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Antimicrobial Susceptibility of Clinical Isolates of *Acinetobacter baumannii*- A Systematic Review and Meta-Analysis

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Abstract **Background:** *Acinetobacter baumannii* has emerged as a significant nosocomial pathogen with a high rate of multidrug resistance (MDR). This review was conducted systematically to meta-analyze the antimicrobial susceptibility of *A. baumannii* isolates, especially focusing on resistance trends, mechanisms and geographic variability. **Methods:** A systematic search was conducted across seven databases: PubMed, Scopus, Web of Science, Embase, Cochrane Library, CINAHL and ScienceDirect. All of the databases were easily modified using appropriate Boolean operators and MeSH terms to further narrow down the specific outcome for the search strategy. All the studies for this systematic review were observational, retrospective, prospective, cross-sectional or in-vitro and involved an analysis of resistance of *A. baumannii* against antimicrobial therapy. **Results:** A total of 21 studies were included, representing diverse geographic regions. The meta-analysis demonstrated that carbapenem resistance persisted at alarmingly high levels across all geographic locations, with the highest rates observed in the Middle Eastern and Asian regions. Despite this, colistin remained largely effective, with susceptibility rates exceeding 90% in most studies. The presence of resistance genes, particularly *blaOXA-23* and *blaOXA-51*, was frequently reported and associated with the widespread emergence of MDR and XDR strains. The overall heterogeneity was significantly high ($I^2 = 99\%$), reflecting variability in study design, sample size and antimicrobial testing methodologies. Sensitivity analysis indicated that excluding smaller and in-vitro studies reduced heterogeneity and strengthened the association of carbapenem resistance trends. Due to substantial inter-study variability and asymmetric study distribution, a funnel plot analysis could not be conducted reliably. **Conclusion:** The findings highlight the global heterogeneity and severity of *A. baumannii* resistance, particularly to carbapenems, which presents ongoing challenges in infection management. While colistin remains a viable last-resort antibiotic, regional variations in resistance patterns emphasize the need for enhanced antimicrobial stewardship and continuous surveillance efforts to mitigate the spread of MDR *A. baumannii*.

Key Words *Acinetobacter baumannii*, Antimicrobial Resistance, Multidrug-Resistant Bacteria, Nosocomial Infections, Carbapenem Resistance, Colistin

INTRODUCTION

Acinetobacter baumannii has emerged as one of the most challenging clinical pathogens, especially in high-risk settings, such as intensive care units. Its notoriety is mainly due to its extensive arsenal of resistance mechanisms against antimicrobial agents and to survive in adverse environmental conditions [1]. This gram-negative bacterium, non-fermenting, can last on dry surfaces and inanimate objects for long periods; hence, it continues transmitting in healthcare facilities, adding to the burden of hospital-acquired infections. Of the species mentioned above, *A. baumannii* is uniquely associated with ventilator-associated pneumonia, bloodstream infections, urinary tract infections, surgical site infections and wound infections of critically ill patients [2-3]. The versatility and robustness of its environment of *A. baumannii* has made it quite challenging to control within healthcare settings, thus emphasizing its role as an emerging healthcare-associated pathogen [4].

Multi-and complex resistance mechanisms of *A. baumannii* infections complicate their clinical impact. These mechanisms include enzymatic degradation of antibiotics, decreased membrane permeability, changes in target sites,

and overexpression of efflux pumps [5]. *A. Baumannii* is highly resistant to all β-lactams: penicillins, cephalosporins and carbapenems, the backbone of treatment of gram-negative infections for decades. The development of CRAB strains presents a significant threat since most first-line drugs will be useless and patients are limited to polymyxins, tigecycline and certain combinations [6]. Polymyxins, such as colistin, have been readmitted as a last resort; however, strains emerging resistant to polymyxins do not make therapy any easier and make alarming treatment failures and raise the risk of mortality in infected patients [7].

Epidemiological studies provided the scientific evidence for intrinsic resistance to antimicrobials and the additional selective forces that developed in the healthcare setting: overuse of antimicrobial agents and deficiencies in infection control [7-9]. This combination is responsible for creating the highly resistant MDR, XDR and PDR phenotypes of *A. baumannii* and positioning this organism among ESKAPE pathogens - a newly designated set of organisms, characterized as able to resist antimicrobial therapy. The MDR nature of *A. baumannii* makes most antibiotics not very effective against it and requires use of combination regimens or novel approaches of therapy [10]. Given the panga-continental spread and versatility of *A. baumannii*, the resistance patterns do vary geographically. Differences in resistance patterns have also been ascribed to geographical variations in local antimicrobial prescribing, infection control practices and available treatments in those different regions [10-12]. Regional differences imply the need for constant vigilance and should inform developing policies that will be best suited to the treatment areas where *A. baumannii* infections are reported to be a problem.

