae* | BSI UTI | BSI UTI | UTI | BSI UTI |
| Cephalosporin, *P. aeruginosa* | BSI | None | None | None |
| Fluoroquinolone, *E. coli* | BSI UTI | BSI | BSI | BSI |
| Fluoroquinolone, *K. pneumoniae* | BSI | BSI | BSI | BSI |
| MDR, *A. baumannii* | BSI PNE | BSI PNE | None | None |
| MDR, *E. coli* | BSI PNE UTI | BSI | UTI | None |
| MDR, *Enterobacter* | None | None | None | None |
| MDR, *K. pneumoniae* | BSI | BSI | None | None |
| MDR, *P. aeruginosa* | BSI PNE UTI | BSI PNE UTI | BSI UTI | BSI |

[a] A high-scoring estimate is one that produces an overall study score >15, indicating high relevance to the task of U.S. AMR burden modeling.
[b] Mortality and LOS refer to resistant-strain mortality and resistant-strain LOS, respectively.
[c] PNE indicates pneumonia.
[d] Cephalosporin refers to third-generation cephalosporin.

In Table 13, a pathogen-drug combination would be sufficiently supported by literature for AMR burden modeling if all four infection sites (BSI, PNE, SSI, UTI) appeared under both Mortality and LOS, indicating that at least one study was available for each required parameter. No study achieves this requirement for infection-specific modeling using the four selected infection sites. Some carbapenem-resistant pathogens have enough literature to support six of the eight required parameters, including *A. baumannii*, *E. aerogenes/E. cloacae*, and *K. pneumoniae*. Carbapenem-resistant *K. pneumoniae* has the most comprehensive literature coverage of specific infection sites. Notably, MDR *E. aerogenes/E. cloacae* does not have any infection-specific estimates, and third-generation cephalosporin-resistant *P. aeruginosa* only has one infection-specific estimate.

In general, literature was much sparser for attributable LOS than for attributable mortality, as Table 13 shows. When restricting to high-scoring studies, five of the 15 pathogen-drug combinations completely lacked infection-specific mortality data, and nine were lacking in infection-specific LOS estimates.

The analysis above shows that none of the pathogen-drug combinations have sufficient literature for infection-site-specific modeling. In some cases (such as carbapenem-resistant *K. pneumoniae*), higher-quality literature is available for most of the required parameters, and it may be possible to supplement the missing data with other assumptions, substitutions, or broadening of

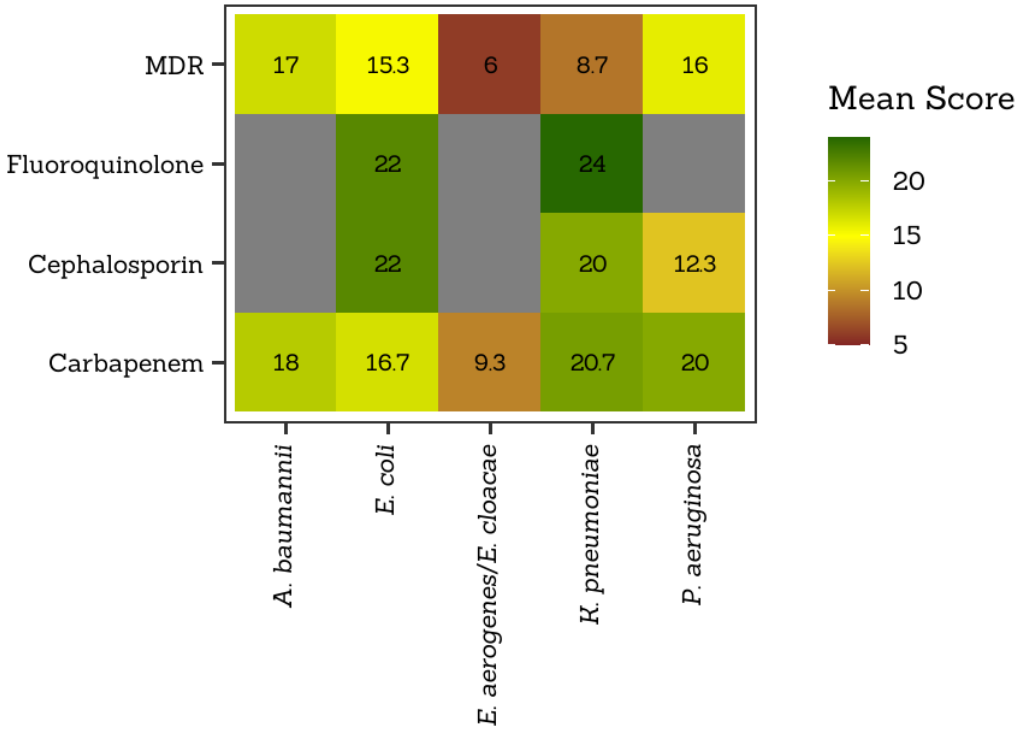
definitions. However, in general, this is not likely to be sufficient to fill in the gaps for the other pathogen-drug combinations.

### 5.2.4 Resistant-Strain Mortality Across Pathogen-Drug Combinations

To evaluate the relative strength of literature for supporting estimates of resistant-strain mortalities, we used the following procedure: each study was scored on the basis of its resistant-strain mortality estimates. Within each pathogen-drug combination, studies with multiple mortality estimates received multiple scores, which were averaged into a single study score. Then, for each pathogen-drug combination, the top three studies were selected, and their scores were averaged, thereby generating a single mean mortality score.

Selecting three studies is likely insufficient for more complex infection-site-level AMR modeling, but it enables insight into the relative strength of the most relevant literature across pathogen-drug combinations. Additionally, restricting to the top three studies effectively controls for differences in the number of studies across pathogen-drug combinations. The heat map of Figure 12 shows the mean study score for the top three resistant-strain mortality studies in each pathogen-drug combination.

**Figure 12. Heat Map of Mean Study Score Among Top Three Resistant-Strain Mortality Studies**



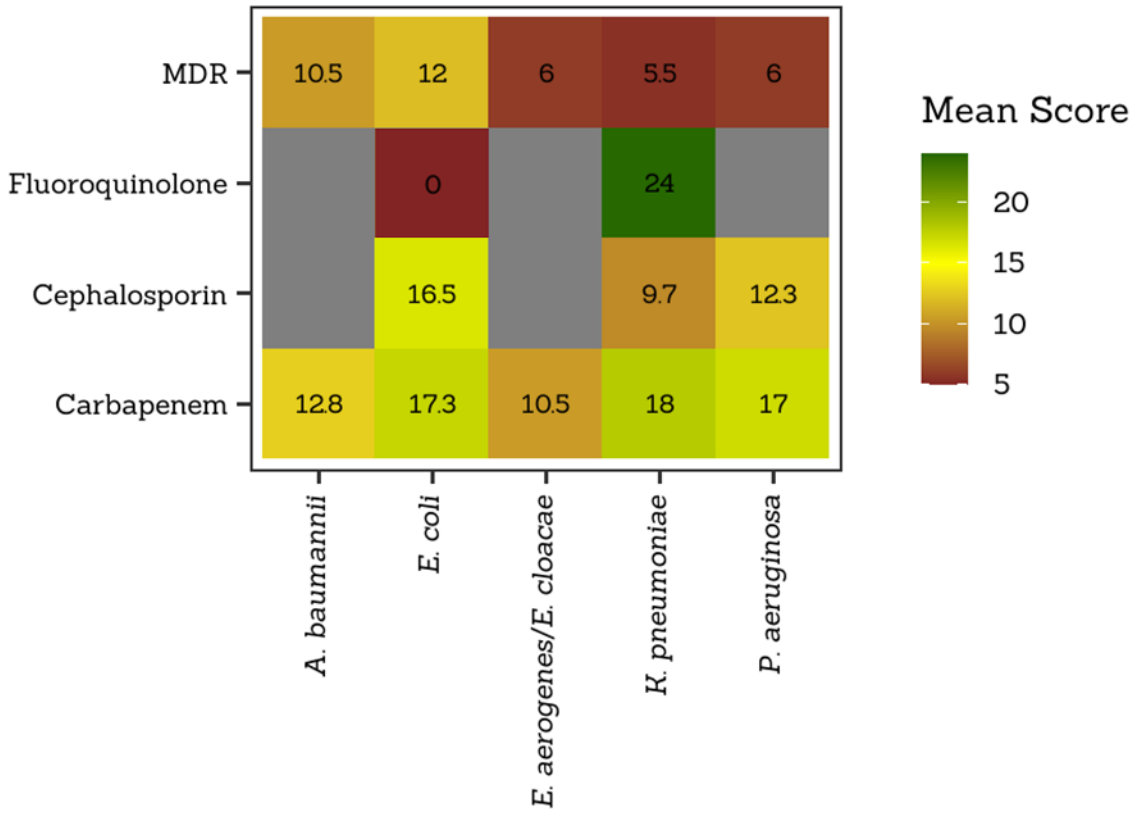

Note: gray cells correspond to pathogen-drug combinations that were not investigated.

Studies on fluoroquinolone resistance and third-generation cephalosporin resistance appear to have more relevant mortality estimates than other forms of resistance—despite the fact that fluoroquinolone resistance is studied at a far lower rate. Among the pathogens, *E. coli* and *K. pneumoniae* tend to have higher mean scores. Mortality studies have much lower relevance scores for three particular pathogen-drug combinations: MDR *E. aerogenes/E. cloacae* (mean of 6.0), MDR *K. pneumonia* (mean of 8.7), and carbapenem-resistant *E. aerogenes/E. cloacae* (mean of 9.3). Of the 15 pathogen-drug combinations, ten cross the threshold of a high-scoring study (i.e., a rounded score >15).

While this analysis is useful for comparing scores across pathogen-drug combinations, it is possible that the higher-scoring studies are infection-site-specific. Because infection-site-specific modeling is unlikely to be feasible, (see Section 5.2.3), high-scoring infection-site-specific studies may not be utilized.

This led us to a secondary analysis wherein the heat map of was adjusted to include only the top three "any infection site" studies (Figure 13). This was done because, in the absence of infection-site-specific modeling, studies about "any infection site" may be sufficiently representative of broader AMR patients to enable more generic AMR burden modeling. We found that restricting to the top three "any infection site" studies produced lower mean mortality scores.

**Figure 13. Heat Map of Mean Study Score Among Top Three Resistant-Strain Mortality Studies on "Any Infection Site"**



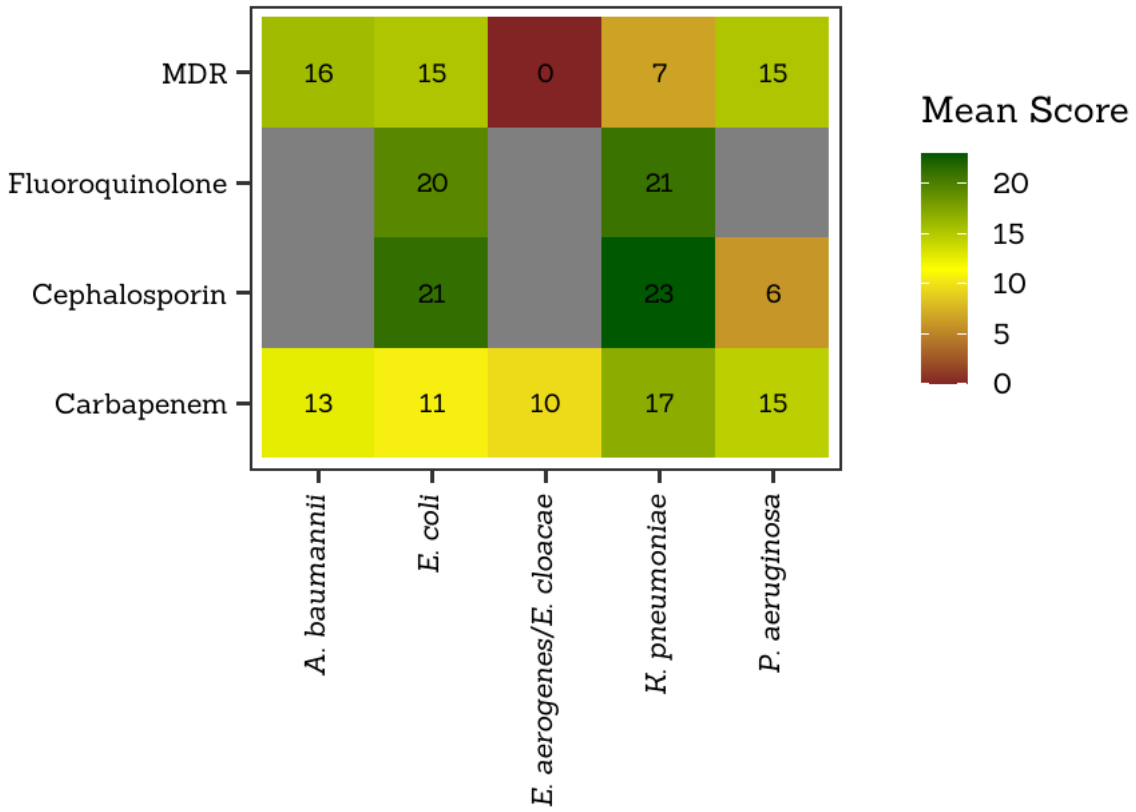

Note: gray cells correspond to pathogen-drug combinations that were not investigated.

After filtering for studies on "any infection site," only five pathogen-drug combinations exceed the threshold for a high score (rounded score >15): fluoroquinolone-resistant *K. pneumoniae,* carbapenem-resistant *K. pneumoniae*, carbapenem-resistant *E. coli*, carbapenem-resistant *P. aeruginosa*, and third-generation cephalosporin-resistant *E. coli*. In the adjusted heat map of Figure 13, there are four pathogen-drug combinations in the low-scoring range (rounded score <9).

### 5.2.5 Resistant-Strain LOS across Pathogen-Drug Combinations

The procedure described in Section 5.2.3 was repeated for LOS, the other primary parameter that is required for AMR burden modeling. We scored the studies based on their resistant-strain LOS estimates and selected and averaged the top three for each pathogen-drug combination. Figure 14 presents the resulting heat map for resistant-strain LOS.

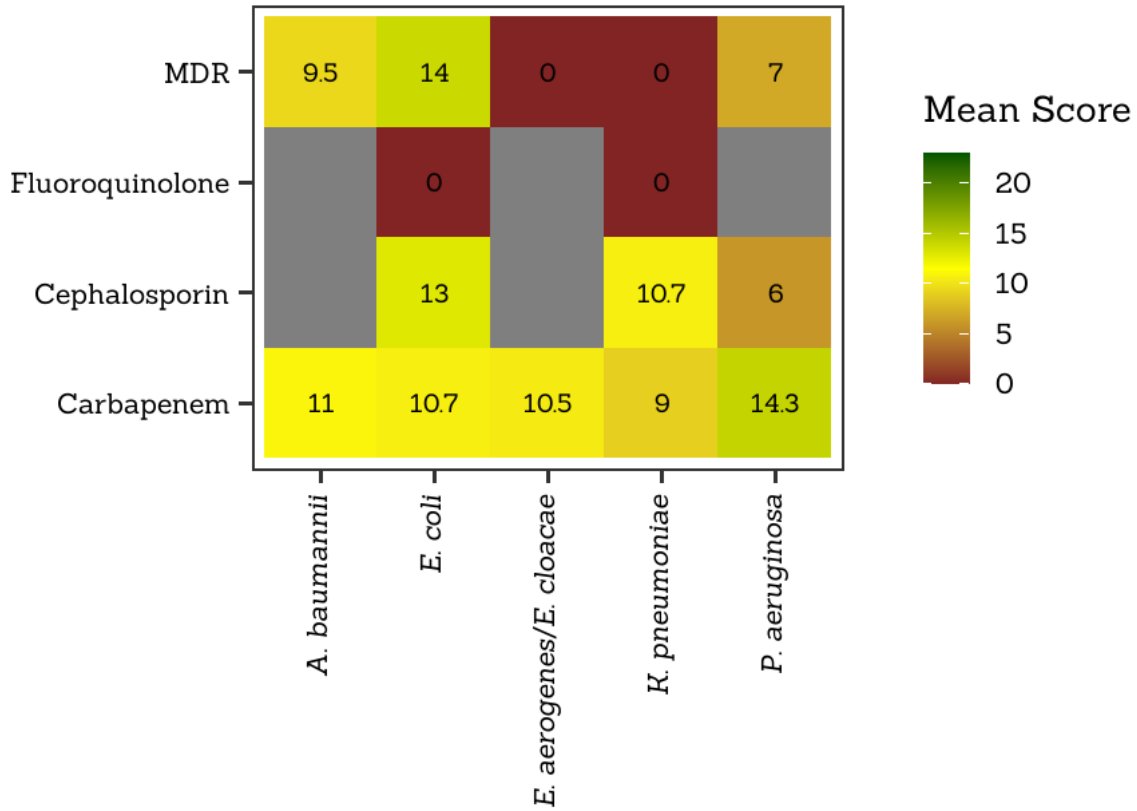
**Figure 14. Heat Map of Mean Study Score Among Top Three Resistant-Strain LOS Studies**




Note: gray cells correspond to pathogen-drug combinations that were not investigated.

Whereas 10 different pathogen-drug combinations have mean mortality scores exceeding 15, only six pathogen-drug combinations have mean LOS scores exceeding this threshold. This indicates that studies on LOS are not only less common, but also less relevant to the task of modeling AMR burden in the U.S. As explained above, the mean scores in Figure 14 do not account for the infection site and may include studies on specific infection sites, which cannot be used in more generic AMR modeling. When we limit the analysis to LOS studies on "any infection site" type (as may be required, given insufficient infection-specific literature), the mean scores decrease. This is shown in Figure 15, which presents mean scores across the top three "any infection site" resistant-strain LOS studies for each pathogen-drug combination.

**Figure 15. Heat Map of Mean Study Score Among Top Three Resistant-Strain LOS Studies on "Any Infection Site"**




Note: gray cells correspond to pathogen-drug combinations that were not investigated.

Notably, none of the pathogen-drug combinations have a mean LOS score in the high-scoring range (>15). In addition, four different pathogen-drug combinations have a score of 0 because no "any infection site" resistant-strain LOS estimates were found in the included studies.

When considering both Figure 13 and Figure 15, MDR *E. coli*, carbapenem-resistant *P. aeruginosa* tend to have higher mean scores across both mortality and LOS estimates, when restricting to the three most relevant "any infection" resistant-strain estimates. On the other hand, consistently lower mean scores were seen across both mortality and LOS for fluoroquinolone-resistant *E. coli*, MDR *K. pneumoniae*, MDR *P. aeruginosa*, MDR *E. aerogenes/E. cloacae*, and MDR *K. pneumoniae*. These lower scores are a result of low-scoring "any infection site" studies and a lack of "any infection site" studies—both of which suggest that the literature may be lacking in studies highly relevant to U.S. AMR burden modeling.

### 5.2.6 Extent of Agreement Among Studies

An additional metric of evaluation is the extent to which comparable estimates agree with each other. As discussed above, all studies were scored on components that would account for some of the variation between estimates. However, disagreement between studies is a broader issue that captures additional threats to generalizability. Even within a given pathogen, drug, and infection site, differences in target populations introduce variation; studies focused on post-transplant patients or patients who were already hospitalized in an ICU at the time of infection are expected to have different underlying AMR mortality rates than studies on the U.S. population in general. As another example, confounding factors can be controlled with varying degrees of

success, even in cohort studies or studies with low SE. Disagreement between a set of study estimates thus can indicate a wider range of issues that threaten the validity of generalizing from those studies to the full U.S. population of AMR patients.

Accordingly, each pathogen-drug-infection site combination was evaluated for the extent of agreement among its studies (using standard deviation as the metric of agreement), and then averages were taken across pathogen-drug combinations. In this analysis, we used only resistant-strain mortality, as LOS estimates are less numerous and reported with less consistency (with some studies reporting mean LOS and others reporting median LOS). To identify the extent of agreement, we grouped studies by pathogen, drug, and infection site. Only studies with medium or high scores were included (i.e., studies whose resistant-strain mortality estimate(s) led to a rounded mean score ≥9).[27] For any grouping of pathogen, drug, and infection site with more than one mortality estimate, we computed the standard deviation (SD) of the estimates. Then, these standard deviations were averaged across all infection sites for a given pathogen-drug combination.[28] The resulting metric is presented in the second column of Table 14 and represents the mean variation in a pathogen-drug's mortality estimates among medium- or high-relevance studies, averaged across well-defined infection sites.

**Table 14. Extent of Agreement Among Resistant-Strain Mortality Estimates with Medium to High Scores, by Pathogen and Drug**

| Pathogen and Drug | Standard Deviation, Averaged over All Infection Sites | Number of Infection Sites with Multiple Estimates | Agreement Score |
|---|---|---|---|
| Fluoroquinolone, *K. pneumoniae* | 0.5% | 1 | 3 |
| Cephalosporin [a], *P. aeruginosa* | 1.6% | 1 | 3 |
| Carbapenem, *A. baumannii* | 8.7% | 1 | 3 |
| Fluoroquinolone, *E. coli* | 9.7% | 1 | 3 |
| Carbapenem, *K. pneumoniae* | 10.8% | 4 | 2 |
| MDR, *P. aeruginosa* | 10.9% | 3 | 2 |
| MDR, *E. coli* | 11.3% | 2 | 2 |
| Cephalosporin, *E. coli* | 11.8% | 2 | 2 |
| Cephalosporin, *K. pneumoniae* | 12.5% | 1 | 2 |
| Carbapenem, *P. aeruginosa* | 14.1% | 2 | 2 |
| MDR, *A. baumannii* | 18.8% | 1 | 1 |
| Carbapenem, *E. coli* | 21.6% | 1 | 1 |
| Carbapenem, *Enterobacter* | Could not be computed [b] | 0 | 1 |
| MDR, *K. pneumoniae* | Could not be computed | 0 | 1 |
| MDR, *Enterobacter* | Could not be computed | 0 | 1 |

[a] Cephalosporin refers to third-generation cephalosporin.
[b] In some cases, it was not possible to calculate the standard deviation between comparable estimates, because the pathogen-drug combination did not have any infection site with more than a single estimate.

Based on the standard deviation (averaged across infection sites), an agreement score was assigned. These agreement scores are presented in the final column of Table 14.

[27] Lower-scoring studies were excluded because we assumed that the existing scoring metric likely already captured study elements that reduce representativeness. This exclusion removed many studies conducted in "Other" regions, primarily leaving only U.S. and European studies.
[28] The infection sites included in this analysis are: BSIs, UTIs, SSIs, pneumonias, and any infection site. While the composition of infection sites included in "any infection site" may change across studies, it was analyzed as a defined, stable infection category insofar as it would be treated as such for AMR burden modeling purposes.

- Agreement Score = 3 if average standard deviation >10 percent.
- Agreement Score = 2 if average standard deviation is 10 – 15 percent.
- Agreement Score = 1 if average standard deviation >15 percent (or could not be determined).

### 5.2.7 Overall Comparison of Pathogen-Drug Combinations

In the preceding sections, we used the following metrics to analyze the relevance of the available literature to U.S. AMR burden modeling for each pathogen-drug combination:

1. Number of distinct studies with a resistant-strain mortality or LOS estimate (Section 5.2.1).
2. Mean score of the top resistant-strain mortality studies, with and without a restriction on "any infection" type (Section 5.2.3).
3. Mean score of the top resistant-strain LOS studies, with and without a restriction on "any infection" type (Section 5.2.5).
4. Agreement score conveying the extent to which medium- or high-scoring resistant-strain mortality estimates agree (Section 5.2.6).

Item 1 was converted into a simple scale ranging from 1 to 3.[29] Items 2 and 3 were also given a simple 1-to-3 point scale.[30] Table 15 presents these summary quantities, along with an overall score. The overall score was calculated by summing across the row and dividing by 18, the maximum possible total.

**Table 15. Overall Summary for each Pathogen-Drug Combination**

| Pathogen and Drug | Number of Studies | Top Mortality Estimates | Top LOS Est. [a] | Top Generic Mortality Est. [b] | Top Generic LOS Est. | Study Agreement Score | Overall Score |
|---|---|---|---|---|---|---|---|
| Carbapenem, *P. aeruginosa* | 3 | 3 | 2 | 3 | 3 | 2 | **89%** |
| Cephalosporin, *E. coli* [c] | 2 | 3 | 3 | 3 | 3 | 2 | **89%** |
| Cephalosporin, *K. pneumoniae* | 2 | 3 | 3 | 3 | 3 | 2 | **89%** |
| Carbapenem, *A. baumannii* | 3 | 3 | 2 | 1 | 2 | 3 | **78%** |
| Carbapenem, *K. pneumoniae* | 3 | 3 | 3 | 1 | 2 | 2 | **78%** |
| Fluoroquinolone, *K. pneumoniae* | 1 | 3 | 3 | 3 | 1 | 3 | **78%** |
| MDR, *E. coli* | 2 | 2 | 2 | 2 | 3 | 2 | **72%** |
| Fluoroquinolone, *E. coli* | 1 | 3 | 3 | 1 | 1 | 3 | **67%** |
| MDR, *A. baumannii* | 2 | 3 | 3 | 1 | 2 | 1 | **67%** |
| MDR, *P. aeruginosa* | 2 | 3 | 2 | 1 | 1 | 2 | **61%** |
| Carbapenem, *E. coli* | 1 | 3 | 2 | 2 | 2 | 1 | **61%** |
| Carbapenem, *Enterobacter* | 1 | 2 | 2 | 2 | 2 | 1 | **56%** |
| Cephalosporin, *P. aeruginosa* | 1 | 2 | 1 | 2 | 1 | 3 | **56%** |
| MDR, *K. pneumoniae* | 1 | 2 | 1 | 1 | 1 | 1 | **39%** |
| MDR, *Enterobacter* | 1 | 1 | 1 | 1 | 1 | 1 | **33%** |

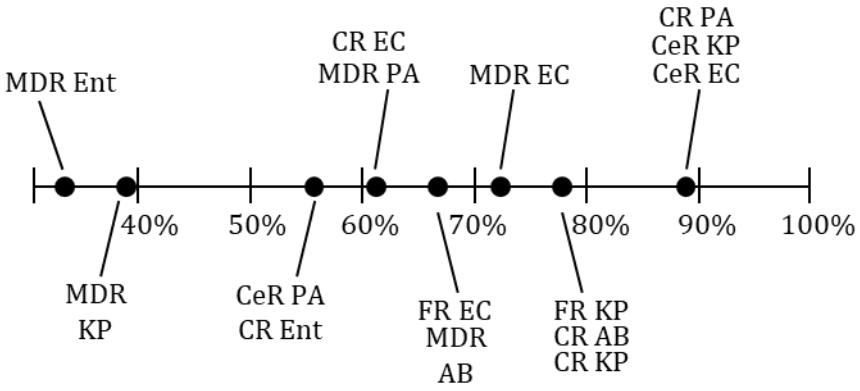
[a] Est. indicates "estimates."
[b] "Generic" indicates that the estimate is not specific to infection site and is instead based on "any infection."
[c] Cephalosporin refers to third-generation cephalosporin.

[29] 1-10 studies = 1 point, 11-20 studies = 2 points, and 21-30 studies = 3 points.
[30] Low mean score (3-8) = 1 point, middle mean score (9-15) = 2 points, and high mean score (16-27) = 3 points.

Aggregating these qualities produces an overall score that ranges from 33 percent (MDR *E. aerogenes/E. cloacae*) to 89 percent (shared by third-generation cephalosporin-resistant *E. coli*, third-generation cephalosporin-resistant *K. pneumoniae*, and carbapenem-resistant *P. aeruginosa*). This score provides an overall comparison of how relevant the available literature is for AMR burden modeling in the U.S., accounting for total number of studies, the relevance of the strongest available studies, the capability for generic ("any infection site") modeling, and the extent of agreement among studies.

Figure 16 plots the overall scores for each pathogen-drug combination. *K. pneumoniae* tend to have higher overall scores than the other pathogens, and *E. aerogenes/E. cloacae* generally has lower overall scores.

**Figure 16. Line Plot of Overall Score for each Pathogen-Drug Combination**




Legend for Drugs
CR = carbapenem-resistant
MDR = multi-drug-resistant
CeR = 3rd gen. cephalosporin-resistant
FR = fluoroquinolone-resistant

Legend for Pathogens
Ent = *E. aerogenes/E. cloacae*
KP = *K. pneumoniae*
AB = *A. baumannii*
EC = *E. coli*
PA = *P. aeruginosa*

### 5.2.8 Susceptible-Strain Estimates

The focus of Section 5.2.7 has been on resistant-strain mortality and LOS, as these estimates are available for all studies and facilitate comprehensive analysis. However, the true modeling parameters for AMR burden are *attributable* mortality and *attributable* LOS, which are only available when a study includes a counterfactual group. In our literature review, the susceptible strain of the pathogen served as the counterfactual, such that excess values would be measured relative to the baseline mortality and LOS among susceptible infections.

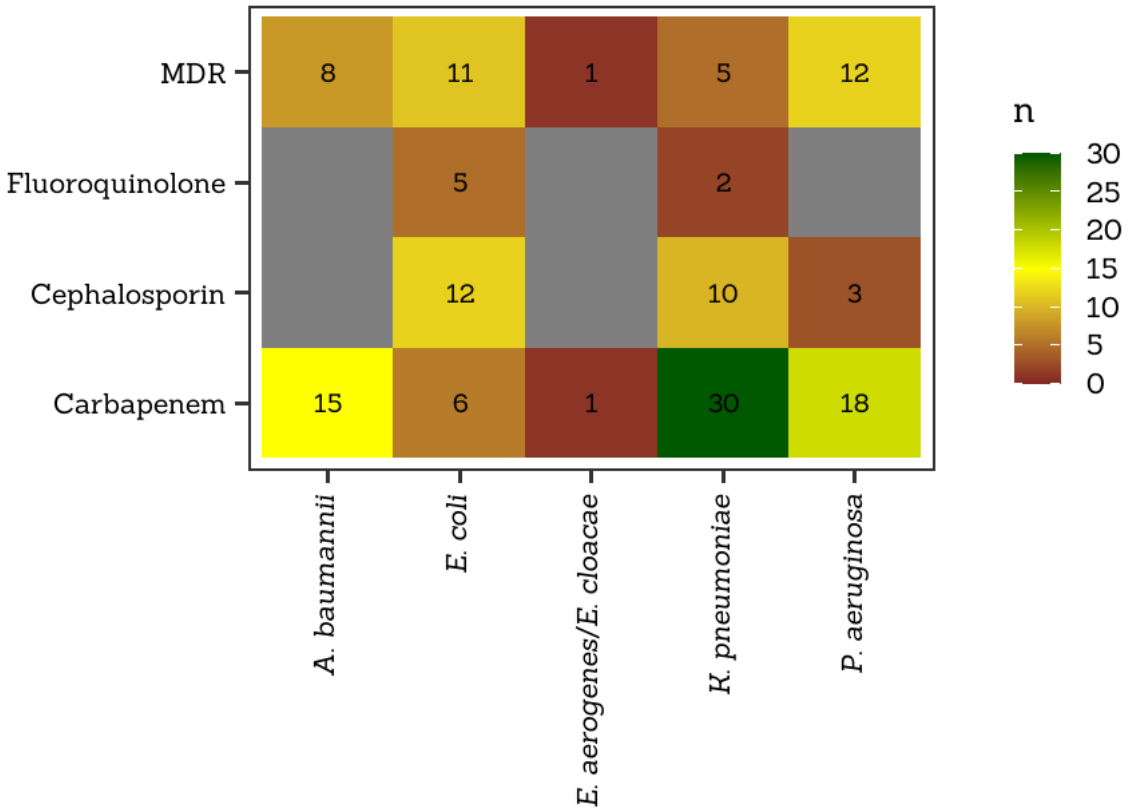
In general, fewer studies report mortality and LOS associated with a susceptible strain.[31] The 167 distinct studies contain 319 resistant-strain mortality and LOS estimates. Of these 319 resistant-strain estimates, 97—or 30.4 percent—do not have an associated susceptible-strain estimate. In cases where a susceptible estimate is available, it tends to be more precise than the resistant-strain estimate. For mortality, the susceptible-strain standard error is 1.8 percentage

[31] Out of studies that only investigate a single study group, many more publications report on the resistant strain than on the susceptible strain, as the resistant strain poses a greater public health concern.

points lower than the resistant-strain standard error, on average. For LOS, the susceptible-strain sample size is 291 larger than the resistant-strain sample size, on average.[32]

Figure 17 presents the number of studies with susceptible counterfactual information, by drug and pathogen. Comparing against Figure 10 confirms that far fewer studies are available with susceptible-strain information, across all pathogen-drug combinations. This gap between available resistant-strain information and susceptible-strain information is largest for *A. baumannii*.

**Figure 17. Heat Map of Number of Studies with Susceptible Strain Information, by Drug and Pathogen**




### 5.2.9 Summary of Pathogen-Drug-Level Comparisons

Large variation exists in the number of included studies per pathogen-drug combination, with some having fewer than 5 and others having more than 25. In general, we found that carbapenem resistance had more studies pertinent to AMR burden modeling than other drug resistance types. Among the five pathogens, *A. baumannii* and *K. pneumoniae* have the most studies, and *E. aerogenes/E. cloacae* had the fewest. However, the number of included studies and the relevance to AMR burden modeling are not always directly correlated. Moreover, even among pathogen-drug combinations with over 25 studies, we found this to be insufficient for infection-site-specific modeling.

[32] Across all studies (those with and without susceptible estimates), the mean resistant-strain SE is 6.4 percent. The mean susceptible-strain SEs is 3.8 percent. The mean resistant-strain LOS sample size is 126.6, and the mean susceptible-strain LOS sample size is 430.9. However, the LOS sample size distributions are heavily right-skewed; their medians are 66 and 104, respectively.

We also compared the relevance scores of the three highest-scoring studies in each pathogen-drug combination, as an attempt to control for the unequal number of studies. However, when we further limited to the three highest-scoring "any infection site" studies—as would likely be required in the absence of infection-site-specific modeling—the relevance scores decreased substantially. To further evaluate the validity of our assumption that the included studies can be generalized to the full U.S. population of AMR patients, we determined the extent of agreement among estimates we assumed to be comparable, because differences in study populations would tend to introduce disagreement between estimates. The mean standard deviation across "comparable" mortality estimates (i.e., a single combination of pathogen, drug, and infection site) ranged from less than two percent (fluoroquinolone-resistant *K. pneumoniae* and third-generation cephalosporin-resistant *P. aeruginosa*) to over 15 percent (MDR *A. baumannii* and carbapenem-resistant *E. coli*).

Combining these factors led to an overall score for each pathogen-drug combination (see, Table 15 and Figure 16). There are no clear patterns of specific pathogens or drugs that earn higher versus lower overall scores, although MDR tends to appear lower on the scale—possibly due to wider variations in the definition and type of MDR—and carbapenem-resistance tends to appear higher on the scale.

While we have focused on resistant-strain data to characterize the pathogen-drug combinations more comprehensively, susceptible-strain data are also needed to generate estimates or projections of attributable mortality and attributable LOS. All of the issues identified above for resistant-strain data are compounded for susceptible-strain data, which are reported 30 percent less frequently in our included studies.

## 5.3 POSSIBLE PUBLICATION BIAS

In 5.1, we presented statistics on the overall state of literature available for modeling AMR burden in the U.S. In 5.2, we compared the 15 pathogen-drug combinations to assess relative capacity for national burden modeling. Next, in 5.3, we consider the extent to which estimates might be affected by publication bias. While Serra-Burriel et al. (2020) found evidence of publication bias in the case of MDR mortality (see section 2.6), our analysis of carbapenem-resistant *A. baumannii* and carbapenem-resistant *P. aeruginosa* does not provide strong evidence of that same finding.

As a case study, we analyzed the possibility for publication bias in three pathogen-drug-infection combinations. In general, publication bias is assumed to impact smaller studies, because large, well-funded studies often enjoy high rates of publication given the magnitude of their investment and likelihood of achieving statistically significant results (even by virtue of sample size alone). On the other hand, smaller studies—while often focused on important or under-studied topics—may contain larger standard errors and wider confidence intervals. This can lead to an effect where, among small studies, only those with aberrantly large effect sizes achieve statistical significance and are more likely to be published.

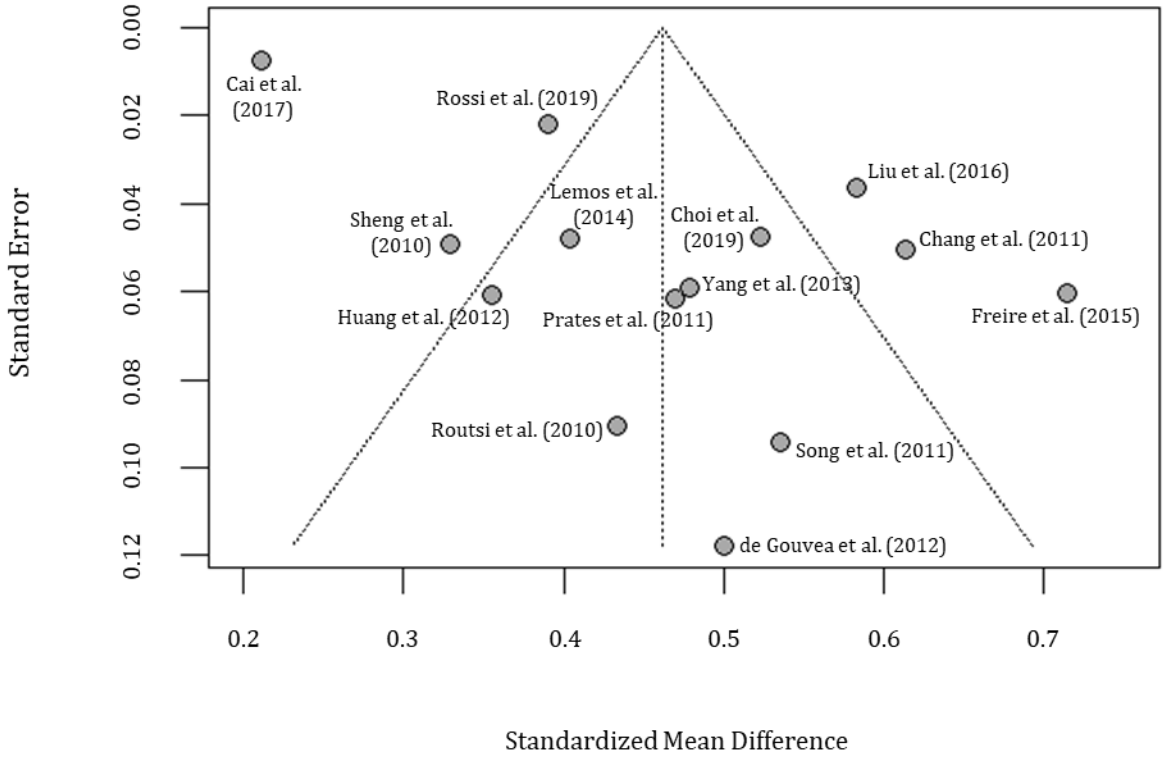
Exploratory modeling revealed that standard error was positively associated with resistant-strain mortality. That is, studies with more uncertainty also tended to report higher mortality rates. Given this initial finding—along with the fact that Serra-Burriel et al. (2020) detected evidence of potential publication bias among mortality estimates—we performed similar analyses as Serra-Burriel et al. (2020) for three pathogen-drug-infection site combinations with sample sizes large enough ($n \geq 10$) to generate funnel plots and perform Egger's regression test for funnel plot asymmetry. A funnel plot is a graph of effect size[33] against SE for a variety of publications that all

[33] In this case, the effect size refers to the study's estimated resistant-strain mortality.

estimate a common quantity. In the absence of publication bias, these graphs generally form a funnel shape. The studies with low SE tend to be closely clustered around a common mean at the top of the graph, and as SE increases (moving down the y-axis), estimates become more dispersed around the common mean. However, publication bias can selectively remove studies with high SE but low effect sizes (i.e., sometimes viewed as uninteresting, non-statistically significant results), thereby removing data points from the bottom-left portion of the plot. This can create the asymmetry characteristic of publication bias.[34]

Our analysis controlled for infection site given its impact on mortality rates. The three pathogen-drug-infection site combinations we analyzed are carbapenem-resistant *A. baumannii* (any infection site), carbapenem-resistant *A. baumannii* (BSI), and carbapenem-resistant *P. aeruginosa* (BSI). Their funnel plots are shown below in Figure 18, Figure 19, and Figure 20.

**Figure 18. Funnel Plot for Carbapenem-Resistant *A. baumannii* (Any Infection Site)**




[34] It is important to note that there can be other causes of the asymmetry, aside from publication bias.

**Figure 19. Funnel Plot for Carbapenem-Resistant *A. baumannii* (BSI)**

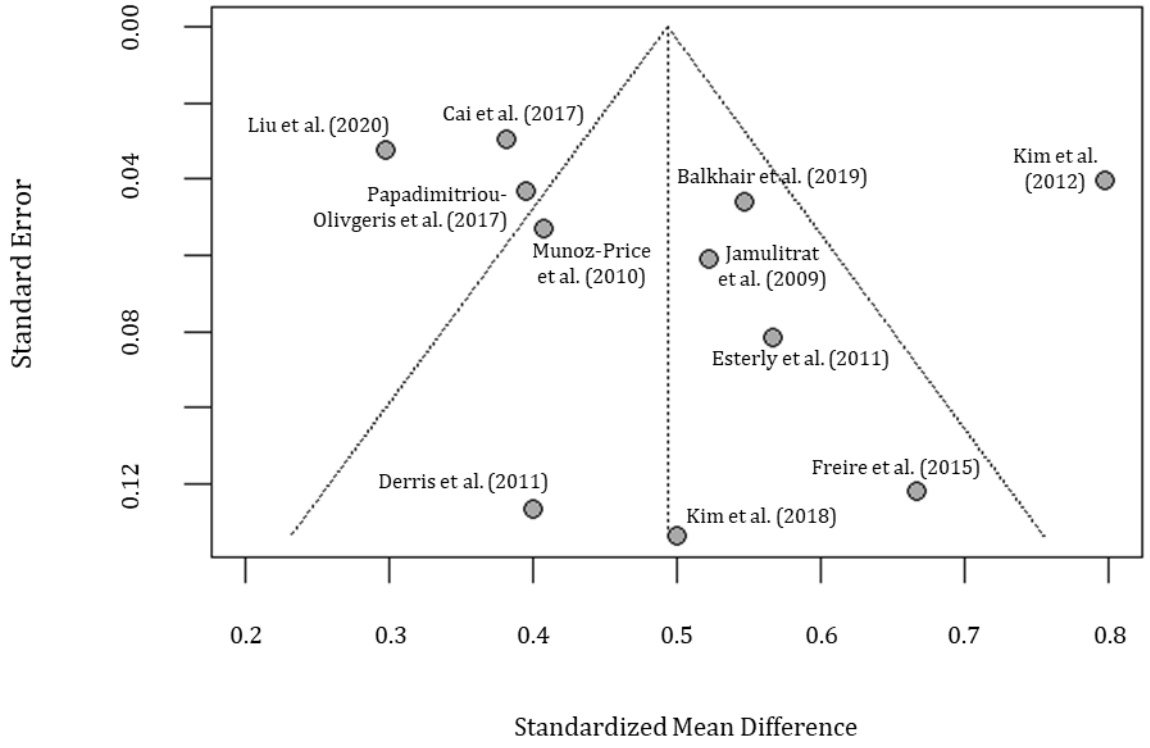
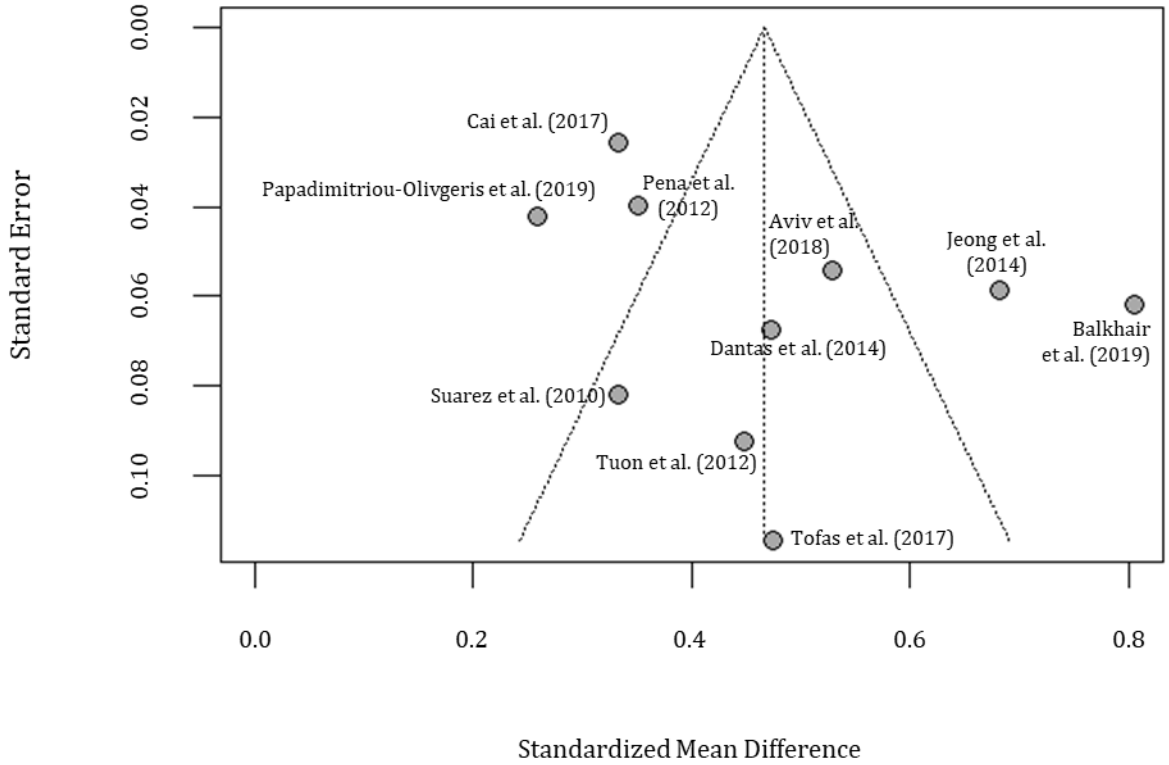



**Figure 20. Funnel Plot for Carbapenem-Resistant *P. aeruginosa* (BSI)**



While the funnel plots have some deviations from the ideal symmetric shape, they do not display the typical pattern associated with publication bias. While studies with high standard error appear to be published less frequently, they are not skewed toward large effect sizes. Egger's regression test showed that carbapenem-resistant *A. baumannii* (any infection site) does have a statistically significant asymmetry, with a bias of $5.5 \pm 1.1$ (estimate $\pm$ SE) and a p-value of 0.0002. Although the results are statistically significant, they are strongly influenced by the estimate from Cai et al. (2017), which was one of the higher-scoring studies we found. Excluding the estimate from Cai et al. caused the p-value to rise above 0.05.

For carbapenem-resistant *A. baumannii* (BSI) and carbapenem-resistant *P. aeruginosa* (BSI)—shown in Figure 19 and Figure 20—Egger's regression test revealed positive but nonsignificant bias, with p-values of 0.407 and 0.139, respectively. This indicates that, while some asymmetry exists, it is not statistically significant at a significance level of $\alpha = 0.05$.[35]

For the statistically significant finding of carbapenem-resistant *A. baumannii*, other possible sources beyond publication bias may explain the asymmetry. For example, it may be the case that smaller studies were simply performed in settings or regions where mortality truly is higher.

## 5.4 OTHER MODELING PARAMETERS AND CONSIDERATIONS

The foregoing analysis in Sections 5.1, 5.2, and 5.3 focused primarily on two critical modeling parameters that were emphasized in the literature review, resistant-strain mortality and resistant-strain LOS. However, additional parameters are needed to estimate or project AMR burden based on literature. In this section, we focus on literature-related issues that complicate estimation for these other modeling parameters.

### 5.4.1 Infection Sites

Analysis of the included literature focused on four infection sites that we deemed particularly important for AMR burden modeling: BSI, UTI, SSI, and pneumonia. These four types represent a substantial majority of publications we found. When excluding multiple or unknown infection sites ("any infection site," "other infection site," and "undetermined" cases), BSIs, UTIs, SSIs, and pneumonia make up 88 percent of estimates based on a single, specified infection. Thus, modeling these four sites may be sufficient for capturing a substantial majority of infection-site-specific variation in mortality and LOS.