For this bacterium, knowledge of the resistance profiles of its clinical isolates in various geographical settings is important. Our review, therefore, aims to integrate and synthesize the available data regarding the antimicrobial susceptibility of clinical isolates of *A. baumannii* in an attempt to present evidence-based overview of effectiveness of the existing antimicrobial agents and highlight possible alternatives in order to guide the decision-making on therapy for patients attending high-incidence clinical settings infected with *A. baumannii*.

MATERIALS AND METHODS

PECOS Protocol and PRISMA Compliance

We utilised the PECOS (Population, Exposure, Comparison, Outcome, Study design) framework in guiding the structured approach of this review. The populations targeted were defined by clinical isolates of *Acinetobacter baumannii* obtained from various healthcare settings. The main exposure assessed was antimicrobial susceptibility, by analyzing in-vitro resistance profiles against a spectrum of antimicrobial agents without a specific comparative intervention, considering the nature of data provided by in-vitro studies. The most relevant outcomes included detailed percentages of resistance, MIC values and phenotypic and genotypic mechanisms responsible for antimicrobial resistance. Only studies that were meeting standard in-vitro methodological criteria and have results transparently applied to antimicrobial susceptibility were considered. Only observational study types were included in the review, including retrospective and cross-sectional studies. Table 1 lists the inclusion and exclusion criteria devised for the review.

Database Search Protocol

The search in the literature was done across seven databases: PubMed, Scopus, Web of Science, Embase, Cochrane Library, CINAHL and ScienceDirect. We adapted Boolean operators and MeSH terms within each database to improve the relevance of retrieval strategies. The search used "AND" to combine the major terms, while "OR" combined the synonyms of each of them. The MeSH keywords furthered precision by capturing studies indexed under specific headings relevant to bacterial resistance and susceptibility testing (Table 2).

Data Extraction Protocol and Selected Data Items

Data extraction included a systematic collection of predefined data items relevant to the evaluation of trends of antimicrobial resistance in *Acinetobacter baumannii*. A standardized form captured study metadata, including authors, year and country; isolate source, including clinical setting and specimen type; methods of identification and resistance testing, including antimicrobial agents tested and MIC values; and detailed resistance data, including percentages of resistant, intermediate and susceptible isolates and MIC50 and MIC90 values. Other data items included resistance mechanisms, presence of resistance genes and overall study conclusions regarding susceptibility patterns. For all included studies, the methodological quality was critically appraised in ensuring that the data extracted independently by two reviewers were free from errors or disagreement.

Bias Evaluation Protocol

Risk of bias was assessed on the basis of a ROBINS-I tool for observational studies, AXIS tool for cross-sectional studies and DARE tool for in-vitro studies, where applicable.

Statistical Analysis Protocol

Meta-analysis was performed using RevMan 5.4.1, employing the Random-Effects (RE) model to account for inter-study heterogeneity. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were used to compare antibiotic resistance rates across studies. Heterogeneity was quantified using the I^2 statistic and Chi^2 test.

Funnel plots are commonly used to assess publication bias by evaluating asymmetry in study distribution. However, in this study, a funnel plot analysis could not be conducted for several reasons. First, extreme heterogeneity ($I^2 = 99\%$) made the interpretation of funnel plots unreliable, as heterogeneity can mimic publication bias. Second, significant variability in study designs, sample sizes and

Table 1: Inclusion and exclusion criteria devised for this review

Criterion	Inclusion	Exclusion
Population	Clinical isolates of Acinetobacter baumannii from any healthcare-associated source	Non-Acinetobacter baumannii species; environmental or non-clinical isolates
Exposure	Antimicrobial susceptibility testing with standardized methods	Non-standardized or unverified susceptibility testing procedures
Comparison	Not required	
Outcome	Quantitative data on resistance levels, MIC values, resistance mechanisms	Studies lacking specific resistance data or MIC measurements
Study Design	Observational (cross-sectional, retrospective, prospective) in-vitro studies	Reviews, editorials, case reports, animal studies
Language	English	Non-English
Date range	Studies published from 2000 onwards	Studies published before 2000