Nevertheless, while literature has focused on BSI, UTI, SSI, and pneumonia, other infection sites contribute to the total AMR burden. These other infection sites must be quantified to capture the full public health and economic impact of AMR in the U.S. For example, the literature we reviewed also included estimates for intra-abdominal infections, sterile body fluids infections, wound infections (both superficial and deep), biliary tract infections, fungal infections, genital tract infections, and skin or soft tissue infections, among others. While it is not feasible to estimate or project attributable mortality and attributable LOS for every one of these infection sites, modeling efforts may need to characterize the prevalence of other infection sites and apply generic rates in order to approximate their contributions.

### 5.4.2 Community-Acquired Infections vs. Healthcare-Associated Infections

The literature review and analysis focused on data about healthcare-associated infections. However, as discussed previously, major differences in outcomes for community-acquired infection can exist. Typically, healthcare-associated infections incur higher raw costs (Roberts, et al., 2009) and produce worse clinical outcomes (Cosgrove, et al., 2002). However, this is an area that requires further study, as confounders can greatly impact findings. Neidell et al. (2012) showed that,

[35] The three p-values presented in this passage are unadjusted.

because healthcare-associated infections affect populations possessing far more risk factors, adjusting for confounders caused community-acquired infections to have *greater* excess costs, attributable LOS, and attributable mortality than healthcare-associated infections.

For example, using an uncensored linear model, Neidell et al. (2012) estimated excess hospital charges to be $8,200 for healthcare-associated infections, compared to $24,000 for community-acquired infections. They also estimated attributable LOS to be 1.1 days for healthcare-associated infections, compared to 2.8 days for community-acquired infections. While these values depend heavily on the pathogen, drug resistance, and infection site being studied, Neidell et al. (2012) showed that the impact of an adjusted analysis can reverse the associations between clinical setting and excess values.

These differences likely warrant separate modeling approaches. This is particularly true given that many studies focus on a single clinical setting, with many studies being conducted in hospitals. Estimates of attributable mortality or attributable LOS generated from these studies likely do not represent the AMR burden associated with community-acquired infections.

### 5.4.3 Representativeness of Study Populations

In some cases, studies were very clearly focused on narrow populations that do not generalize to the broader U.S. population. Issues of representativeness can pose major threats to the validity of estimates for modeling AMR burden in the U.S..

For example, Freire et al. (2015) performed a prospective cohort study on carbapenem-resistant *A. baumannii* (CRAB) among liver transplant patients in Brazil. Participants of the study acquired the infection prior to transplantation, and the health endpoint was 60-day mortality. Those with the resistant strain experienced a mortality rate 46.4 percent higher than the susceptible group—a result that was statistically significant. Freire et al. (2015) also reported the resistant-strain mortality for several infection sites, presented in Table 16 with 95 percent confidence intervals.[36] For comparison, Table 16 also shows the mean CRAB mortality reported by other studies on the same pathogen, drug resistance, and infection site.

**Table 16. Comparing CRAB Estimates by Freire et al. (Post-Liver Transplant Patients) to Other Studies**

| Infection Site | Freire et al. CRAB Mortality Estimate | 95% CI for Freire et al. Mortality Estimate | Mean CRAB Mortality Among Other Studies [a] | Difference between Freire et al. and Other Studies |
|---|---|---|---|---|
| Any | 71% | (58%, 83%) | 47% | +24% |
| BSI | 67% | (38%, 88%) | 48% | +19% |
| PNE | 58% | (33%, 80%) | 41% | +17% |
| SSI | 50% | (27%, 73%) | Not available [b] | Not available |
| UTI | 0% [c] | Not available | 17% | -17% |

[a] For "any infection site," the other available studies are Choi et al. (2019), de Gouvêa et al. (2012), Henig et al. (2015), Huang et al. (2012), Lemos et al. (2014), Liu CP et al. (2016), Nutman et al. (2014), Prates et al. (2011), Routsi et al. (2010), Sheng et al. (2010), Song et al. (2011), Yang et al. (2013), Chang et al. (2011), and Cai et al. (2017). For BSI, the other studies were Balkhair et al. (2019), Esterly et al. (2011), Kim SY et al. (2012), Liu Y et al. (2020), Munoz-Price et al. (2010), Papadimitriou-Olivgeris et al. (2017), Deris et al. (2011), Jamulitrat et al. (2009), and Cai et al. (2017). Kim YJ et al. (2018), discussed below as another special case, was excluded from the BSI other-study estimate. For pneumonia (PNE), the other available studies are Choi et al. (2019), Zheng et al. (2013), and Cai et al. (2017). For UTI, the other available studies are Choi et al. (2019) and Cai et al. (2017).
[b] Other studies were not available with estimates of CRAB mortality among SSIs patients.

[36] 95 percent confidence intervals were computed using the Clopper-Pearson method.

[c] Freire et al. reported all results, including this UTI outcome, which had a sample size of 1. As the estimate is 0 percent, standard error cannot be reliably estimated.

As another example, Chaves et al. (2017) studied blood marrow transplant patients in Brazil with carbapenem-resistant *P. aeruginosa* (CRPA). Among patients with BSIs, Chaves et al. (2017) reported CRPA mortality of 79.0 percent, which is 32.1 percent above the mean mortality of 46.9 percent from other available CRPA BSI studies.[37] As a final example, Kim YJ et al. (2018) studied CRAB among individuals with BSIs in Korea who underwent living donor liver transplantation. Kim YJ et al. (2018) showed that the CRAB mortality among its BSI subjects was 50.0 percent, which is extremely close to the mean estimate of 49.8 percent from other CRAB BSI estimates.[38]

When selecting studies for AMR modeling purposes, the original intent and study population must be evaluated to determine representativeness for the broader population of AMR patients.

In a study on the global burden of AMR, Pezzani et al. (2021) developed methodologies for evaluating representativeness, which potentially could be adapted to our purposes to aid in analyzing studies' generalizability from their original purpose to the task of modeling the economic burden of AMR. For cohort studies, Pezzani et al. (2021) assessed whether the exposed cohort and non-exposed cohort were drawn from the same community. For case-control studies, Pezzani et al. (2021) considered whether cases were drawn consecutively, the extent of potential selection bias, and whether community controls or hospital controls were used. For both study designs, they reviewed the quality of records that were used to determine whether the participant experienced exposure.

# 6 CONCLUSION

We found that a variety of factors complicate modeling of current as well as future AMR burden. Long-term trends, particularly the efficacy of strategies for combatting AMR, can have potentially large impacts on drug resistance but are difficult to predict. Foundational modeling parameters such as LOS are not consistently defined in literature. Attributable values (of mortality and LOS) must be calculated relative to a counterfactual group, but there is disagreement on whether the counterfactual should be the susceptible strain or the no infection case. Secondary burden can be substantial but it is difficult to fully quantify. Hence, it is not as well-understood.

In general, the parameters that would be used to model AMR burden vary widely across infection site and healthcare setting, for example, with BSI infections having higher mortality rates than UTI infections. Healthcare-associated infections are generally associated with higher attributable mortality and higher attributable LOS than community-acquired resistant infections. However, adjusting for confounders such as age and comorbidities can affect the results, as hospital patients tend to be older with more risk factors than patients in community settings. While building an AMR model to account for these differences in outcomes across infection site and healthcare setting would improve the model's accuracy, it also rapidly increases the number of parameters that must be estimated. This poses a challenge, as we found there are often insufficient

[37] The other available studies for CRPA, BSI are: Aviv et al. (2018) , Balkhair et al. (2019), Jeong et al. (2014), Peña et al. (2012), Suárez et al. (2010), Tofas et al. (2017), Tuon et al. (2012), Dantas et al. (2014), Papadimitriou-Olivgeris et al. (2019), and Cai et al. (2017).

[38] The other available studies for CRAB, BSI are: Balkhair et al. (2019), Esterly et al. (2011), Kim SY et al. (2012), Liu Y et al. (2020), Munoz-Price et al. (2010), Papadimitriou-Olivgeris et al. (2017), Deris et al. (2011), Jamulitrat et al. (2009), and Cai et al. (2017). Freire et al. (2015) was excluded as it was identified as having a nonrepresentative study population.

data to estimate or project all of the required parameters. For example, while BSIs are well-studied, other common infection sites (particularly UTIs, SSIs, and pneumonia) are not as frequently studied. None of the 15 pathogen-drug combinations contained enough data to estimate or project AMR burden by these four distinct infection sites.

We inspected four study components that can impact a study's relevance to AMR burden modeling: region, year when enrollment was closed (i.e., the age of the underlying data), precision of estimates, and study design. Region generally appeared to have the largest impact on a study's reported estimates than the other three factors, and this is likely due to regional differences in AMR rates; studies conducted in a region with different healthcare practices may be estimating a fundamentally different quantity from U.S. AMR rates. When evaluating trends over time, literature relating to AMR burden parameters has been consistent since 2007. U.S. studies tended to have good precision and used a cohort design more frequently than any other study design. In general, data on mortality was far more abundant than data on LOS. Furthermore, LOS data were reported inconsistently (sometimes as a mean and in other instances as a median). Often, range information was not reported at all for LOS, making it difficult to estimate adequately the uncertainty associated with LOS—and consequently, any models based on that parameter.

When comparing the relative strength of literature across different pathogen-drug combinations, several patterns appeared. *E. aerogenes/E. cloacae* tends to receive the least research attention across the drug types, while *A. baumannii* and *K. pneumoniae* were found to have the most publications. Among the drug resistances, carbapenem is studied most, and fluoroquinolone is studied least. However, further analysis showed that the number of studies does not necessarily imply that they are highly relevant to modeling the AMR burden in the U.S.

Using the extracted study information, we computed an overall total score for each pathogen-drug combination. We found that third-generation cephalosporin-resistant *E. coli*, third-generation cephalosporin-resistant *K. pneumoniae*, and carbapenem-resistant *P. aeruginosa* had the highest scores (suggesting better capacity for AMR burden modeling). MDR *K. pneumoniae* and MDR *E. aerogenes/E. cloacae* had the least literature to support models of AMR burden in the U.S.

We found that there is wide variation in AMR rates across infection sites, pathogens, and AM drug resistance. Existing studies generally do not provide the necessary data for modeling specific infection sites or for modeling all pathogen-drug combinations. Overall, we found that literature is likely an insufficient data source for modeling the full economic burden of AMR in the U.S., as estimates from literature are rarely generated with this purpose in mind, leading to limitations in applicability and generalizability. However, other data sources may exist for estimating parameters (e.g., electronic health records and, potentially, CMS claims data).

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# A APPENDIX – AMR SURVEILLANCE SYSTEMS

## A.1 U.S. SURVEILLANCE

In the U.S., most antimicrobial resistance tracking is managed by the Centers for Disease Control and Prevention (CDC). CDC manages a network of laboratories, the AR lab network, in 50 states and Puerto Rico that uses modern technology to detect antimicrobial resistance and prevent its spread (CDC, 2020).

CDC's National Healthcare Safety Network (NHSN) "is the nation's most widely used healthcare-associated infection tracking system," serving about 25,000 medical facilities (CDC, 2021). NHSN includes data on antibiotic resistance, outpatient antibiotic use, hospital antibiotic stewardship, healthcare-associated infections, and data from public health laboratories. CDC's Antibiotic Resistance & Patient Safety Portal currently provides National Healthcare Safety Network antimicrobial resistance data from 2011 to 2020 and healthcare-associated infection data from 2015 to 2021. Data are gathered from individual facilities so they can be used to track these metrics at different levels (e.g., facility-, state-, or national-level). The NHSN also tracks prescriptions for individual drugs to assess trends in prescription levels. Antibiotic resistance and healthcare-associated infection data also include hospital type and associated event (e.g., SSIs, catheter-associated UTIs, and central line-associated BSIs). The hospital antibiotic stewardship data provide information on inpatient antibiotic stewardship in acute care hospitals from 2014 through 2019, tracking individual elements of the programs (CDC, n.d.).

Additional surveillance systems include CDC's Emerging Infections Program, which includes components focused on identifying, understanding, and responding to emerging infections, including monitoring for healthcare-associated infections (CDC, 2022a). Information on all tuberculosis cases, including drug resistance, in the U.S. is monitored through CDC's National Tuberculosis Surveillance System (Centers for Disease Control and Prevention, 2022b). Enteric (intestinal) bacteria are tracked through the National Antimicrobial Resistance Monitoring System for Enteric Bacteria, under a coordinated effort by CDC, Department of Agriculture, Food and Drug Administration, and state and local health departments. NARMS monitors AMR among enteric bacteria in humans, meat, and food animals (CDC, 2022c).

## A.2 OTHER SURVEILLANCE

Trends and emerging AMR infections in other countries are relevant to the U.S., as infections can spread rapidly across the globe. Trends in AMR may be driven by local conditions, but monitoring global trends provides clues as to what problems could arise in the U.S. In 2015, the World Health Organization (WHO) launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS). GLASS collaborates with and supports regional AMR surveillance networks including networks in Europe, Latin America, Central Asia, and the Western Pacific. GLASS collects a range of data including surveillance of antimicrobial consumption, detection of emerging AMR infections, and targeted surveys and studies (World Health Organization, 2021). As of 2019, 66 countries reported data to the GLASS – AMR program, including 64,761 institutions and over two million European Antimicrobial Resistance Surveillance Network patients (Pessoa-Silva, 2020).

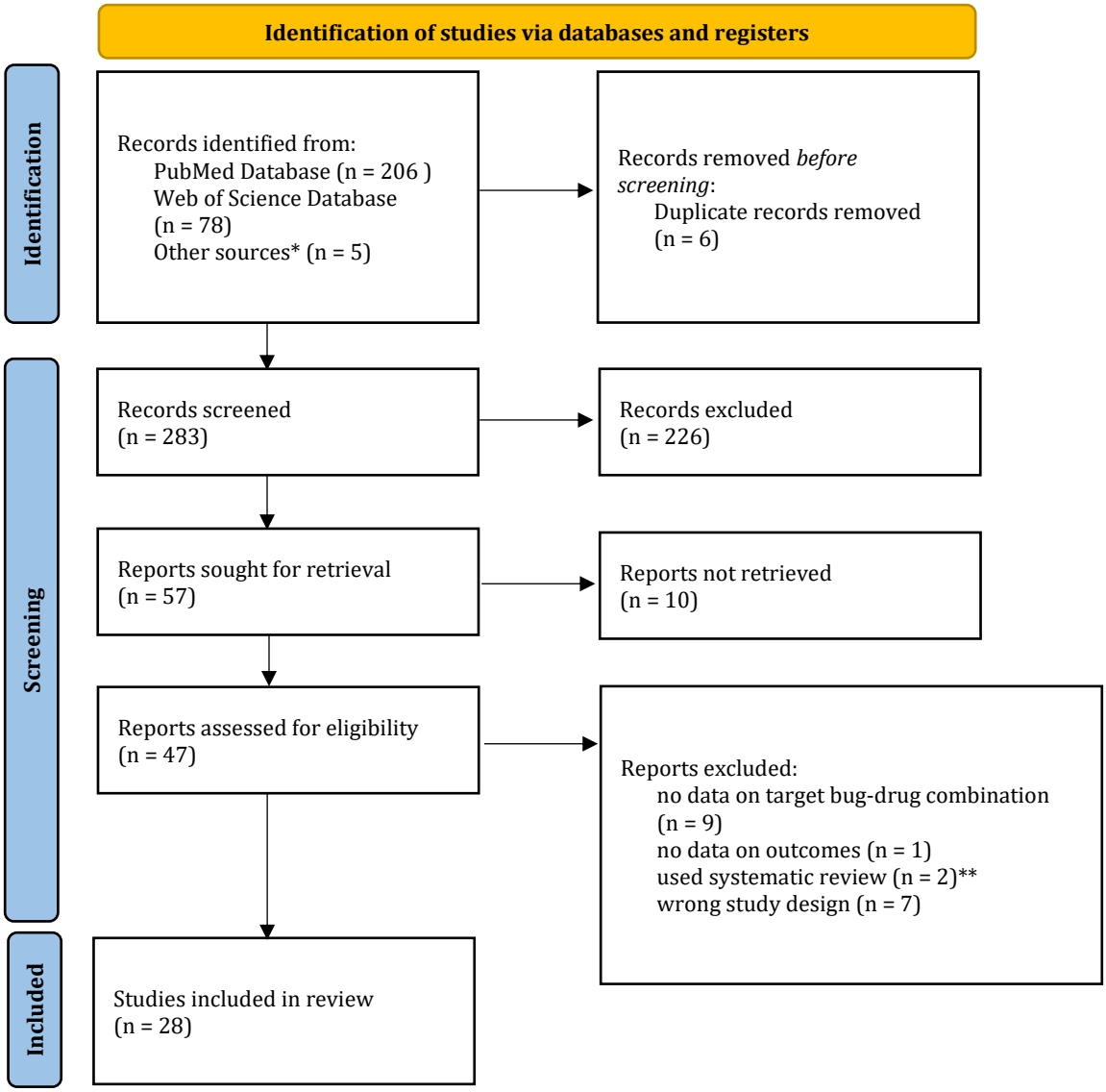
European antimicrobial resistance is tracked by the (EARS-Net). EARS-Net's predecessor was established in 1998 and became EARS-Net in 2010 (European Centre for Disease Prevention and Control, 2021). EARS-Net collects data on AMR "based on antimicrobial susceptibility testing (AST) results from invasive (blood or cerebrospinal fluid) isolates of eight bacterial species" of public health importance in Europe, including data from 30 EU and European Economic Area countries (European Centre for Disease Prevention and Control, 2020).

The Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) is a surveillance network covering all countries in the WHO European region that are not part of EARS-Net (World Health Organization Regional Office for Europe, 2021).

Some global efforts attempt to track AMR worldwide. The SENTRY surveillance system provides global surveillance via a network of medical centers in the U.S., Canada, Latin America, Europe, and Asia-Pacific. ResistanceOpen compiles surveillance data to present information on prevalence of resistance in specific pathogens in a geographic area.

# B APPENDIX – PRISMA DIAGRAMS

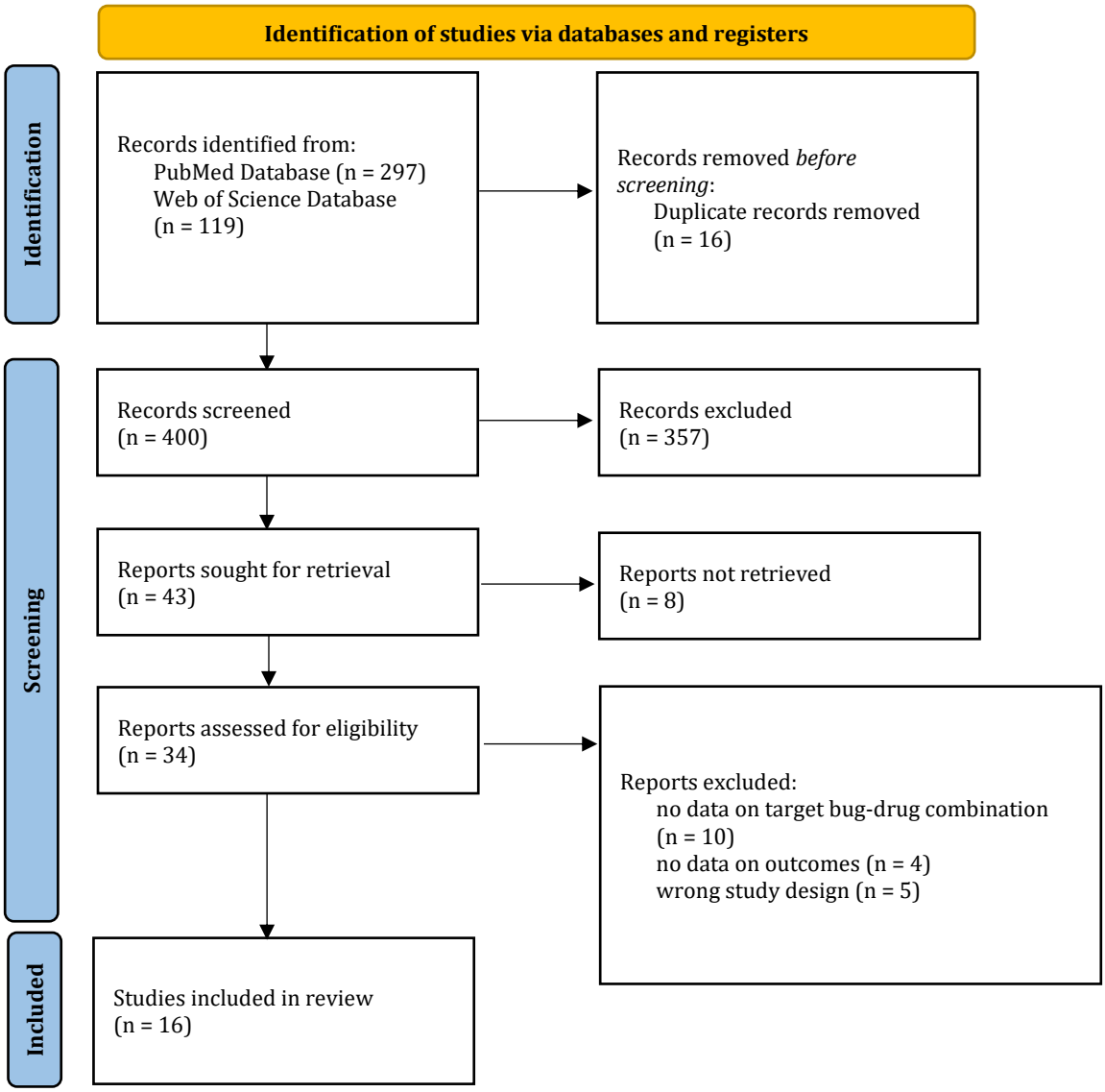
## *Acinetobacter baumannii* - Carbapenems



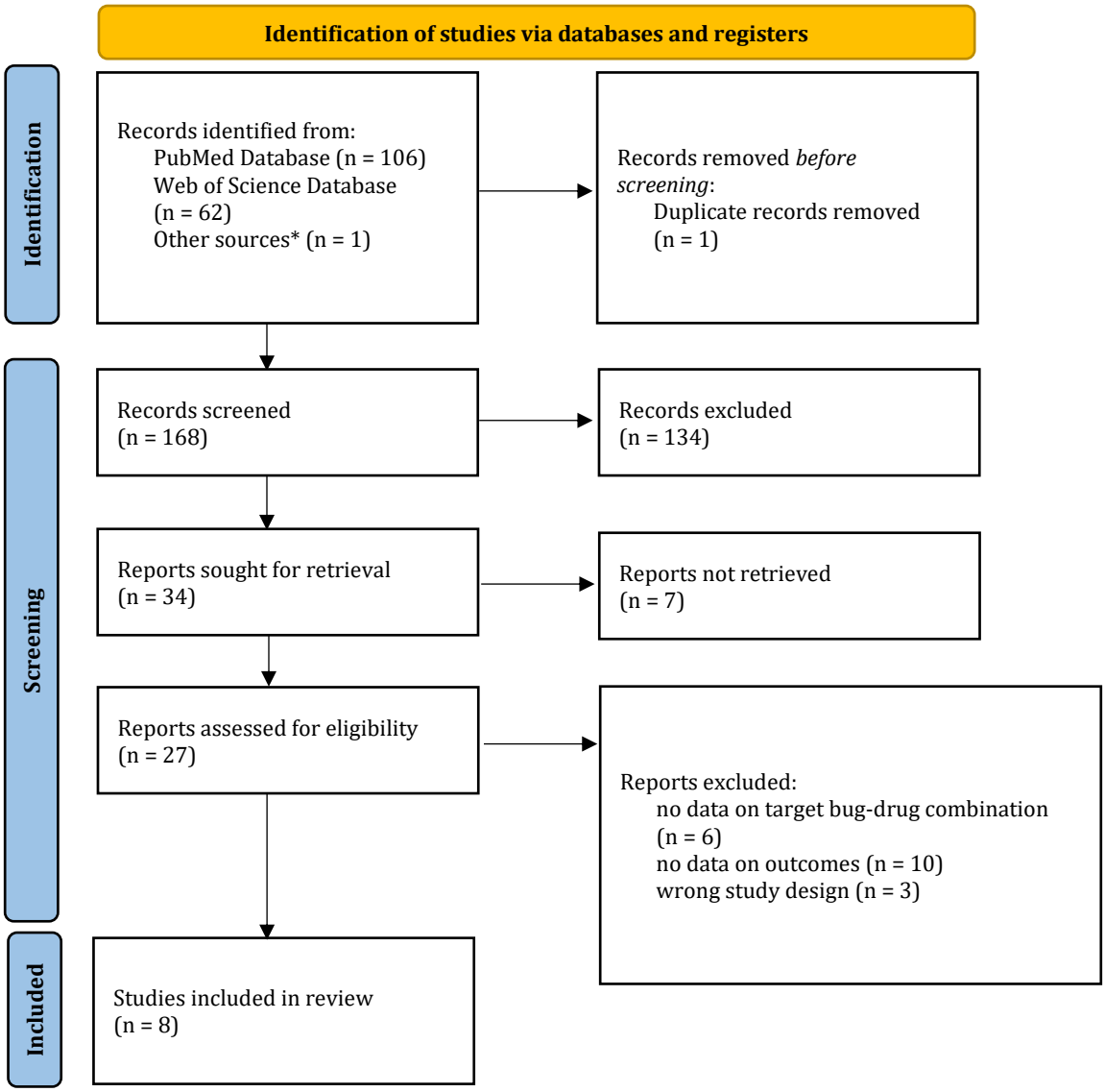

*May include studies reviewed for a different pathogen-drug combination and deemed relevant or studies from a supplementary Google search.

**No data was extracted from systematic review, but it was used to identify other studies to include.

## *Acinetobacter baumannii* – Resistant to all three classes

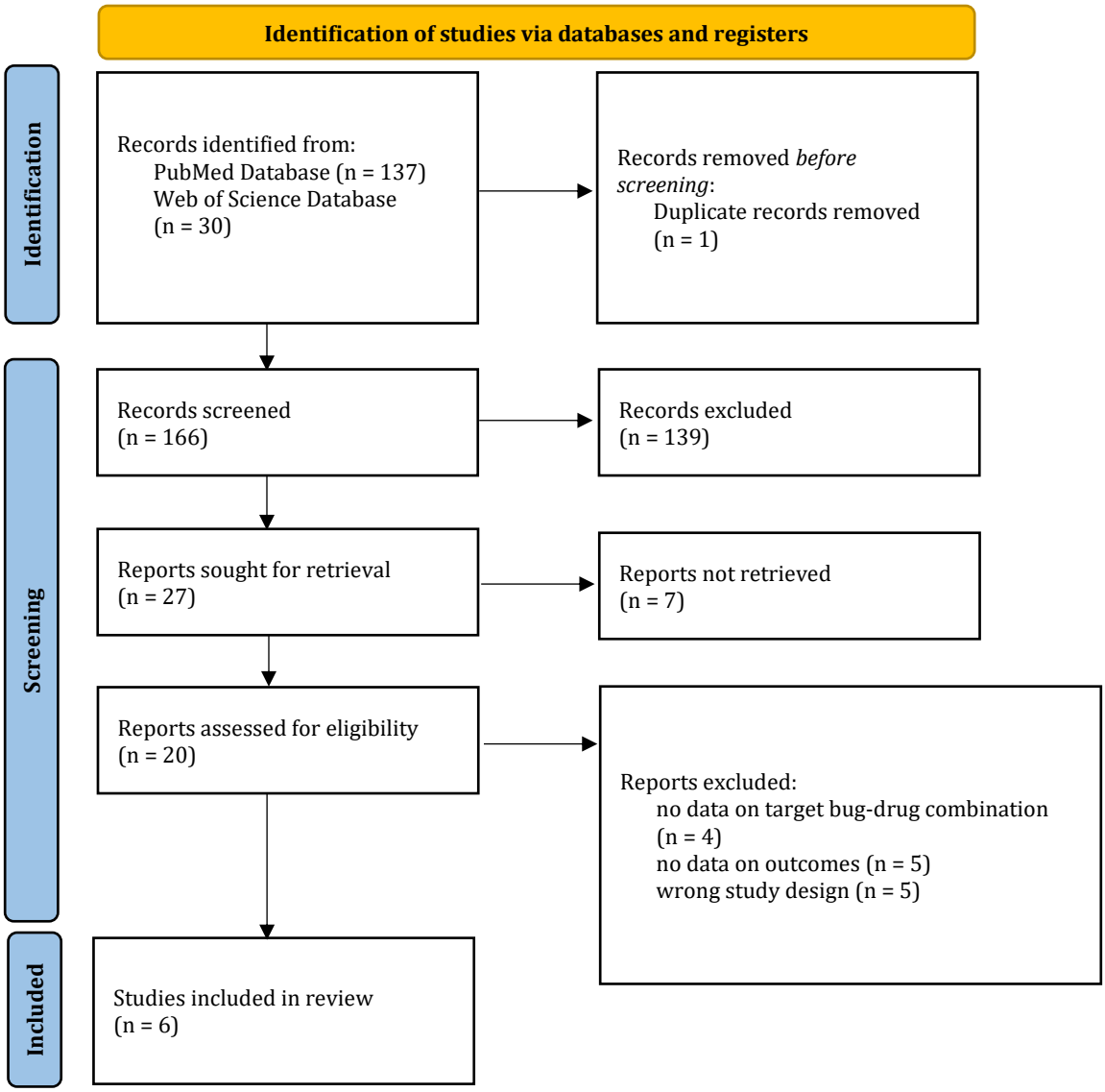


# *Escherichia coli* - Carbapenems

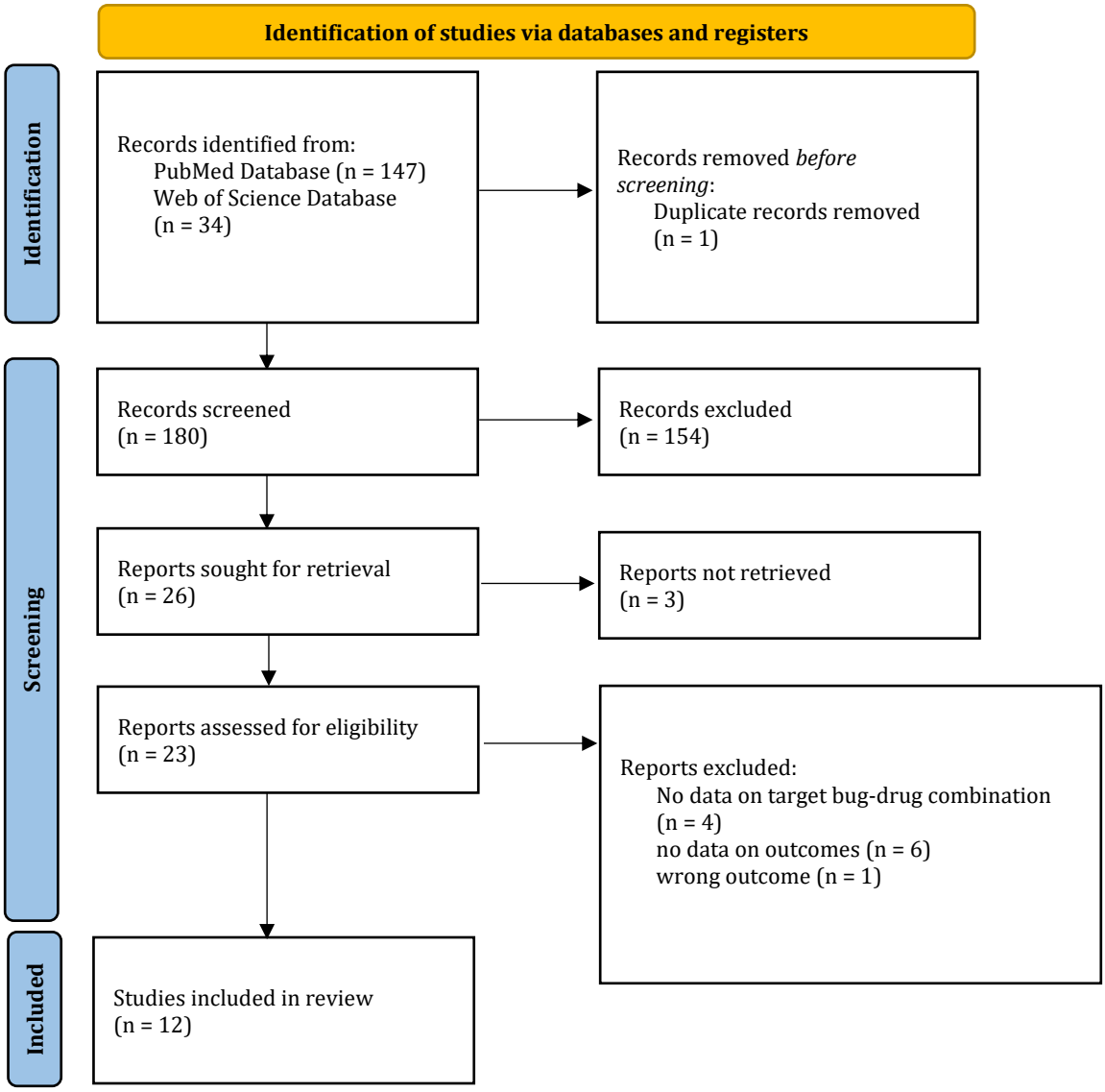



*May include studies reviewed for a different pathogen-drug combination and deemed relevant or studies from a supplementary Google search.

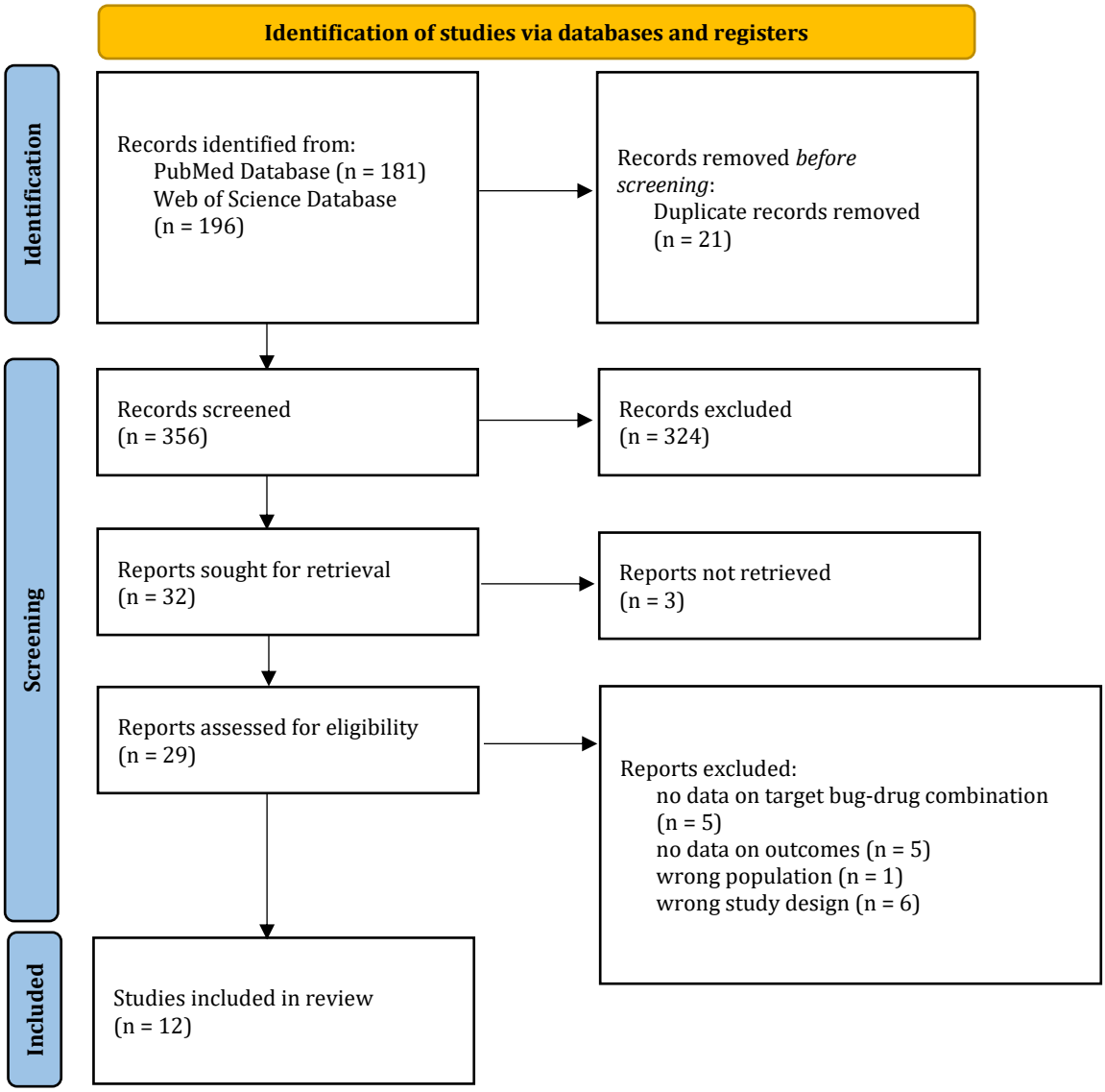
# *Escherichia coli* – Fluoroquinolones



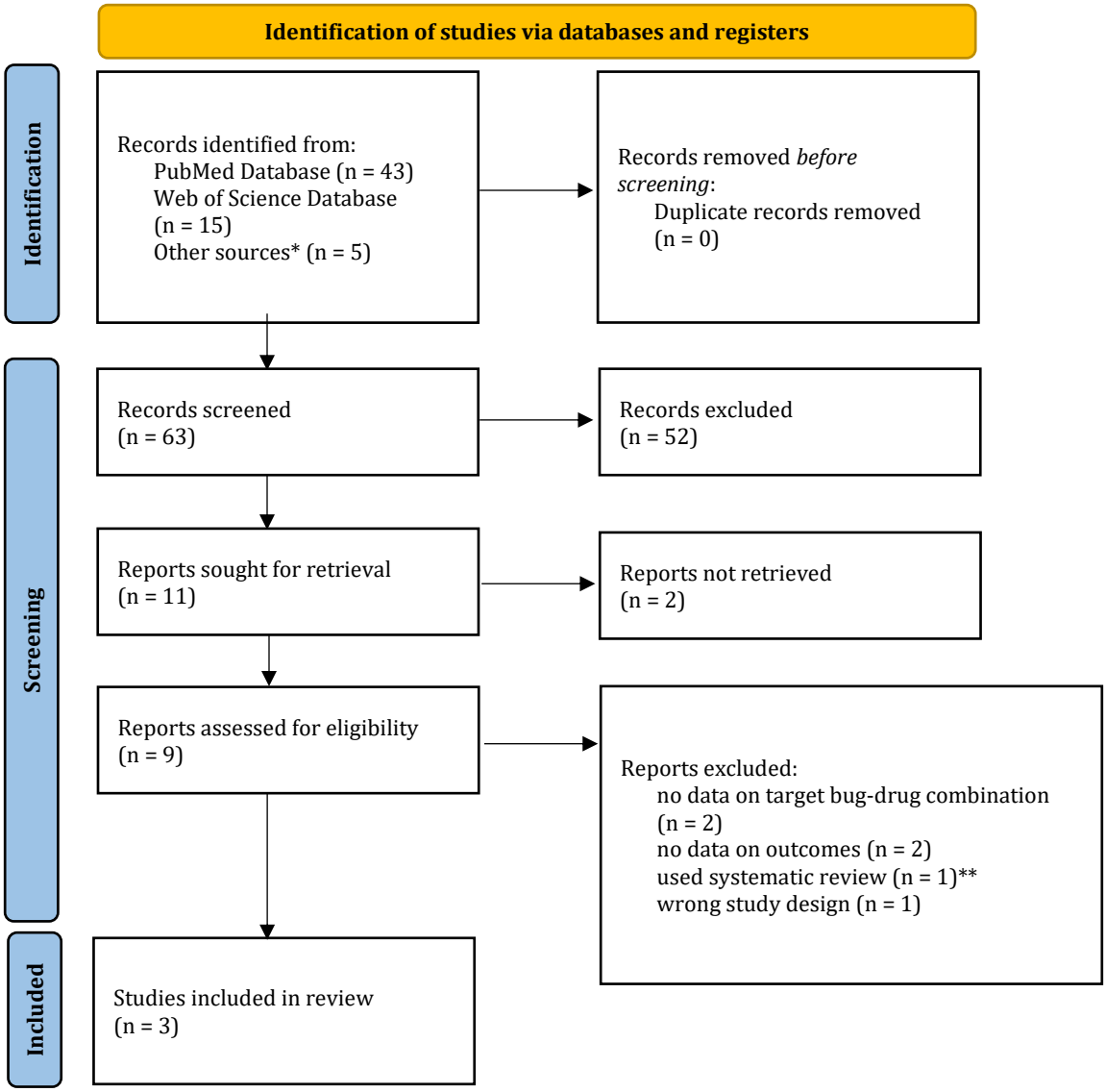
# *Escherichia coli* – 3rd Generation Cephalosporins



## *Escherichia coli* - Resistant to all three classes

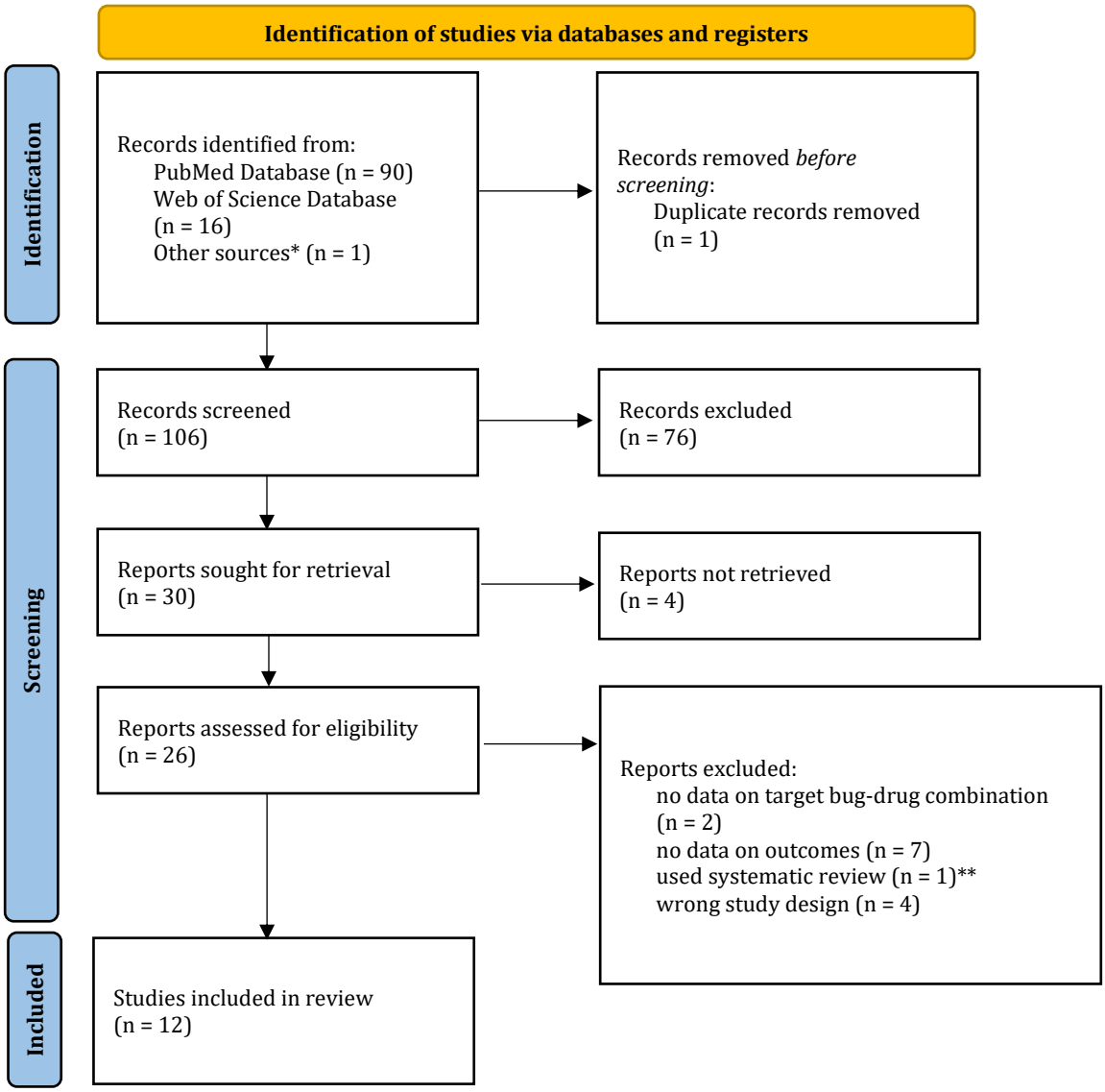


## *Klebsiella pneumonia* – Fluoroquinolones




**No data was extracted from systematic review, but it was used to identify other studies to include.

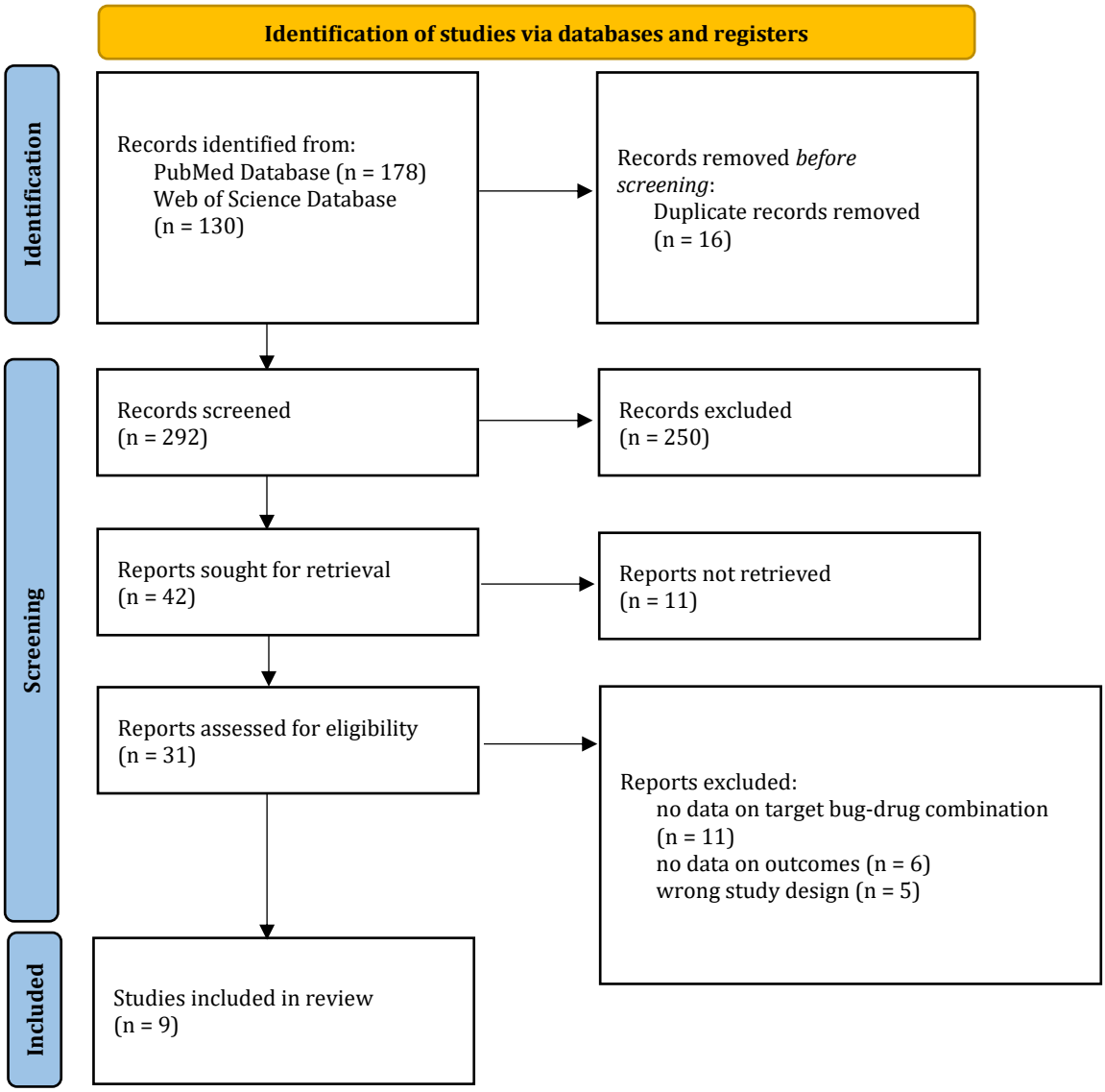
## *Klebsiella pneumoniae* – 3rd Generation Cephalosporins



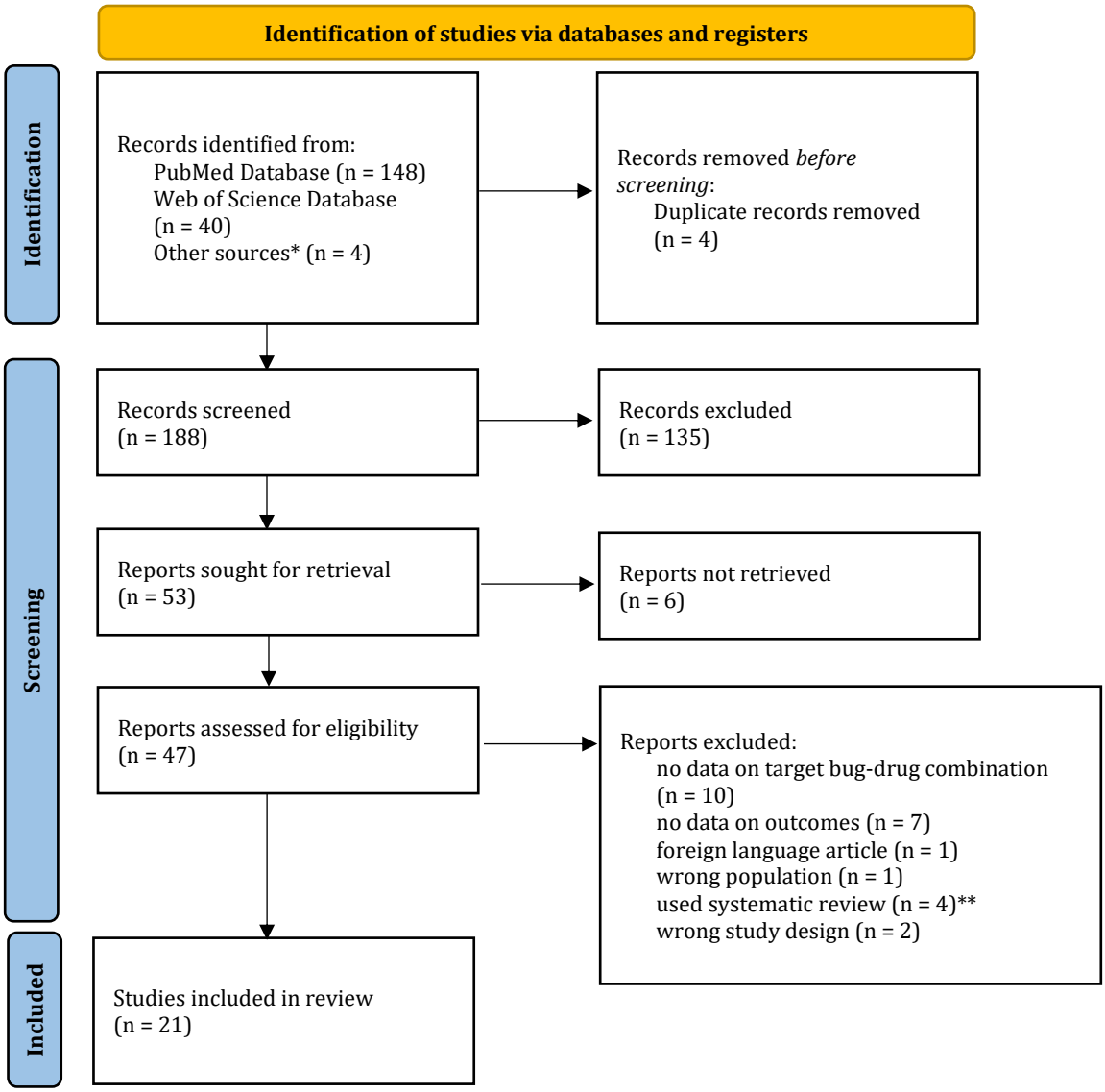

*May include studies reviewed for a different pathogen-drug combination and deemed relevant or studies from a supplementary Google search.

**No data was extracted from systematic review, but it was used to identify other studies to include.

## *Klebsiella pneumoniae* – Resistant to all three classes



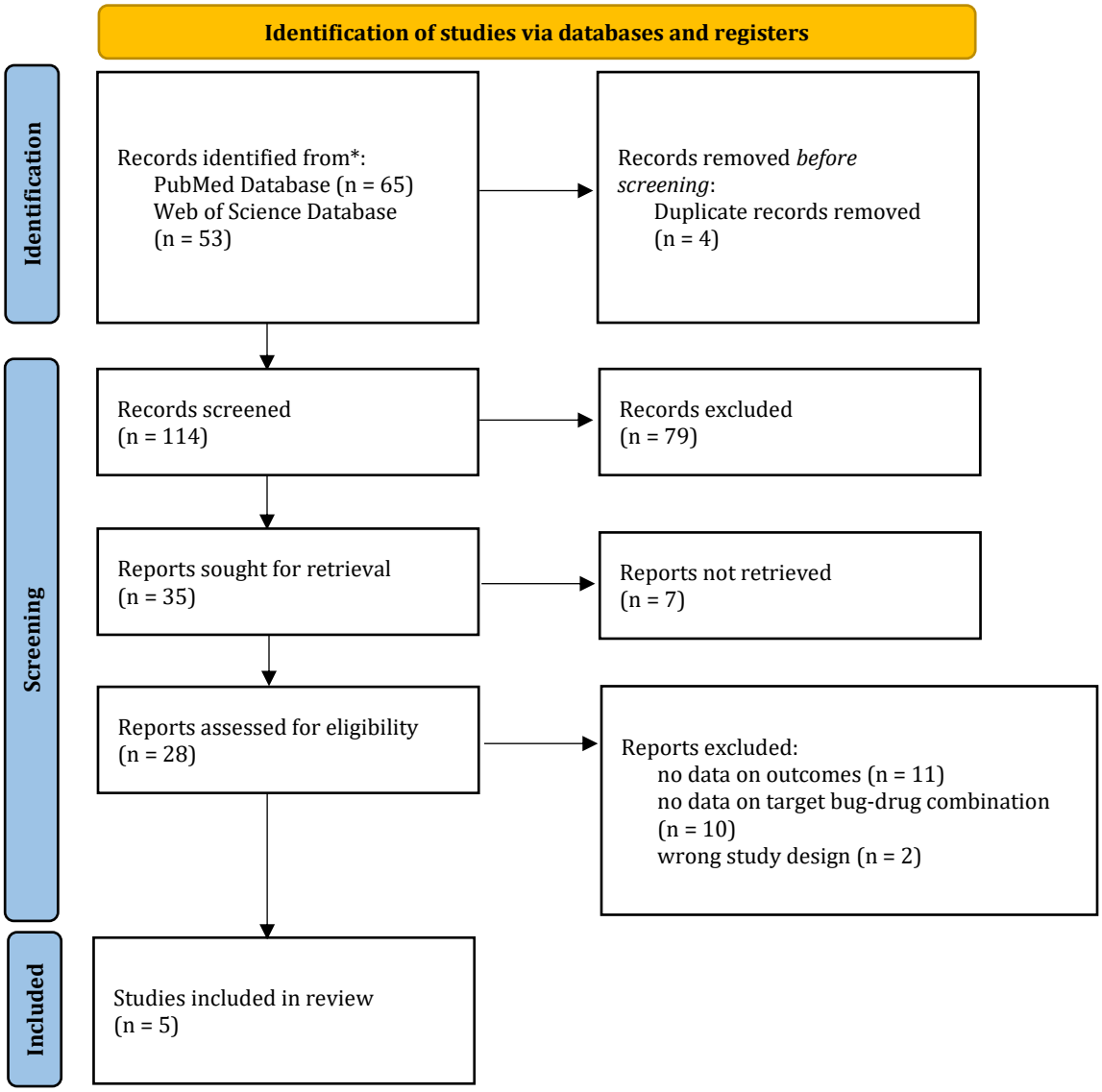
# *Pseudomonas aeruginosa* – Carbapenem



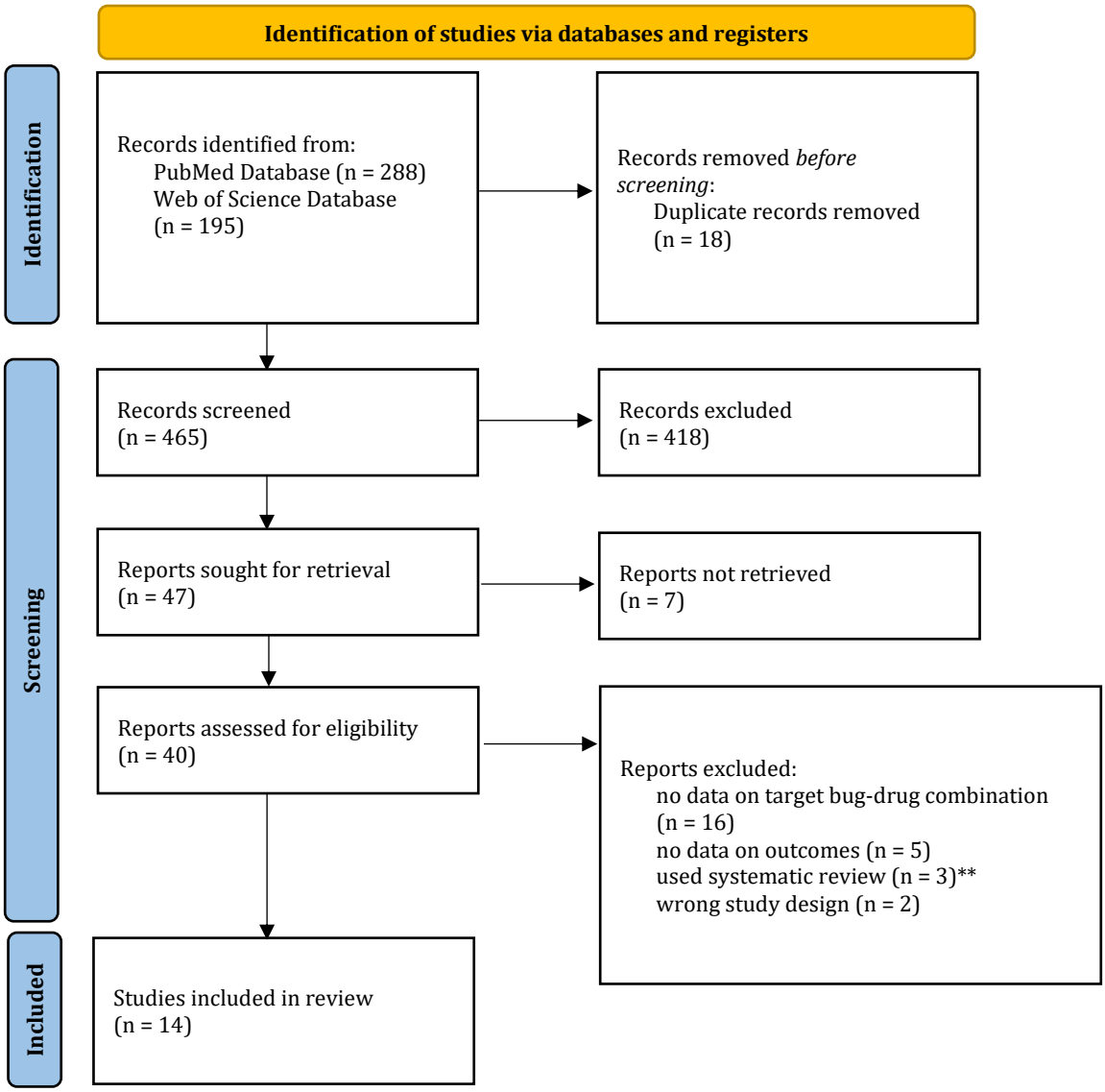

*May include studies reviewed for a different pathogen-drug combination and deemed relevant or studies from a supplementary Google search.

**No data were extracted from systematic review, but it was used to identify other studies to include.

## *Pseudomonas aeruginosa* - Ceftazidime

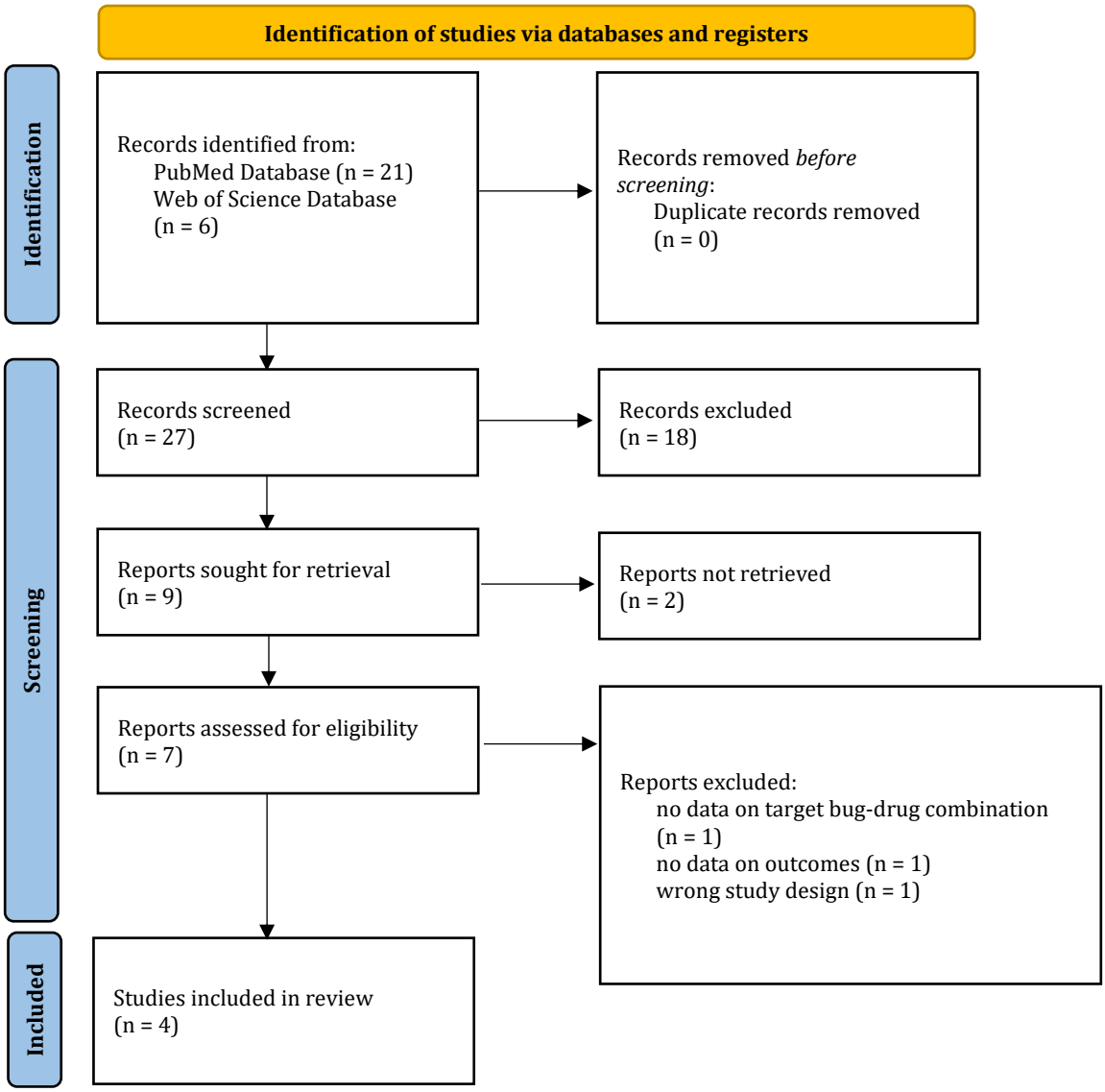


## *Pseudomonas aeruginosa* – Resistant to all three classes

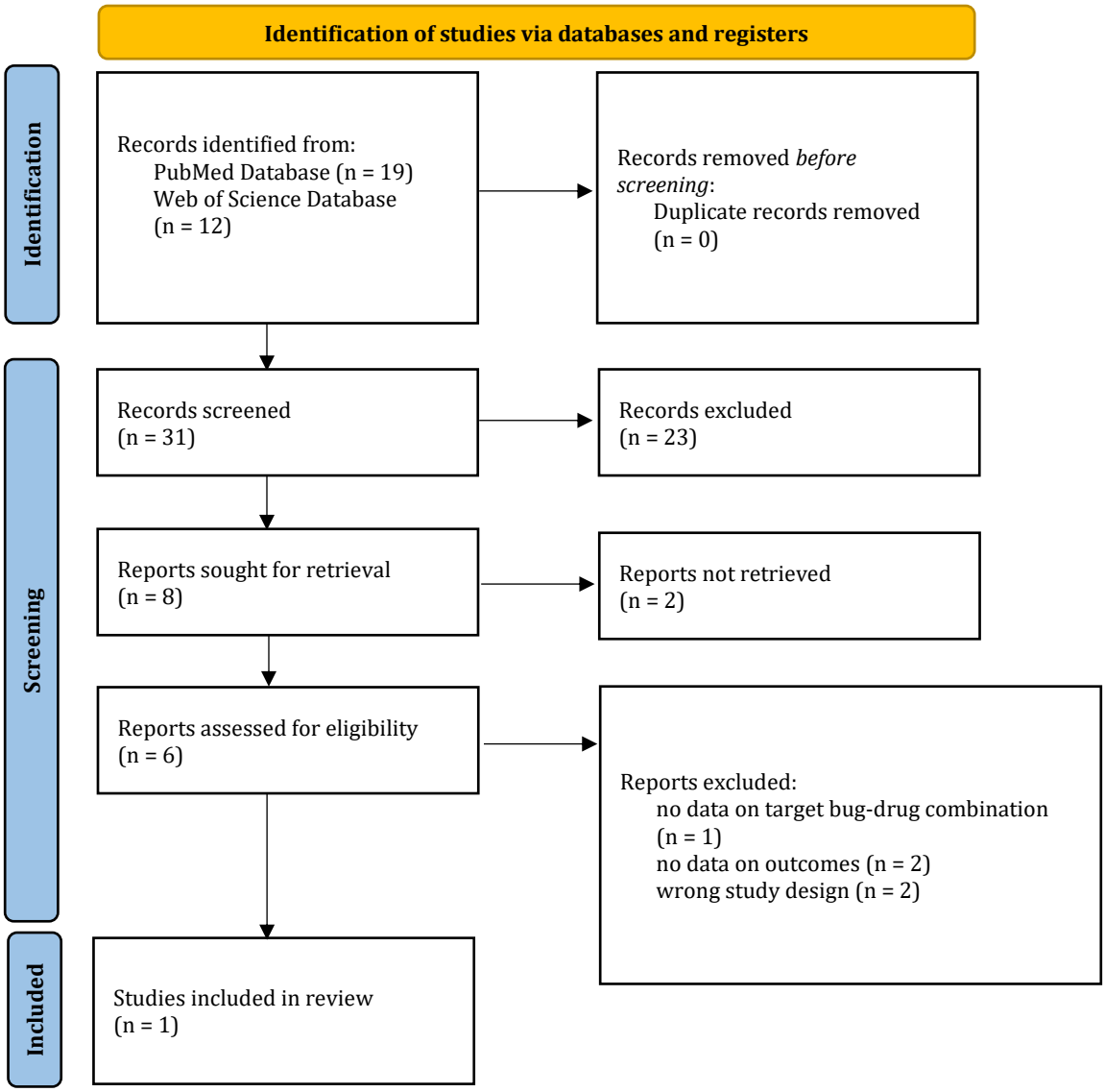



**No data was extracted from systematic review, but it was used to identify other studies to include

## *Enterobacter aerogenes/cloacae* – Carbapenems



## *Enterobacter aerogenes/ cloacae* – Resistant to all three classes



# C APPENDIX – INCLUDED STUDIES BY PATHOGEN AND DRUG

**Table C-17. General Study Information, Carbapenem-Resistant *A. baumannii***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Aydemir, et al., 2012) | Retrospective case-control study | 1/2005-12/2006 | Turkey | CLSI | Single (350-bed referral and tertiary care hospital) | Not determined | 5.5 |
| (Balkhair, et al., 2019) | Retrospective study | 1/2007-12/2016 | Oman | CLSI | Single (600 bed teaching and referral hospital) | BSI | 6.0 |
| (Baran, et al., 2008) | Prospective case-control study | 1/2004-12/2004 | Turkey | Not reported | Single (1100-bed referral and tertiary-care hospital) | Any infection | 5.0 |
| (Cai, et al., 2017) | Cohort study | 1/1/2009-12/31/2013 | U.S. | CLIA | Premier Healthcare Database | BSI; respiratory; urinary; other; any infection | 24.0 |
| (Chang, et al., 2011) | Retrospective observational study | 1/2005-12/2007 | Taiwan | Not reported | Single (2500-bed primary care facility and tertiary referral center) | VAP | 5.5 |
| (Choi, et al., 2019) | Retrospective cohort study | 1/2006-12/2016 | Korea | CLSI | Single (850-bed tertiary care-affiliated hospital) | Any infection; lungs; central venous catheter; biliary tract; central nervous system; abdomen; UTI; skin/soft tissue | 7.2 |
| (de Gouvêa, et al., 2012) | Retrospective study | 1/2002-1/2009 | Brazil | CLSI | Single | Any infection | 4.0 |
| (Deris, et al., 2011) | Cross sectional descriptive | Not Reported | Malaysia | CLSI | Single (teaching hospital) | BSI | 4.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| | and case-control study | | | | | | |
| (Esterly, et al., 2011) | Retrospective cohort study | 1/2005-12/2008 | U.S. | CLSI | Single | BSI | 18.0 |
| (Freire, et al., 2015) | Prospective cohort study | 10/2009-10/2011 | Brazil | CLSI | Single | Any infection; surgical wound/organ space; respiratory tract; BSI; skin or soft tissue; UTI | 6.2 |
| (Henig, et al., 2015) | Matched case-control study | 1/2007-8/2012 | Israel | Not reported | Database | Any infection | 6.3 |
| (Huang, et al., 2012) | Retrospective cohort study | 6/2002-12/2007 | Taiwan | CLSI | Single (veterans general hospital) | Any infection | 7.0 |
| (Jamulitrat, et al., 2009) | Retrospective cohort study | 7/2004-9/2007 | Thailand | Not reported | Single (three ICUs at 850-bed medical school, training, and referral center) | BSI | 7.0 |
| (Kim, et al., 2012) | Retrospective case-control study | 1/2008-12/2009 | Korea | CLSI | Single ICU (2000-bed university, tertiary, referral hospital with 117-bed ICU) | BSI | 7.0 |
| (Kim, et al., 2018) | Retrospective cohort study | 1/2008-4/2015 | Korea | CLSI | Single (1200-bed tertiary care university hospital) | BSI | 7.0 |
| (Lemos, et al., 2014) | Prospective cohort study | 4/2006-4/2010 | Columbia | CLSI | Multi (3 ICUs consisting of 42 beds, at 3 tertiary-care hospitals consisting of 887 beds) | Any infection | 7.5 |
| (Liu, et al., 2016) | Retrospective study | 1/2009-12/2012 | Taiwan | CLSI | Single (2200-bed tertiary teaching hospital) | Any infection | 6.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Liu, et al., 2020) | Prospective study | 1/2007-12/2016 | China | CLSI | Multi (13 tertiary-care hospitals each with over 1500 beds) | BSI | 7.0 |
| (Munoz-Price, et al., 2010) | Retrospective medical chart review | 1/2005-4/2006 | U.S. | Not Reported | Multi (4 tertiary care hospitals and a long-term acute care hospital) | BSI | 12.0 |
| (Nutman, et al., 2014) | Case-control study | 7/2008-6/2011 | Israel | CLSI | Single (1300-bed tertiary care teaching hospital) | Any infection | 5.0 |
| (Papadimitriou-Olivgeris, et al., 2017) | Retrospective case-control study | 1/2010-12/2005 | Greece | EUCAST | Single (13-bed ICU at university general hospital) | BSI | 12.0 |
| (Prates, et al., 2011) | Retrospective cohort study | 3/2006-12/2008 | Brazil | CLSI | Single (ICU at 300-bed tertiary-care hospital) | Any infection | 7.0 |
| (Rossi, et al., 2019) | Retrospective study | 1/2013-12/2017 | Brazil | Not reported | Single (530-bed teaching medical center) | BSI, respiratory tract, UTI, & SSI | 7.0 |
| (Routsi, et al., 2010) | Prospective observational study | 9/2004-1/2006 | Greece | CLSI | Single (25-bed university ICU in a 1000-bed, tertiary-care, teaching hospital for adults) | Any infection | 6.0 |
| (Sheng, et al., 2010) | Retrospective study | 5/2004-12/2006 | Taiwan | CLSI | Multi (7 medical centers that provide both primary and tertiary care, and 3 community hospitals that provide primary care) | Any infection | 4.0 |
| (Song, et al., 2011) | Retrospective study | 1/2005-12/2010 | Korea | CLSI | Single (1000-bed tertiary care university hospital) | Any infection | 4.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Yang, et al., 2013) | Retrospective study | 1/2000-12/2008 | Taiwan | CLSI | Single (2900-bed tertiary-care teaching hospital) | Any infection | 5.0 |
| (Zheng, et al., 2013) | Retrospective cohort study | 1/2006-12/2011 | China | CLSI | Single (1,500-bed referral and tertiary care hospital) | Any infection | 6.0 |

**Table C-18. Study Mortality Information, Carbapenem-Resistant *A. baumannii***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Aydemir, et al., 2012) | 62% | 53% | 9% | 0.341 | 5% |
| (Balkhair, et al., 2019) | 55% | 8% | 40% | 0.000 | 5% |
| (Cai, et al., 2017) | 38% | 14% | 25% | Not reported | 3% |
| (Cai, et al., 2017) [a] | 26% | 20% | 6% | Not reported | 1% |
| (Cai, et al., 2017) | 10% | 6% | 3% | Not reported | 2% |
| (Cai, et al., 2017) | 16% | 8% | 8% | Not reported | 1% |
| (Cai, et al., 2017) | 21% | 12% | 9% | Not reported | 1% |
| (Chang, et al., 2011) | 61% | 46% | 15% | 0.039 | 5% |
| (Choi, et al., 2019) | 52% | Not studied | Not studied | Not studied | 5% |
| (Choi, et al., 2019) | 57% | Not studied | Not studied | Not studied | Unknown |
| (Choi, et al., 2019) | 68% | Not studied | Not studied | <.001 | 6% |
| (Choi, et al., 2019) | 13% | Not studied | Not studied | 0.001 | 9% |
| (Choi, et al., 2019) | 60% | Not studied | Not studied | 0.52 | 13% |
| (Choi, et al., 2019) | 0% | Not studied | Not studied | 0.01 | Unknown |
| (Choi, et al., 2019) | 50% | Not studied | Not studied | 1 | 25% |
| (Choi, et al., 2019) | 50% | Not studied | Not studied | 1 | 25% |
| (Choi, et al., 2019) | 25% | Not studied | Not studied | 0.35 | 22% |
| (Choi, et al., 2019) | 0% | Not studied | Not studied | 0.48 | Unknown |
| (de Gouvêa, et al., 2012) | 50% | Not studied | Not studied | 0.15 | 12% |
| (Deris, et al., 2011) | 40% | 22% | 18% | 0.201 | 13% |
| (Esterly, et al., 2011) | 57% | 24% | 33% | <.001 | 8% |
| (Freire, et al., 2015) | 71% | Not studied | Not studied | Not studied | 6% |
| (Freire, et al., 2015) | 50% | Not studied | Not studied | Not studied | 11% |
| (Freire, et al., 2015) | 58% | Not studied | Not studied | Not studied | 11% |
| (Freire, et al., 2015) | 67% | Not studied | Not studied | Not studied | 12% |

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Freire, et al., 2015) | 100% | Not studied | Not studied | Not studied | Unknown |
| (Freire, et al., 2015) | 0% | Not studied | Not studied | Not studied | Unknown |
| (Henig, et al., 2015) | 73% | 55% | 18% | Not reported | Unknown |
| (Huang, et al., 2012) | 35% | 20% | 15% | Not reported | 6% |
| (Jamulitrat, et al., 2009) | 52% | 20% | 32% | <.001 | 6% |
| (Kim, et al., 2012) | 80% | Not studied | Not studied | Not studied | 4% |
| (Kim, et al., 2018) | 50% | Not studied | Not studied | Not studied | 13% |
| (Lemos, et al., 2014) | 40% | 21% | 19% | 0.018 | 5% |
| (Liu, et al., 2016) | 58% | Not studied | Not studied | Not studied | 4% |
| (Liu, et al., 2020) | 30% | 5% | 25% | <.001 | 3% |
| (Munoz-Price, et al., 2010) | 41% | Not studied | Not studied | Not studied | 5% |
| (Nutman, et al., 2014) | 45% | Not studied | Not studied | Not studied | Unknown |
| (Papadimitriou-Olivgeris, et al., 2017) | 40% | Not studied | Not studied | Not studied | 4% |
| (Prates, et al., 2011) | 47% | Not studied | Not studied | Not studied | 6% |
| (Rossi, et al., 2019) | 39% | Not studied | Not studied | <.0001 | 2% |
| (Routsi, et al., 2010) | 43% | 47% | -4% | 0.74 | 9% |
| (Sheng, et al., 2010) | 33% | 18% | 15% | 0.01 | 5% |
| (Song, et al., 2011) | 54% | Not studied | Not studied | Not studied | 9% |
| (Yang, et al., 2013) | 48% | Not studied | Not studied | 0.001 | 6% |
| (Zheng, et al., 2013) | 30% | 46% | -16% | 0.02 | Unknown |
| [a] For studies with multiple mortality estimates (e.g., associated with different pathogen-drug combinations, or with different infection sites), all extracted estimates are listed in these tables. | | | | | |

**Table C-19. Study Length of Stay Information, Carbapenem-Resistant *A. baumannii***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Aydemir, et al., 2012) | 110 | 55 | 40.5 | 32.2 | 8.3 | Not Reported |
| (Baran, et al., 2008) | 66 | 57 | 43 | 23 | 20 | 0.006 |
| (Chang, et al., 2011) | 93 | 87 | 23.1 | 26.7 | -3.6 | 0.331 |
| (Deris, et al., 2011) | 15 | 41 | 32.3 | 32.8 | -0.5 | 0.939 |
| (Esterly, et al., 2011) | 37 | 42 | 28 | 6 | 22 | Not Reported |
| (Henig, et al., 2015) | 1190 | 1190 | 18 | 17 | 1 | <.0001 |

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Henig, et al., 2015) | 241 | 241 | 16 | 15 | 1 | Not Reported |
| (Jamulitrat, et al., 2009) | 67 | 131 | 37 | 27 | 10 | 0.07 |
| (Kim, et al., 2018) | 14 | Not Studied | 17.7 | Not Studied | Not Studied | 0.05 |
| (Lemos, et al., 2014) | 104 | 61 | 19.3 | 16.2 | 3.1 | 0.58 |
| (Munoz-Price, et al., 2010) | 86 | Not Studied | 36 | Not Studied | Not Studied | Not Studied |
| (Rossi, et al., 2019) | 489 | Not Studied | 58 | Not Studied | Not Studied | <.0001 |
| (Routsi, et al., 2010) | 30 | 66 | 8 | 15.5 | -7.5 | 0.834 |
| (Sheng, et al., 2010) | 91 | 97 | 37 | 23 | 14 | 0.009 |

**Table C-20. General Study Information, MDR *A. baumannii***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Almomani, et al., 2015) | Retrospective case series study | 1/2007-6/2013 | Jordan | CLSI | Single (critical care units at 497-bed tertiary referral teaching hospital) | Ventilator-associated pneumonia | 6.0 |
| (Anunnatsiri & Tonsawan, 2011) | Retrospective study | 2005-2007 | Thailand | CLSI | Single (1,000-bed tertiary-care university hospital) | Intra-abdominal, UTI, sinus & skin/soft tissue | 4.5 |
| (Blanco, et al., 2018) | Retrospective cohort analysis | 5/2005-11/2009 | U.S. | CLSI | Single (medical intensive care unit and surgical intensive care unit at 816-bed university hospital) | Not Reported | 18.0 |
| (Brahmi, et al., 2007) | Prospective study | 1/2004-12/2005 | Tunisia | CLSI | Single (16-bed ICU) | Not Reported | 3.0 |
| (Brotfain, et al., 2017) | Retrospective study | 1/2005-6/2011 | Israel | Not reported | Single (1000-bed tertiary-care university teaching hospital) | Respiratory tract infections from ventilator associated pneumonia | 6.0 |
| (Cornejo-Juárez, et al., 2020) | Retrospective study | 1/2011-12/2015 | Mexico | CLSI | Single (six bed ICU at 135-bed tertiary-care cancer hospital) | Any infection | 6.5 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Daniels, et al., 2008) | Retrospective propensity-matched cohort study | 7/2003-6/2006 | U.S. | CLSI | Single (large university affiliated tertiary care facility) | Ventilator-associated pneumonia, BSI, UTI | 19.5 |
| (Fukuta, et al., 2013) | Case-control study | 1/2008-12/2011 | U.S. | CLSI | Single (520-bed major tertiary care facility with 53 beds for oncology and hematology patients) | Respiratory | 15.0 |
| (Guo, et al., 2016) | Retrospective study | 6/2012-6-2015 | China | CLSI | Single | Any infection | 6.0 |
| (Kuo, et al., 2007) | Retrospective study | 1/2003-2/2005 | Taiwan | CLSI | Single (2200-bed tertiary care center | Any infection | 4.0 |
| (Lee, et al., 2007) | Retrospective, matched-cohort study | 4/1996-8/2001 | Taiwan | Not reported | Single (900 beds including 67 ICU- tertiary university hospital) | BSI | 5.5 |
| (Liu, et al., 2015) | Retrospective study | 1/2009-12/2013 | China | CLSI | Single (4,000 bed tertiary hospital) | Any infection | 6.0 |
| (Pierri, et al., 2016) | Retrospective cohort | 9/2009-12/2011 | Italy | CLSI | Single (893 bed tertiary-7 ICUs and 1 Emergency Medicine) | Any infection | 12.0 |
| (Prata-Rocha, et al., 2012) | Prospective study | 8/2009-10/2010 | Brazil | CLSI | Single (530-bed tertiary safety net hospital) | Any infection | 4.0 |
| (Trottier, et al., 2007) | Retrospective review | 1/2004-11/2005 | U.S. | Not reported | Single- BICU (Burn Intensive Care Unit) | Any infection | 9.0 |
| (Zhou, et al., 2019) | Retrospective study | 1/2013-12/2017 | China | CLSI | Single (2,000 bed referral hospital) | Any infection | 7.0 |

**Table C-21. Study Mortality Information, MDR *A. baumannii***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Almomani, et al., 2015) | 42% | Not Studied | Not Studied | Not Studied | 5% |
| (Anunnatsiri & Tonsawan, 2011) | 92% | 48% | 44% | 0.001 | 6% |
| (Blanco, et al., 2018) | 24% | Not Studied | Not Studied | Not Studied | Unknown |

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Brahmi, et al., 2007) | 68% | 47% | 21% | 0.004 | Unknown |
| (Brotfain, et al., 2017) | 29% | Not Studied | Not Studied | 0.003 | 4% |
| (Cornejo-Juárez, et al., 2020) | 50% | Not Studied | Not Studied | <.001 | 5% |
| (Daniels, et al., 2008) | 14% | 10% | 5% | 74.00% | 5% |
| (Daniels, et al., 2008) | 16% | 10% | 6% | 0.45 | 3% |
| (Fukuta, et al., 2013) | 42% | Not Studied | Not Studied | 0.2 | Unknown |
| (Guo, et al., 2016) | 59% | 4% | 55% | 0.003 | 6% |
| (Kuo, et al., 2007) | 49% | Not Studied | Not Studied | Not Studied | 7% |
| (Lee, et al., 2007) | 48% | 39% | 9% | 0.53 | 7% |
| (Liu, et al., 2015) | 29% | Not Studied | Not Studied | Not Studied | 3% |
| (Pierri, et al., 2016) | 57% | Not Studied | Not Studied | 0.6 | 13% |
| (Prata-Rocha, et al., 2012) | 43% | 33% | 10% | 0.28 | 7% |
| (Trottier, et al., 2007) | 31% | 25% | 6% | Not Studied | 9% |
| (Zhou, et al., 2019) | 59% | 13% | 46% | <0.001 | 3% |

**Table C-22. Study Length of Stay Information, MDR *A. baumannii***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Anunnatsiri & Tonsawan, 2011) | 24 | 25 | 21.5 | 14 | 7.5 | 0.18 |
| (Brahmi, et al., 2007) | 29 | 34 | 27.3 | 32.3 | -5 | 0.2 |
| (Brotfain, et al., 2017) | 129 | Not Studied | 48.02 | Not Studied | Not Studied | 0.028 |
| (Cornejo-Juárez, et al., 2020) | 106 | Not Studied | 8 | Not Studied | Not Studied | 0.154 |
| (Daniels, et al., 2008) | 146 | 42 | 32.5 | 26.5 | 6 | 0.11 |
| (Fukuta, et al., 2013) | Not Studied | Not Studied | 28 | Not Studied | Not Studied | 0.001 |
| (Lee, et al., 2007) | 46 | 46 | 54.2 | 34.1 | 20.1 | 0.006 |
| (Pierri, et al., 2016) | 14 | Not Studied | 36 | Not Studied | Not Studied | 0.09 |
| (Zhou, et al., 2019) | 274 | 64 | 29 | 22.5 | 6.5 | 0.015 |

**Table C-23. General Study Information, Carbapenem-Resistant *E. coli***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Ahn, et al., 2014) | Retrospective matched case-control study | 1/2006-12/2010 | South Korea | CLSI | Single (2000-bed tertiary care center) | Any infection | 6.0 |
| (Budak, et al., 2014) | Prospective study | 6/2009-1/2011 | Turkey | Not Reported | Single (6 ICUs in 1,000 bed training hospital) | Any infection | 4.0 |
| (Cai, et al., 2017) | Cohort study | 1/1/2009-12/31/2013 | U.S. | CLIA | Premier Healthcare Database | BSI; respiratory; urinary; other; any infection | 22.2 |
| (Chang, et al., 2015) | Retrospective study | 1/2012-12/2012 | Taiwan | CLSI & EUCAST | Multi (9 medical centers and 8 regional hospitals) | Any infection | 5.0 |
| (Ghafur, et al., 2014) | Retrospective analysis | 1/2012-12/2012 | India | Not Reported | Single (300-bed tertiary care specialty hospital) | BSI | 4.0 |
| (Huang, et al., 2014) | Not listed | 1/2010-12/2011 | Taiwan | EUCAST & CLSI | Single (veterans general hospital) | Any infection | 4.0 |
| (Marchaim, et al., 2011) | retrospective cohort study | 9/2008-8/2009 | U.S. | CLSI | Multi (8 tertiary referral hospitals with > 2,200 beds) | Any infection | 21.0 |
| (Meng, et al., 2017) | Retrospective, matched case-control-control, parallel study | 1/2012-12/2015 | China | EUCAST & CLSI | Single (3500-bed tertiary teaching hospital) | Any infection | 7.0 |

**Table C-24. Study Mortality Information, Carbapenem-Resistant *E. coli***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Ahn, et al., 2014) | 14% | 10% | 4% | 0.39 | 5% |
| (Cai, et al., 2017) | 16% | 9% | 7% | Not Reported | 7% |
| (Cai, et al., 2017) | 27% | 22% | 5% | Not Reported | 8% |
| (Cai, et al., 2017) | 7% | 4% | 3% | Not Reported | 2% |

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Cai, et al., 2017) | 10% | 6% | 4% | Not Reported | 3% |
| (Cai, et al., 2017) | 10% | 5% | 5% | Not Reported | 2% |
| (Chang, et al., 2015) | 50% | Not Studied | Not Studied | Not Studied | 6% |
| (Ghafur, et al., 2014) | 64% | 38% | 25% | 0.008 | 7% |
| (Huang, et al., 2014) | 35% | 41% | -6% | 0.852 | 8% |
| (Marchaim, et al., 2011) | 37% | Not Studied | Not Studied | Not Studied | 5% |
| (Meng, et al., 2017) | 12% | 1% | 11% | 0.01 | 5% |

**Table C-25. Length of Stay Information, Carbapenem-Resistant *E. coli***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Ahn, et al., 2014) | 57 | 114 | 26.63 | 13.11 | 13.52 | <.05 |
| (Budak, et al., 2014) | 13 | 95 | 57 | 30 | 27 | <.0001 |
| (Chang, et al., 2015) | 66 | Not Studied | 36.2 | Not Studied | Not Studied | Not Studied |
| (Marchaim, et al., 2011) | 57 | Not Studied | 18.6 | Not Studied | N/A | Not Studied |
| (Meng, et al., 2017) | 49 | 98 | <6 month | <6 month | Not Studied | 0.06 |

**Table C-26. General Study Information, Third-Generation Cephalosporin-Resistant *E. coli***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Apisarnthanarak, et al., 2007) | Matched case-control study | 7/2003-6/2004 | Thailand | CLSI | Single (university hospital) | UTI, pneumonia, BSI | 5.0 |
| (de Kraker, et al., 2011) | Prospective parallel matched cohort study | 7/2007-6/2008 | 13 European countries[39] | Not Reported | Multi (13 tertiary hospitals, ranging from 819 to 2344 beds) | BSI | 16.0 |
| (Fitzpatrick, et al., 2016) | Retrospective case-case-control study | 1/2012-12/2013 | U.S. | Not Reported | Multi (VA medical facilities throughout USA) | Any infection | 21.0 |

[39] 13 European Countries include: Austria, Belgium, Croatia, England, Germany, Greece, Ireland, Italy, Latvian, Malta, Romania, Scotland, Slovenia

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Kang, et al., 2012) | Nationwide surveillance study | 10/2006-9/2007 | South Korea | CLSI | Multi (18 hospitals) | Any infection | 4.0 |
| (Lee, et al., 2021) | Retrospective case-cohort Study | 1/2012-12/2016 | Australia | EUCAST | Multi (all hospitals in Queensland, totaling 134) | BSI; UTI | 7.3 |
| (Lin, et al., 2019) | Retrospective observational study | 1/2005-12/2005 | Taiwan | CLSI & EUCAST | Single (2323-bed university tertiary-care teaching hospital) | Any infection | 5.0 |
| (Mark, et al., 2021) | Retrospective cohort study | 1/2017-6/2019 | U.S. | Not Reported | Multi (21 Kaiser Permanente Northern California Eds) | UTI | 27.0 |
| (Rodríguez-Baño, et al., 2010) | Case-control-control study | 10/2004-1/2006 | Spain | CLSI | Multi (13 tertiary-care hospitals) | Any infection | 12.0 |
| (Song, et al., 2009) | Retrospective matched case-control study | 1/2000-12/2006 | Korea | CLSI | Single (database at university hospital) | Liver cirrhosis and spontaneous bacterial peritonitis | 4.0 |
| (Superti, et al., 2009) | Case-control study | 6/2004-3/2006 | Brazil | CLSI | Single (600-bed tertiary-care teaching hospital) | BSI | 5.0 |
| (Trecarichi, et al., 2019) | Prospective cohort study | 1/2016-12/2017 | Italy | Not Reported | Multi (15 hematological wards of tertiary care centers or university hospitals) | BSI | 18.0 |
| (Zhen, et al., 2020) | Retrospective study | 2013-2015 | China | CLSI | Multi (4 tertiary-case hospitals with 3200, 3500, 1727, & 2100 beds) | Any infection | 5.0 |

**Table C-27. Study Mortality Information, Third-Generation Cephalosporin-Resistant *E. coli***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Apisarnthanarak, et al., 2007) | 35% | 16% | 19% | <.05 | 6% |
| (de Kraker, et al., 2011) | 32% | 17% | 16% | <.01 | 5% |
| (Fitzpatrick, et al., 2016) | 2% | 5% | -3% | Not Reported | 1% |
| (Kang, et al., 2012) | 45% | 14% | 31% | <.001 | 9% |
| (Lee, et al., 2021) | 16% | 17% | -1% | Not Reported | 5% |
| (Lee, et al., 2021) | 3% | 5% | -2% | Not Reported | 1% |
| (Lin, et al., 2019) | 16% | 8% | 8% | 0.005 | 3% |
| (Mark, et al., 2021) | 12% | 8% | 4% | Not Reported | 1% |
| (Rodríguez-Baño, et al., 2010) | 17% | 8% | 9% | 2.00% | 4% |
| (Song, et al., 2009) | 46% | 14% | 32% | 0.001 | 10% |
| (Superti, et al., 2009) | 51% | 30% | 21% | 0.019 | 7% |
| (Trecarichi, et al., 2019) | 14% | 5% | 9% | 0.004 | 4% |
| (Zhen, et al., 2020) | 3% | 2% | 1% | 0.281 | Unknown |

**Table C-28. Study Length of Stay Information, Third-Generation Cephalosporin-Resistant *E. coli***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Apisarnthanarak, et al., 2007) | 74 | 74 | 22.5 | 17.5 | 5 | <.05 |
| (de Kraker, et al., 2011) | 111 | 1110 | 12 | 10 | 2 | <.05 & <.01, respectively |
| (Fitzpatrick, et al., 2016) | 492 | Not Studied | 22 | Not Studied | Not Studied | Not Studied |
| (Lee, et al., 2021) | 45 | 543 | 24 | 22 | 2 | Not Reported |
| (Lee, et al., 2021) | 448 | 8504 | 19 | 18 | 1 | Not Reported |
| (Lin, et al., 2019) | 133 | 543 | 18 | 14 | 4 | <.001 |
| (Mark, et al., 2021) | 530 | 3577 | 88.8 | 67.2 | 21.6 | Not Reported |
| (Superti, et al., 2009) | 51 | 94 | 26 | 16 | 10 | 0.002 |

**Table C-29. General Study Information, Fluoroquinolone-Resistant *E. coli***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Brigmon, et al., 2015) | Retrospective cohort study | 1/2010-12/2012 | U.S. | CLSI | Multi (two hospitals with | BSI | 22.5 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| | | | | | combined capacity of >1,100 beds). | | |
| (Camins, et al., 2011) | Retrospective case-control study | 1/2000-12/2005 | U.S. | Not Reported | Single (1250-bed tertiary academic medical center) | BSI | 18.0 |
| (Kadri, et al., 2018) | Retrospective cohort analysis | 2009-2013 | U.S. | Not Reported | Multi (173 hospitals) | BSI | 24.0 |
| (Ortega, et al., 2009) | Analysis of cases prospectively collected through surveillance program | 1/1991-12/2007 | Spain | CLSI | Single (700 bed university tertiary center) | BSI | 12.0 |
| (Suzuki, et al., 2019) | Matched cohort study | 1/2003-12/2013 | U.S. | Not Reported | Multi (129 Veteran Health Administration hospitals) | Hospital-onset BSI | 18.0 |
| (van der Starre, et al., 2011) | Nested case-control study | 1/2004 – 12/2009 | Netherlands | EUCAST | Multi (7 hospitals) | UTI | 12.0 |

**Table C-30. Study Mortality Information, Fluoroquinolone-Resistant *E. coli***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Brigmon, et al., 2015) | 19% | 12% | 7% | 0.1 | 4% |
| (Camins, et al., 2011) | 26% | 8% | 18% | 0.002 | 5% |
| (Kadri, et al., 2018) | 18% | Not Studied | Not Studied | Not Studied | 1% |
| (Ortega, et al., 2009) | 12% | 8% | 4% | <.001 | 1% |
| (Suzuki, et al., 2019) | 38% | 26% | 11% | Not Reported | 3% |
| (van der Starre, et al., 2011) | 18% | 11% | 7% | Not Reported | 5% |

**Table C-31. Study Length of Stay Information, Fluoroquinolone-Resistant *E. coli***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Brigmon, et al., 2015) | 90 | 384 | 11.6 | 9.3 | 2.3 | 0.03 |
| (Camins, et al., 2011) | 93 | 93 | 9 | 6 | 3 | 0.002 |

**Table C-32. General Study Information, MDR *E. coli***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (de Laroche, et al., 2021) | Retrospective cohort study | 4/2010-12/2016 | France | EUCAST | Single (524 bed-university hospital) | Any infection | 14.0 |
| (Gudiol, et al., 2011) | Prospective observational study | 1/2006-12/2009 | Spain | CLSI | Single (200-bed university referral cancer center) | Any infection | 10.0 |
| (Hristea, et al., 2011) | Retrospective study | 1/2009-1/2011 | Romania | CLSI | Not Reported | BSI | 10.0 |
| (Karve, et al., 2018) | Retrospective cohort study | 7/2013-6/2014 | Brazil, France, Italy, Russia, Spain | Not Reported | Multi-center | UTI | 18.0 |
| (Kumar, et al., 2018) | Prospective study | 2013-2015 | India | CLSI | Single (800-bed tertiary-care hospital) | Pneumonia | 7.0 |
| (Majangara, et al., 2018) | Prospective descriptive cohort study | 11/2014-7/2015 | Zimbabwe | Not Reported | Multi-center | Female genital tract & BSI | 7.0 |
| (Mauldin, et al., 2010) | Retrospective | 1/2000-6/2008 | U.S. | Not Reported | Single | Any infection | 24.0 |
| (Nemeth, et al., 2012) | Retrospective study | 1/2009-11/2011 | Switzerland | Not Reported | Single (university hospital) | Any infection | 11.0 |
| (Parveen, et al., 2015) | Retrospective study | 12/2012-11/2013 | Pakistan | CLSI | Single (cancer hospital and research center) | Any infection | 5.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Peralta, et al., 2007) | Retrospective cohort study | 1/1997-6/2005 | Spain | CLSI | Single (250-bed adult acute-care community teaching hospital) | BSI | 13.0 |
| (Tseng, et al., 2018) | Retrospective cohort study | 2009 | Taiwan | Not Reported | Single-center (2200-bed teaching hospital providing both primary and tertiary care) | Any infection | 8.0 |
| (Tu, et al., 2020) | Retrospective study | 1/2015-12/2018 | China | CLSI | Multi (2 hospitals) | Not specified | 7.0 |

**Table C-33. Study Mortality Information, MDR *E. coli***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (de Laroche, et al., 2021) | 28% | 17% | 11% | Not Significant | 7% |
| (Gudiol, et al., 2011) | 39% | 20% | 19% | 0.003 | 7% |
| (Hristea, et al., 2011) | 26% | 13% | 13% | 0.070 | 7% |
| (Karve, et al., 2018) | 40% | 30% | 10% | Not Reported | 4% |
| (Kumar, et al., 2018) | 29% | Not Studied | Not Studied | Not Significant | 5% |
| (Majangara, et al., 2018) | 17% | 6% | 10% | 0.19 | 11% |
| (Nemeth, et al., 2012) | 11% | 2% | 9% | 0.018 | 5% |
| (Parveen, et al., 2015) | 45% | 28% | 17% | Not Reported | 5% |
| (Peralta, et al., 2007) | 14% | 4% | 10% | Not Reported | 4% |
| (Tu, et al., 2020) | 33% | 19% | 15% | 0.021 | 4% |

**Table C-34. Study Length of Stay Information, MDR *E. coli***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Majangara, et al., 2018) | 15 | 114 | 23 | 10.5 | 12.5 | 0.009 |
| (Mauldin, et al., 2010) | 103 | 559 | 47 | 30 | 17 | 0.0001 |
| (Nemeth, et al., 2012) | 46 | 213 | 8 | 3.5 | 4.5 | 0.011 |
| (Peralta, et al., 2007) | 87 | 576 | 17.01 | 12.15 | 4.86 | 0.03 |
| (Tseng, et al., 2018) | 125 | 692 | 19 | 9 | 10 | 0.001 |

**Table C-35. General Study Information, Carbapenem-Resistant *K. pneumoniae***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Ben-David, et al., 2012) | Retrospective cohort study | 1/2006-12/2006 | Israel | CLSI | Not extracted | BSI | 5.0 |
| (Brizendine, et al., 2015) | Retrospective cohort study | 2006-2012 | U.S. | Not Reported | Not extracted | UTI | 18.0 |
| (Cai, et al., 2017) | Cohort study | 1/1/2009-12/31/2013 | U.S. | CLIA | Not extracted | BSI; respiratory; urinary; other; any infection | 24.0 |
| (Ulu, et al., 2015) | Retrospective cohort | 1/2012-12/2012 | Turkey | Not Reported | Single center, ICUs | Any infection | 14.0 |
| (Cober, et al., 2013) | Retrospective cohort study | 2006-2009 | U.S. | Not Reported | Not extracted | BSI | 18.0 |
| (Cubero, et al., 2015) | Retrospective cohort study | 1/2010-12/2012 | Spain | EUCAST | Not extracted | Any infection | 12.0 |
| (Daikos, et al., 2009) | Prospective observational study | 2/2005-3/2006 | Greece | CLSI | Not extracted | BSI | 6.0 |
| (Gaviria, et al., 2011) | Retrospective matched case-control study | 4/2009-12/2011 | U.S. | CLSI | Not extracted | Not determined | 18.0 |
| (Falagas, et al., 2007) | Retrospective matched case-control study | 1/2000-5/2006 | Greece | Not Reported | Multicenter (2 hospitals) | Any infection | 10.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Gasink, et al., 2009) | Case-control study | 1/2006-4/2008 | U.S. | Not Reported | Not extracted | Any infection | 18.0 |
| (Giannella, et al., 2015) | Prospective cohort | 6/2010-12/2013 | Italy | Not Reported | Single Center | BSI and pneumonia | 12.0 |
| (Hauck, et al., 2016) | Prospective cohort | 12/2011-10/2014 | U.S. | Not Reported | Multicenter (5 health systems) | BSI; UTI; pneumonia | 25.0 |
| (Hoxha, et al., 2016) | Prospective cohort | 12/2012-7/2013 | Italy | Not Reported | Multicenter (10 Italian hospitals) | BSI and pneumonia | 14.0 |
| (Hu, et al., 2016) | Case-control | 1/2011-6/2013 | China | Not determined | Single center, a 67-bed ICU | Any infection | 6.0 |
| (Hussein, et al., 2013) | Retrospective case-control study | 1/2006-12/2008 | Israel | CLSI | Single center | BSI | 6.0 |
| (Kadri, et al., 2019) | Retrospective matched case-control study | 1/2010-12/2013 | U.S. | Not Reported | Not extracted | BSI; UTI; pneumonia | 16.5 |
| (Liu, et al., 2012) | Matched case-control study | 1/2007-12/2009 | Taiwan | CLSI | Not extracted | BSI | 5.0 |
| (Correa, et al., 2013) | Matched case-control study | 1/2006-8/2008 | Brazil | CLSI | Not extracted | BSI, SSI, UTI, skin and soft tissue | 5.0 |
| (Mouloudi, et al., 2010) | Retrospective nested case-control study | 1/2007-12/2008 | Greece | CLSI | Not extracted | BSI | 10.0 |
| (Ny, et al., 2015) | Retrospective cohort study | 1/2011-12/2013 | U.S. | Not Reported | Not extracted | UTI and pneumonia; pneumonia | 20.0 |
| (Orsi, et al., 2011) | Retrospective case-control study | 7/2008-12/2009 | Italy | EUCAST | Not extracted | Not determined | 10.0 |
| (Orsi, et al., 2013) | Case-control study | 7/2008-6/2011 | Italy | EUCAST | Not extracted | Not determined | 12.0 |
| (Pan, et al., 2019) | Retrospective cohort | 2014 | China | Not Reported | Single center | Not determined | 8.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Patel, et al., 2008) | Retrospective matched case-control study | 7/2004-6/2006 | U.S. | CLSI | Single center | Not determined | 15.0 |
| (Pouch, et al., 2015) | Nested case-control study | 1/2007-12/2010 | U.S. | CLSI | Not extracted | UTI | 15.0 |
| (Schwaber, et al., 2008) | Retrospective cohort study | 2003-2006 | Israel | CLSI | Not extracted | Any infection | 5.0 |
| (Simkins, et al., 2014) | Retrospective case-control study | 1/2006-12/2010 | U.S. | Not Reported | Single center | Not determined | 15.0 |
| (Vardakas, et al., 2015) | Retrospective cohort study | 1/2006-1/2009 | Greece | CLSI | Single center, an 8-bed ICU | BSI | 14.0 |
| (Rueda & Tobón, 2014) | Case-case-control study | 1/2008-1/2011 | Colombia | CLSI | Not extracted | Any infection | 6.0 |
| (Wang, et al., 2018) | Case-control | 1/2010-12/2014 | China | Not Reported | Single center | Any infection | 7.0 |

**Table C-36. Study Mortality Information, Carbapenem-Resistant *K. pneumoniae***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Ben-David, et al., 2012) | 69% | 30% | 39% | <0.001 | 7% |
| (Brizendine, et al., 2015) | 18% | 2% | 17% | Not Reported | 8% |
| (Cai, et al., 2017) | 38% | 14% | 25% | Not Reported | 3% |
| (Cai, et al., 2017) | 26% | 20% | 6% | Not Reported | 1% |
| (Cai, et al., 2017) | 10% | 6% | 3% | Not Reported | 2% |
| (Cai, et al., 2017) | 16% | 8% | 8% | Not Reported | 1% |
| (Cai, et al., 2017) | 21% | 12% | 9% | Not Reported | 1% |
| (Cober, et al., 2013) | 42% | 15% | 27% | 0.005 | 11% |
| (Cubero, et al., 2015) | 40% | 11% | 29% | Not Reported | 11% |
| (Daikos, et al., 2009) | 43% | 17% | 26% | Not Reported | 13% |
| (Gaviria, et al., 2011) | 5% | 8% | -3% | Not Reported | 5% |
| (Falagas, et al., 2007) | 30% | 34% | -4% | Not Reported | 6% |
| (Gasink, et al., 2009) | 32% | 10% | 22% | Not Reported | 6% |
| (Hoxha, et al., 2016) | 61% | 20% | 41% | Not Reported | 7% |
| (Hussein, et al., 2013) | 44% | 29% | 15% | Not Reported | 5% |

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Kadri, et al., 2019) | Not Studied | Not Studied | 5% | Not Studied | Unknown |
| (Kadri, et al., 2019) | 36% | Not Studied | 11% | p<0.001 | 2% |
| (Kadri, et al., 2019) | 35% | 20% | 16% | p<0.0001 | 1% |
| (Kadri, et al., 2019) | 29% | 17% | 13% | Not Reported | Unknown |
| (Liu, et al., 2012) | 60% | 40% | 20% | 0.102 | 10% |
| (Correa, et al., 2013) | 50% | 28% | 23% | 0.085 | 11% |
| (Mouloudi, et al., 2010) | 68% | 41% | 27% | 0.03 | 8% |
| (Ny, et al., 2015) | 15% | 10% | 4% | 0.76 | 5% |
| (Ny, et al., 2015) | 29% | 15% | 15% | 0.14 | 7% |
| (Ny, et al., 2015) | 24% | 14% | 10% | 0.31 | 9% |
| (Orsi, et al., 2011) | 39% | 28% | 11% | Not Reported | 9% |
| (Orsi, et al., 2013) | 38% | 28% | 11% | Not Reported | 6% |
| (Patel, et al., 2008) | 48% | 20% | 28% | <0.001 | 5% |
| (Pouch, et al., 2015) | 30% | 10% | 20% | 0.03 | 10% |
| (Schwaber, et al., 2008) | 44% | 13% | 31% | Not Reported | 7% |
| (Simkins, et al., 2014) | 46% | 8% | 38% | 0.005 | 14% |
| (Vardakas, et al., 2015) | 73% | 58% | 14% | 0.19 | 5% |
| (Rueda & Tobón, 2014) | 51% | 33% | 18% | Not Reported | 6% |

**Table C-37. Study Length of Stay Information, Carbapenem-Resistant *K. pneumoniae***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Ulu, et al., 2015) | 47 | 51 | 37.3 | 29.94 | 7.36 | 0.026 |
| (Giannella, et al., 2015) | 20 | 217 | 99.5 | 17 | 82.5 | <0.001 |
| (Hauck, et al., 2016) | 90 | 223 | 14 | 9 | 5 | <0.01 |
| (Hauck, et al., 2016) | 121 | 223 | 10 | 9 | 1 | 0.76 |
| (Hauck, et al., 2016) | 49 | 223 | 19 | 9 | 10 | <0.0001 |
| (Hu, et al., 2016) | 65 | 65 | 33.49 | 30.98 | 2.51 | 0.561 |
| (Pan, et al., 2019) | 66 | 132 | 46 | 23 | 23 | Not Studied |
| (Wang, et al., 2018) | 48 | 48 | 84 | 33 | 51 | 0.097 |

**Table C-38. General Study Information, Third-Generation Cephalosporin-Resistant *K. pneumoniae***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Apisarnthanarak, et al., 2007) | Matched case-control study | 7/2003-6/2004 | Thailand | CLSI | Single (university hospital) | Any infection | 4.0 |
| (Fitzpatrick, et al., 2016) | Retrospective case-case-control study | 1/2012-12/2013 | U.S. | Not Reported | Single (Veterans' Affairs med center) | Any infection | 19.5 |
| (Gallagher, et al., 2014) | Retrospective case-case-control study | 1/2005-10/2010 | U.S. | CLSI | Single (university hospital) | BSI | 18.0 |
| (Kang, et al., 2012) | Post-hoc analysis of nationwide surveillance studies | 10/2006-11/2007 | South Korea | CLSI | Multi (18 hospitals) | Any infection | 4.0 |
| (Li, et al., 2014) | Retrospective study | 1/2009-12/2011 | China | CLSI | Single (university cancer institute & hospital with 2,400 beds) | BSI | 4.0 |
| (Mark, et al., 2021) | Retrospective cohort study | 1/2017-6/2019 | U.S. | Not Reported | 21 emergency departments | UTI | 27.0 |
| (Martelius, et al., 2016) | Prospective study | 1999-2013 | Finland | CLSI | Multi (17 acute care hospitals nationwide) | BSI | 12.0 |
| (Mosqueda-Gómez, et al., 2008) | Retrospective case-control study | 1/1993-12/2002 | Mexico | CLSI | Single (250-bed referral hospital) | BSI | 4.0 |
| (Seboxa, et al., 2015) | Retrospective study | 2012-2013 | Ethiopia | CLSI | Single (tertiary teaching hospital) | BSI | 4.0 |
| (Superti, et al., 2009) | Case-control study | 6/2004-3/2006 | Brazil | CLSI | Single (600 bed tertiary-care teaching hospital) | BSI | 5.0 |
| (Tsui, et al., 2012) | Retrospective study | 1/2006-12/2009 | Taiwan | CLSI | Single | Any infection | 4.0 |
| (Zhen, et al., 2020) | Retrospective study | 2013-2015 | China | CLSI | Multi (4 tertiary-care hospitals, with 3,200, 3,500, 1,727, and 2,100 beds) | Any infection | 7.0 |

**Table C-39. Study Mortality Information, Third-Generation Cephalosporin-Resistant *K. pneumoniae***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Apisarnthanarak, et al., 2007) | 35% | 16% | 19% | >.05 | 6% |
| (Fitzpatrick, et al., 2016) | 2% | 2% | 0% | 1.000 | 1% |
| (Gallagher, et al., 2014) | 32% | Not Studied | Not Studied | Not Studied | Unknown |
| (Kang, et al., 2012) | 45% | 14% | 31% | <.001 | 9% |
| (Li, et al., 2014) | 27% | 18% | 9% | 0.431 | Unknown |
| (Mark, et al., 2021) | 12% | 8% | 4% | Not Studied | 1% |
| (Martelius, et al., 2016) | 14% | 12% | 2% | 0.42 | 3% |
| (Mosqueda-Gómez, et al., 2008) | 35% | 27% | 8% | 47.00% | Unknown |
| (Seboxa, et al., 2015) | 100% | 11% | 89% | 0.020 | Unknown |
| (Superti, et al., 2009) | 51% | 30% | 21% | 0.019 | 7% |
| (Tsui, et al., 2012) | 21% | Not Studied | Not Studied | 0.27 | 8% |
| (Zhen, et al., 2020) | 7% | 4% | 3% | <.000 | 1% |

**Table C-40. Study Length of Stay Information, Third-Generation Cephalosporin-Resistant *K. pneumoniae***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Apisarnthanarak, et al., 2007) | 74 | 74 | 22.5 | 17.5 | 5 | <.05 |
| (Fitzpatrick, et al., 2016) | 492 | 492 | 22 | 11 | 11 | 0.001 |
| (Gallagher, et al., 2014) | 111 | Not Studied | 63 | Not Studied | Not Studied | Not Studied |
| (Mark, et al., 2021) | 530 | 3577 | 4.8 | 3.6 | 1.2 | Not Reported |
| (Mosqueda-Gómez, et al., 2008) | 17 | 104 | 20.9 | 15.9 | 5 | 0.49 |
| (Superti, et al., 2009) | 51 | 94 | 26 | 16 | 10 | Not Reported |
| (Zhen, et al., 2020) | 1617 | 1617 | 31 | 20 | 11 | <.000 |

**Table C-41. General Study Information, *Fluoroquinolone-Resistant K. pneumoniae***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Brigmon, et al., 2015) | Retrospective cohort study | 1/2010 - 12/2012 | U.S. | Not Reported | Single health system (>1100 beds) | BSI | 22.5 |
| (Kadri, et al., 2018) | Retrospective cohort study | 2009 - 2013 | U.S. | Not Reported | Multi (173 US hospitals) | BSI | 24.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Suzuki, et al., 2019) | Matched cohort study | 1/2003-12/2013 | U.S. | Not Reported | Multi (129 Veteran Health Administration hospitals) | Hospital-Onset BSI | 24.0 |

**Table C-42. Study Mortality Information, Fluoroquinolone-Resistant *K. pneumoniae***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Brigmon, et al., 2015) | 19% | 12% | 7% | 0.1 | Unknown |
| (Kadri, et al., 2018) | 18% | Not Studied | Not Studied | Not Studied | 1% |
| (Suzuki, et al., 2019) | 38% | 26% | 11% | Not Reported | 3% |

**Table C-43. Study Length of Stay Information, Fluoroquinolone-Resistant *K. pneumoniae***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Brigmon, et al., 2015) | 90 | 384 | 11.6 | 9.3 | 2.3 | 0.03 |

**Table C-44. General Study Information, MDR *K. pneumoniae***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Amanati, et al., 2021) | Retrospective study | 7/2015-8/2019 | Iran | CLSI | Single (educational 100-bed inpatient center) | BSI | 5.0 |
| (Chittawatanarat, et al., 2014) | Retrospective analysis | 1/2008-12/2012 | Thailand | Not Reported | Single (21 bed general surgical ICU at 1,400 bed tertiary-care university based hospital) | Respiratory | 4.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Gandra, et al., 2019) | Retrospective observational study | 1/2015-12/2015 | India | CLSI | Multi (10 tertiary and quaternary referral hospitals, each ranging in size from 120 to 350 beds) | Any infection | 5.0 |
| (Garnica, et al., 2009) | Retrospective case-control study | 7/1994-1/2005 | Brazil | Not Reported | Single | Any infection | 4.0 |
| (Khairy, et al., 2020) | Cross-sectional study | 3/2017-6/2017 | Egypt | Not Reported | Multi (2 hospitals: an 800-bed adult and pediatric teaching hospital and a 120-bed tertiary care hospital) | Multiple infections | 5.0 |
| (Liu, et al., 2020) | Retrospective study | 1/2012-5/2018 | China | CLSI | Multi (11 teaching hospitals) | Any infection | 6.0 |
| (Michalopoulos, et al., 2011) | Retrospective cohort study | 1/2005-12/2007 | Greece | CLSI | Single (24-bed ICU at tertiary care hospital) | BSI | 12.0 |
| (Ning, et al., 2019) | Prospectively maintained database study | 1/2010-5/2019 | China | Reported as "the standard protocol" | Single (a large tertiary-care hospital) | BSI | 6.5 |
| (Siwakoti, et al., 2018) | Prospective cohort study | 7/2017-12/2017 | Nepal | CLSI | Single (7-bed general ICU) | Multiple infections | 8.0 |

**Table C-45. Study Mortality Information, MDR *K. pneumoniae***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Amanati, et al., 2021) | 20% | Not Studied | Not Studied | Not Studied | Unknown |
| (Chittawatanarat, et al., 2014) | 30% | 19% | 11% | 0.02 | 10% |
| (Gandra, et al., 2019) | 18% | Not Studied | Not Studied | Not Reported | Unknown |
| (Garnica, et al., 2009) | 40% | Not Studied | Not Studied | 0.03 | Unknown |
| (Liu, et al., 2020) | 33% | 28% | 5% | 0.267 | 5% |
| (Michalopoulos, et al., 2011) | 48% | 19% | 29% | 0.01 | 8% |
| (Ning, et al., 2019) | 35% | 11% | 24% | 0.00% | 5% |
| (Siwakoti, et al., 2018) | 38% | 20% | 18% | 0.007 | 6% |

**Table C-46. Study Length of Stay Information, MDR *K. pneumoniae***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Khairy, et al., 2020) | 42 | 208 | 8.14 | Not Studied | Not Studied | Not Studied |
| (Ning, et al., 2019) | 108 | 80 | 67.7 | 51.2 | 16.5 | 0.001 |
| (Siwakoti, et al., 2018) | 64 | 10 | 14 | 9 | 5 | 0.93 |

**Table C-47. General Study Information, Carbapenem-Resistant *P. aeruginosa***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Aviv, et al., 2018) | Retrospective matched case-case-control analysis | 2007-2012 | Israel | CLSI | Single | BSI | 6.0 |
| (Balkhair, et al., 2019) | Retrospective study | 1/2007-12/2016 | Oman | CLSI | Single (600 bed teaching and referral hospital) | BSI | 6.0 |
| (Cai, et al., 2017) | Cohort study | 1/1/2009-12/31/2013 | U.S. | CLIA | Premier Healthcare Database | BSI; respiratory; urinary; other; any infection | 24.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Chaves, et al., 2017) | Case-control study | 12/2011-1/2013 | Brazil | CLSI | Single-center (12-room unit in 1000-bed tertiary-care hospital) | BSI | 5.0 |
| (Chen, et al., 2019) | Retrospective propensity score-matched cohort | 2/2014-3/2018 | China | CLSI | Single | Any infection | 9.0 |
| (Crusio, et al., 2014) | Prospective observational cohort study | 11/2009-11/2010 | U.S. | CLSI | Single (700-bed community teaching hospital) | Any infection | 18.0 |
| (Dantas, et al., 2014) | Retrospective study | 5/2009 - 8/2011 | Brazil | Not Reported | Single (530-bed tertiary-care university hospital) | BSI | 5.0 |
| (de Souza, et al., 2021) | Retrospective cohort study | 11/2015-10/2016 | Brazil | CLSI | Single (ICU at 237-bed public tertiary care hospital) | Any infection | 7.0 |
| (Djordjevic, et al., 2013) | Prospective cohort study | 1/2009-12/2011 | Serbia | Not Reported | Single (large hospital) | Any infection | 16.0 |
| (Huang, et al., 2019) | Retrospective study | 1/2015-12/2015 | Taiwan | CLSI | Single-center (2900-bed medical center and teaching hospital) | Any infection | 5.0 |
| (Jeong, et al., 2014) | Retrospective cohort study | 1/2007-12/2009 | South Korea | CLSI | Single (2000 bed teaching hospital) | BSI | 7.0 |
| (Lin, et al., 2016) | Retrospective cohort study | 2000-2010 | Taiwan | CLSI | Multi (5 hospitals) | Any infection | 8.0 |
| (Luyt, et al., 2014) | Prospective, observational study | Not Reported | France | EUCAST | Single (2 ICU wards in a hospital) | LRTI | 8.0 |
| (Meradji, et al., 2015) | Retrospective case-control study | 1/2012 - 12/2013 | Algeria | CLSI | Multi (3 hospitals) | Any infection | 5.0 |
| (Papadimitriou-Olivgeris, et al., 2019) | Retrospective cohort study | 2012-2016 | Greece | EUCAST | Single (ICU at university general hospital) | BSI | 18.0 |
| (Peña, et al., 2012) | Prospective cohort study | 1/2007-12/2009 | Spain | CLSI | Multi (10 public hospitals in four areas of Spain) | BSI | 16.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Rossi, et al., 2017) | Case-control study | 5/2009-12/2012 | Brazil | CLSI | Single | Any infection | 6.0 |
| (Suárez, et al., 2010) | Retrospective cohort study | 1/2005-12/2005 | Spain | CLSI | Single (900 bed tertiary-care teaching hospital) | BSI | 10.0 |
| (Tofas, et al., 2017) | Case-control study | 1/2012-12/2014 | Greece | CLSI | Multi (3 hospitals) | BSI | 12.0 |
| (Tuon, et al., 2012) | Case-control study | 2/2006-1/2009 | Brazil | CLSI | Single (660 bed tertiary-care hospital) | BSI | 5.0 |
| (Zhang, et al., 2018) | Retrospective study | 1/2014 - 6/2016 | China | CLSI | Single | Any infection | 7.0 |

**Table C-48. Study Mortality Information, Carbapenem-Resistant *P. aeruginosa***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Aviv, et al., 2018) | 53% | 54% | -1% | 0.9 | 5% |
| (Balkhair, et al., 2019) | 80% | 22% | 59% | 0 | 6% |
| (Cai, et al., 2017) | 33% | 20% | 13% | Not Reported | 3% |
| (Cai, et al., 2017) | 21% | 15% | 6% | Not Reported | 1% |
| (Cai, et al., 2017) | 10% | 6% | 4% | Not Reported | 1% |
| (Cai, et al., 2017) | 17% | 7% | 10% | Not Reported | 1% |
| (Cai, et al., 2017) | 17% | 10% | 7% | Not Reported | 0% |
| (Chaves, et al., 2017) | 79% | Not Studied | Not Studied | Not Reported | Unknown |
| (Chen, et al., 2019) | 13% | 8% | 5% | 0.044 | 2% |
| (Crusio, et al., 2014) | 50% | Not Studied | Not Studied | Not Reported | Unknown |
| (Dantas, et al., 2014) | 47% | 37% | 10% | 0.33 | 7% |
| (de Souza, et al., 2021) | 39% | Not Studied | Not Studied | Not Reported | Unknown |
| (Huang, et al., 2019) | 41% | Not Studied | Not Studied | Not Reported | 12% |
| (Jeong, et al., 2014) | 68% | 27% | 41% | Not Reported | 6% |
| (Lin, et al., 2016) | 22% | 20% | 2% | 0.925 | 5% |
| (Luyt, et al., 2014) | 37% | 31% | 6% | Not Reported | 6% |
| (Meradji, et al., 2015) | 13% | 2% | 12% | 0.09 | 9% |
| (Papadimitriou-Olivgeris, et al., 2019) | 26% | 13% | 13% | 0.004 | 4% |
| (Peña, et al., 2012) | 35% | 27% | 8% | 0.06 | 4% |

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Rossi, et al., 2017) | 70% | 50% | 20% | 1.65% | 6% |
| (Suárez, et al., 2010) | 33% | 30% | 4% | 0.69 | 8% |
| (Tofas, et al., 2017) | 47% | 31% | 16% | 0.26 | 11% |
| (Tuon, et al., 2012) | 45% | 54% | -9% | 0.288 | 9% |
| (Zhang, et al., 2018) | 9% | 4% | 6% | 0 | 2% |

**Table C-49. Study Length of Stay Information, Carbapenem-Resistant *P. aeruginosa***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Aviv, et al., 2018) | 85 | 85 | 37 | 35 | 2 | 0.932 |
| (Chaves, et al., 2017) | 29 | 58 | 35.1 | 43.6 | -8.5 | 0.12 |
| (Chen, et al., 2019) | 270 | 270 | 29 | 25.5 | 3.5 | 0.026 |
| (Crusio, et al., 2014) | 11 | Not Studied | 51 | Not Studied | Not Studied | Not Studied |
| (Dantas, et al., 2014) | 55 | 65 | 48 | 41 | 7 | 0.65 |
| (de Souza, et al., 2021) | 28 | Not Studied | 34.4 | Not Studied | Not Studied | Not Studied |
| (Djordjevic, et al., 2013) | 167 | 94 | 34.17 | 30.69 | 3.48 | 0.083 |
| (Jeong, et al., 2014) | 63 | 179 | 52.7 | Not Studied | 52.7 | 0.635 |
| (Luyt, et al., 2014) | 68 | 101 | 37 | 29 | 8 | Not Reported |
| (Meradji, et al., 2015) | 15 | 65 | 82.5 | 63.44 | 19.06 | 0.04 |
| (Rossi, et al., 2017) | 69 | 88 | 60 | 65.70125 | -5.69125 | 0.3477 |
| (Suárez, et al., 2010) | 33 | 88 | 19 | 9 | 10 | 0.03 |
| (Tuon, et al., 2012) | 29 | 48 | 43 | 43.1 | -0.1 | 0.987 |
| (Zhang, et al., 2018) | 264 | 624 | 31.67 | 22.33 | 9.34 | 0 |

**Table C-50. General Study Information, Third-Generation Cephalosporin-Resistant *P. aeruginosa***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Akhabue, et al., 2011) | Case-control study | 1/2001-12/2006 | U.S. | CLSI | Multi (725-bed tertiary care center and 344-bed urban community hospital) | Any infection | 18.0 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Dantas, et al., 2014) | Retrospective study | 5/2009-8/2011 | Brazil | CLSI | Single (530-bed tertiary-care university hospital) | Any infection | 5.0 |
| (Joo, et al., 2011) | Retrospective cohort study | 10/2006-3/2009 | Korea | CLSI | Single (1,900 bed tertiary care university hospital) | Any infection | 7.0 |
| (Picot-Guéraud, et al., 2015) | Monocentric retrospective observational cohort study | 1/2011-12/2013 | France | CLSI | Single (university hospital w/ 2,200 acute and long-term beds) | Any infection | 12.0 |
| (Su, et al., 2015) | Retrospective study | 1/2006-12/2011 | Taiwan | CLSI | Single (3715-bed university-affiliated tertiary care w/ 308 ICU beds | BSI | 5.0 |

**Table C-51. Study Mortality Information, Third-Generation Cephalosporin-Resistant *P. aeruginosa***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Akhabue, et al., 2011) | 20% | 13% | 7% | 0.007 | 3% |
| (Dantas, et al., 2014) | 48% | 41% | 8% | 0.550 | 6% |
| (Joo, et al., 2011) | 38% | 18% | 20% | 0.0002 | 6% |
| (Picot-Guéraud, et al., 2015) | 18% | Not studied | Not studied | Not Studied | 7% |
| (Su, et al., 2015) | 65% | Not studied | Not studied | Not Studied | 5% |

**Table C-52. Study Length of Stay Information, Third-Generation Cephalosporin-Resistant *P. aeruginosa***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Dantas, et al., 2014) | 66 | 44 | 48.5 | 40.5 | 8 | 0.73 |
| (Joo, et al., 2011) | 74 | 128 | 23 | 15 | 8 | 0.023 |
| (Picot-Guéraud, et al., 2015) | 28 | 200 | Not Studied | Not Studied | Not Studied | Not Studied |

Table C-53. General Study Information, MDR *P. aeruginosa*

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Borgatta, et al., 2017) | Retrospective study | 1/2010 - 4/2015 | Spain | EUCAST | Multi (4 ICUs) | Pneumonia (HAP/VAP) | 10.0 |
| (Cillóniz, et al., 2016) | Prospective observational study | 1/1999 - 12/2014 | Spain | EUCAST | Single | Pneumonia CAP | 10.0 |
| (Dantas, et al., 2014) | Retrospective study | 5/2009 - 8/2011 | Brazil | CLSI | Single (530-tertiary-care university hospital) | BSI; respiratory tract; UTI | 4.5 |
| (Lu, et al., 2012) | Prospective, observational, and comparative study | 1/2006 - 12/2010 | France | Not Reported | Single (26-bed multidisciplinary ICU) | Pneumonia VAP | 13.0 |
| (Micek, et al., 2015) | Retrospective cohort study | Not Reported | U.S., France, Germany, Italy, Spain | CLSI and EUCAST | Multi (12 hospitals) | Pneumonia nosocomial | 14.0 |
| (Morata, et al., 2012) | Prospective study | 1/2000 - 12/2008 | Spain | CLSI | Single (850-bed university center) | BSI; respiratory | 10.5 |
| (Peña, et al., 2013) | Retrospective study | 1/2006 - 12/2011 | Spain | CLSI | Single (tertiary-care university hospital) | VAP | 10.0 |
| (Peng, et al., 2014) | Case-control surveillance study | 7/2008-12/2012 | China | CLSI | Multi (5 randomly selected tertiary care hospitals) | Any infection | 7.0 |
| (Tam, et al., 2010) | Retrospective cohort study | 1/2005-12/2008 | US | Not Reported | Single (900-bed acute-care teaching hospital) | BSI | 18.0 |
| (Trecarichi, et al., 2011) | Prospective study | 1/2009-9/2010 | Italy | Not Reported | Multi (9 tertiary care centers or university hospitals) | BSI | 8.0 |
| (Tumbarello, et al., 2011) | Retrospective (case-control & cohort study) | 1/2006-12/2007 | Italy | CLSI | Multi (2 hospitals-1600-bed and 1500-bed) | BSI; UTI | 12.0 |
| (Tumbarello, et al., 2020) | Retrospective case-case-control study | 1/2016-12/2017 | Italy | EUCAST | Multi-center (2 hospitals) | UTI | 15.0 |
| (Zhang, et al., 2020) | Retrospective multicenter study | 2012-2019 | China | CLSI | Multi (5 hospitals) | Lung; UTI; BSI | 5.3 |

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Zhao, et al., 2020) | Retrospective study | 1/2014-12/2019 | China | CLSI | Single-center (767-bed blood diseases hospital) | BSI | 5.0 |

**Table C-54. Study Mortality Information, MDR *P. aeruginosa***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Borgatta, et al., 2017) | 68% | Not Studied | Not Studied | Not Studied | 8% |
| (Cillóniz, et al., 2016) | 23% | 17% | 5% | 0.6 | 9% |
| (Dantas, et al., 2014) | 42% | 41% | 1% | 0.92 | 7% |
| (Dantas, et al., 2014) | 59% | Not Studied | Not Studied | 19.00% | 12% |
| (Dantas, et al., 2014) | 40% | Not Studied | Not Studied | 1 | 22% |
| (Lu, et al., 2012) | 16% | 23% | -7% | 0.357 | 6% |
| (Micek, et al., 2015) | 45% | 32% | 13% | 0.001 | 3% |
| (Morata, et al., 2012) | 32% | 17% | 15% | <0.0001 | 4% |
| (Morata, et al., 2012) | 64% | 44% | 20% | Not Reported | 10% |
| (Morata, et al., 2012) | 5% | 8% | -3% | Not Reported | 5% |
| (Peña, et al., 2013) | 50% | 55% | -5% | 0.33 | 6% |
| (Peng, et al., 2014) | 26% | 13% | 14% | <0.01 | 3% |
| (Tam, et al., 2010) | 40% | 12% | 28% | 0.003 | 10% |
| (Trecarichi, et al., 2011) | 41% | 9% | 32% | 0.06 | 9% |
| (Tumbarello, et al., 2011) | 50% | 24% | 26% | 0.006 | 8% |
| (Tumbarello, et al., 2020) | 9% | 12% | -3% | 0.49 | 4% |
| (Zhang, et al., 2020) | 71% | Not Studied | Not Studied | 0.042 | 7% |
| (Zhang, et al., 2020) | 50% | Not Studied | Not Studied | <0.001 | 6% |
| (Zhang, et al., 2020) | 0% | Not Studied | Not Studied | 0.066 | Unknown |
| (Zhao, et al., 2020) | 29% | 5% | 23% | <0.001 | 7% |

**Table C-55. Study Length of Stay Information, MDR *P. aeruginosa***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Borgatta, et al., 2017) | 21 | Not Studied | 25 | Not Studied | Not Studied | 0.42 |
| (Cillóniz, et al., 2016) | 22 | 46 | 14 | 11 | 3 | 0.046 |

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Dantas, et al., 2014) | 57 | 63 | 59 | 62 | -3 | 0.41 |
| (Lu, et al., 2012) | 43 | 122 | 54 | 25 | Not Studied | <0.001 |
| (Micek, et al., 2015) | 226 | 514 | 27 | 25 | Not Studied | 0.09 |
| (Morata, et al., 2012) | 127 | 582 | 31.83 | 16.38 | Not Studied | <0.0001 |
| (Peng, et al., 2014) | 188 | 160 | 39 | 24 | 15 | <0.01 |
| (Tam, et al., 2010) | 25 | 84 | 26.4 | 16.5 | 9.9 | 0.12 |
| (Tumbarello, et al., 2011) | 40 | 66 | 27 | 17 | 10 | 0.01 |
| (Tumbarello, et al., 2020) | 65 | 177 | 48 | 22 | 26 | <0.001 |
| (Zhang, et al., 2020) | 38 | 225 | 27 | 26 | 1 | 0.44 |

**Table C-56. General Study Information, Carbapenem-Resistant *E. aerogenes/E. cloacae***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Pang, et al., 2018) | Retrospective study | 1/2010-12/2016 | China | CLSI | Multi (3 large comprehensive tertiary hospitals) | Any infection; ventilator-associated bacterial pneumonia; BSI; complicated UTI / acute pyelonephritis; hospital-acquired bacterial pneumonia; superficial wound infection; biliary tract infection; deep wound infection; sterile body fluids infection | 5.3 |
| (Tuon, et al., 2017) | Retrospective cross-sectional study | 1/2010-8/2014 | Brazil | CLSI | Multi | Ventilator-associated pneumonia | 6.5 |
| (Vargas-Alzate, et al., 2018) | Cohort study | 10/2014-9/2015 | Columbia | CLSI | Single (754-bed university hospital) | Pneumonia, BSI, SSI and intra-abdominal | 8.0 |
| (Zhao, et al., 2021) | Retrospective observational study | 1/2003-12/2017 | Scotland | Not Reported | Multi | Any infection | 14.0 |

**Table C-57. Study Mortality Information, Carbapenem-Resistant *E. aerogenes/E. cloacae***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Pang, et al., 2018) | 23% | Not Studied | Not Studied | Not Studied | 4% |
| (Pang, et al., 2018) | 32% | Not Studied | Not Studied | Not Studied | 8% |
| (Pang, et al., 2018) | 45% | Not Studied | Not Studied | Not Studied | 11% |
| (Pang, et al., 2018) | 6% | Not Studied | Not Studied | Not Studied | 5% |
| (Pang, et al., 2018) | 25% | Not Studied | Not Studied | Not Studied | 11% |
| (Pang, et al., 2018) | 6% | Not Studied | Not Studied | Not Studied | 6% |
| (Pang, et al., 2018) | 0% | Not Studied | Not Studied | Not Studied | Unknown |
| (Pang, et al., 2018) | 14% | Not Studied | Not Studied | Not Studied | 13% |
| (Pang, et al., 2018) | 20% | Not Studied | Not Studied | Not Studied | 18% |
| (Tuon, et al., 2017) | 57% | Not Studied | Not Studied | Not Studied | 5% |
| (Vargas-Alzate, et al., 2018) | 23% | 13% | 10% | 0.12 | 6% |
| (Zhao, et al., 2021) | 15% | Not Studied | Not Studied | Not Studied | 3% |

**Table C-58. Study Length of Stay Information, Carbapenem-Resistant *E. aerogenes/E. cloacae***

| Reference | Resistant Strain Sample Size | Susceptible Strain Sample Size | Resistant Strain LOS (Days) | Susceptible Strain LOS (Days) | Excess LOS (Days) | p-value |
|---|---|---|---|---|---|---|
| (Pang, et al., 2018) | 124 | Not Studied | 11.3 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 31 | Not Studied | 15.8 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 22 | Not Studied | 14.6 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 18 | Not Studied | 6.7 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 16 | Not Studied | 10.5 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 16 | Not Studied | 9.3 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 9 | Not Studied | 7.6 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 7 | Not Studied | 8.3 | Not Studied | Not Studied | Not Studied |
| (Pang, et al., 2018) | 5 | Not Studied | 10.4 | Not Studied | Not Studied | Not Studied |
| (Tuon, et al., 2017) | 112 | Not Studied | 31 | Not Studied | Not Studied | <.001 |
| (Vargas-Alzate, et al., 2018) | 48 | 170 | 15 | 11 | 4 | 0.016 |
| (Zhao, et al., 2021) | 211 | Not Studied | 8 | Not Studied | Not Studied | Not Studied |

**Table C-59. General Study Information, MDR *E. aerogenes/E. cloacae***

| Reference | Study Design | Enrollment Period | Country | Resistance Reference | Setting | Infection Site | Overall Score |
|---|---|---|---|---|---|---|---|
| (Zhong, et al., 2012) | Retrospective cohort study | 1/2007-4/2010 | China | CLSI | Single (1586-bed tertiary-care institute specializing in organ transplantation) | Any infection | 6.0 |

**Table C-60. Study Mortality Information, MDR *E. aerogenes/E. cloacae***

| Reference | Mortality for Resistant Strain | Mortality for Susceptible Strain | Excess Mortality | p-value | Standard Error in Resistant-Strain Mortality |
|---|---|---|---|---|---|
| (Zhong, et al., 2012) | 38% | 24% | 14% | 0.292 | 8% |

# D APPENDIX – HEALTHCARE COST STUDIES

| Source | Pathogen | Infection Site | Resistance | Parameter Reported | Year | Cost (in Year Reported $) | Cost (in 2020 $) | Lower Bound | Upper Bound |
|---|---|---|---|---|---|---|---|---|---|
| (CDC, 2019) | Enterobacterales | Any Infection | Carbapenem Resistance | Excess Healthcare Cost | 2017 | $9,924 | $10,771 | NA | NA |
| (Branch-Elliman, et al., 2013) | *Staphylococcus aureus* | ABSSSI | Multi-Drug Resistance | Excess Healthcare Cost | 2012 | $507 | $627 | -$1,011 | $2,277 |
| (Kadri, et al., 2019) | GNI | Any Infection | Proxy of resistance (Colistin for 4 days equates to XDR) | Excess Healthcare Cost | 2014 | $35,856 | $42,207 | NA | NA |
| (MacVane, et al., 2014) | ESBL+*E. coli* | UTI | Not determined | Excess Healthcare Cost | 2012 | $3,658 | $4,523 | NA | NA |
| | ESBL+*Klebsiella* spp. | UTI | Not determined | Excess Healthcare Cost | 2012 | $3,658 | $4,523 | NA | NA |
| (Neidell, et al., 2012) | *K. pneumoniae* | Any Infection | Carbapenem Resistance | Excess Healthcare Cost | 2008 | $13,200 | $18,602 | -$8,315 | $45,378 |
| | *P. aeruginosa* | Any Infection | Fluoroquinolone Resistance | Excess Healthcare Cost | 2008 | $31,400 | $44,251 | $14,234 | $74,409 |
| | Not determined | BSI | Resistant | Excess Healthcare Cost | 2008 | $27,100 | $38,191 | $8,456 | $67,927 |
| | Not determined | UTI | Resistant | Excess Healthcare Cost | 2008 | $4,300 | $6,060 | -$28,608 | $40,587 |
| | Not determined | Pneumonia | Resistant | Excess Healthcare Cost | 2008 | $14,300 | $20,153 | $7,751 | $32,695 |
| (Nelson, et al., 2021) | Invasive Enterobacterales | Any Infection | Carbapenem Resistance | Healthcare Cost | 2017 | $8,354 | $9,067 | -$1,293 | $19,427 |
| | Non-invasive Enterobacterales | Any Infection | Carbapenem Resistance | Healthcare Cost | 2017 | $5,154 | $5,594 | $985 | $10,202 |
| | Invasive Enterobacteriacea | Any Infection | Extended-Spectrum Cephalosporin Resistance | Healthcare Cost | 2017 | $33,637 | $36,508 | $21,787 | $51,228 |

| Source | Pathogen | Infection Site | Resistance | Parameter Reported | Year | Cost (in Year Reported $) | Cost (in 2020 $) | Lower Bound | Upper Bound |
|---|---|---|---|---|---|---|---|---|---|
| | Non-invasive Enterobacteriacea | Any Infection | Extended-Spectrum Cephalosporin Resistance | Healthcare Cost | 2017 | $16,240 | $17,626 | $12,282 | $22,969 |
| | Invasive *Acinetobacter* | Any Infection | Carbapenem Resistance | Healthcare Cost | 2017 | $74,306 | $80,648 | $22,116 | $139,180 |
| | Non-invasive *Acinetobacter* | Any Infection | Carbapenem Resistance | Healthcare Cost | 2017 | $30,590 | $33,201 | $13,875 | $52,527 |
| | Invasive *Pseudomonas* | Any Infection | Multi-Drug Resistance | Healthcare Cost | 2017 | $66,934 | $72,647 | $35,755 | $109,539 |
| | Non-invasive *Pseudomonas* | Any Infection | Multi-Drug Resistance | Healthcare Cost | 2017 | $50,810 | $55,147 | $44,567 | $65,727 |
| | Invasive Enterobacteriacea e | Any Infection | Multi-Drug Resistance | Healthcare Cost | 2017 | $54,614 | $59,275 | $29,296 | $89,255 |
| | Non-invasive Enterobacteriacea e | Any Infection | Multi-Drug Resistance | Healthcare Cost | 2017 | $16,606 | $18,023 | $9,425 | $26,623 |
| (Thaden, et al., 2017) | *E. coli* | BSI | Resistant & Susceptible | Healthcare Cost | 2015 | $14,776 | $16,960 | $4,937 | $15,435 |
| | *E. coli* | BSI | Multi-Drug Resistance | Healthcare Cost | 2015 | $18,917 | $21,714 | $6,789 | $22,553 |
| | *K. pneumoniae* | BSI | Resistant & Susceptible | Healthcare Cost | 2015 | $28,877 | $33,146 | $6,835 | $33,806 |
| | *K. pneumoniae* | BSI | Multi-Drug Resistance | Healthcare Cost | 2015 | $115,868 | $132,998 | $14,314 | $176,631 |
| | Enterobacter spp. | BSI | Resistant & Susceptible | Healthcare Cost | 2015 | $42,717 | $49,032 | $7,682 | $50,070 |
| | Enterobacter spp. | BSI | Multi-Drug Resistance | Healthcare Cost | 2015 | $108,163 | $124,154 | $22,128 | $190,846 |
| (Thorpe, et al., 2018) | Not determined | Any Infection | Resistant | Excess Healthcare Cost | 2014 | $1,383 | $1,628 | $1,234 | $2,021 |
| (Zimlichman, et al., 2013) | Not determined | SSI | Resistant & Susceptible | Healthcare Cost | 2012 | $20,785 | $25,698 | $23,369 | $28,024 |

| Source | Pathogen | Infection Site | Resistance | Parameter Reported | Year | Cost (in Year Reported $) | Cost (in 2020 $) | Lower Bound | Upper Bound |
|---|---|---|---|---|---|---|---|---|---|
| | *Staphylococcus aureus* | SSI | Multi-Drug Resistance | Healthcare Cost | 2012 | $42,300 | $52,298 | $4,952 | $102,209 |
| | Not determined | BSI | Resistant & Susceptible | Healthcare Cost | 2012 | $45,814 | $56,642 | $38,227 | $80,666 |
| | *Staphylococcus aureus* | BSI | Multi-Drug Resistance | Healthcare Cost | 2012 | $58,614 | $72,467 | $20,721 | $216,058 |
| | Not determined | UTI | Resistant & Susceptible | Healthcare Cost | 2012 | $896 | $1,108 | $746 | $1,470 |
| | Not determined | Pneumonia | Resistant & Susceptible | Healthcare Cost | 2012 | $40,144 | $49,632 | $44,862 | $54,671 |