Table 2: Database search strings utilised for this review

Database	Search String
PubMed	("Acinetobacter baumannii" [MeSH] OR "A. baumannii") AND ("antimicrobial resistance" OR "antibiotic resistance") AND ("clinical isolates" OR "hospital isolates") AND ("susceptibility testing")
Scopus	TITLE-ABS-KEY("Acinetobacter baumannii") AND TITLE-ABS-KEY("antibiotic resistance" OR "antimicrobial resistance") AND ("MIC" OR "susceptibility pattern")
Web of Science	("Acinetobacter baumannii" AND "drug resistance") AND ("in-vitro" OR "antimicrobial susceptibility" AND "ICU isolates")
Embase	('Acinetobacter baumannii'/exp OR 'A. baumannii') AND ('antimicrobial resistance'/exp OR 'drug resistance') AND ('MIC' OR 'in-vitro study')
Cochrane Library	("Acinetobacter infections" AND "antibiotic susceptibility" AND "observational studies")
CINAHL	("Acinetobacter baumannii" AND "antibiotic susceptibility" OR "hospital isolates") AND "resistance mechanisms"
ScienceDirect	("Acinetobacter baumannii" AND "antimicrobial testing") AND ("ICU-associated infection" OR "antibiotic resistance rates")

resistance testing methodologies prevented a meaningful assessment of small-study effects. Third, the dataset lacked a sufficient number of studies per antibiotic class to generate a stable funnel plot. Due to these factors, funnel plot analysis was not performed, as any results would have been statistically invalid and misleading.

The statistical methods used were chosen to accommodate the high heterogeneity across studies. The RE model was selected over a fixed-effects model because it accounts for variability in study design, methodology and sample size. Additionally, sensitivity analyses were conducted to determine the effect of excluding smaller studies and in-vitro designs on overall resistance trends.

RESULTS

Study Selection Process

From database searches, 342 records were identified with no records from registers. After eliminating 37 duplicate records, 305 unique records were screened. Of these, 22 were excluded because the full text was unavailable. Of the 283 reports sought for retrieval, 34 could not be retrieved, leaving 249 reports for eligibility assessment. Of these, 228 reports were excluded due to lack of relevance, n = 44; literature reviews, n = 31; scoping reviews, n = 24; gray literature, n = 34; case reports, n = 56; and animal studies, n = 39. Altogether, 21 studies [17-37] were eligible and included in this review (Figure 1).

Demographic Variables Assessed

Table 3 summarizes the demographic characteristics and study designs of the selected studies [17-37]. Altun *et al.* [17] conducted an observational study in Ankara, Turkey with a subset of 30 isolates from an initial 300 collected over a period from January 2010 to March 2012, while Bansal *et al.* [18] in Washington DC, USA, also conducted an observational study but analyzed 28 isolates without any specific follow-up period. Chang *et al.* [19] and Chuang *et al.* [20] of Taiwan, utilized a retrospective and observational study respectively with sample sizes of 262 and 151 isolates, thus implying that the study has a strong focus on retrospective and cross-sectional analysis.

Dafopoulou *et al.* [21] had the largest study with 12,646 isolates over six years in Greece showing a strong longitudinal perspective. In Portugal, Duarte *et al.* [22] used an observational setting and assessed 79 individuals. Ghaima *et al.* [23] in Iraq conducted a prospective study where 96 isolates were collected over a short period of time between February and July 2015. Guckan *et al.* [24] in Turkey conducted a retrospective observational study with a follow-up of 163 isolates for 3.5 years. It can be seen that there is considerable variability in the length of the study and design used in the retrospective studies (Table 4).

Hsueh *et al.* [26] typified international surveillance with an in-vitro study of 2905 isolates, thus showing international large-scale data collection. Most studies from India were retrospective in design, as in the case of Jaggi *et al.* [27] with 155 isolates from Gurgaon and Tewari *et al.* [36] with 67 isolates from Delhi. In addition, cross-sectional observational studies were found in Kafshnouchi *et al.* [28] in Iran and Sohail *et al.* [34] in Pakistan with sample sizes of 100 and 716 isolates respectively, which indicate an extensive focus on regional and cross-sectional assessments.

Liu *et al.* [30] conducted a nation-wide surveillance study in China by covering 20 provinces that had 245 CRAB

Table 3: Demographic variables assessed

Study Name	Year	Location	Study Design	Sample Size	Follow-up Period
Altun *et al.* [17]	2014	Ankara, Turkey	Observational study	30 (subset from initial 300 isolates)	January 2010 - March 2012
Bansal *et al.* [18]	2020	Washington DC, USA	Observational study	28 isolates	Not applicable
Chang *et al.* [19]	2021	Taiwan	Retrospective observational study	262 isolates	Not applicable
Chuang *et al.* [20]	2014	Taiwan	Observational study	151 isolates	Not applicable
Dafopoulou *et al.* [21]	2018	Greece	Retrospective	12,646 isolates	6 years
Duarte *et al.* [22]	2016	Covilhã, Portugal	Observational study	79 individuals	Not applicable
Ghaima *et al.* [23]	2016	Baghdad hospitals, Iraq	Prospective	96 A. baumannii isolates	Feb - July 2015
Guckan *et al.* [24]	2017	Amasya, Turkey	Retrospective observational study	163 isolates	3.5 years (January 2012 - June 2015)
Gupta *et al.* [25]	2015	Pune, India	Observational study	111 isolates	2 years
Hsueh *et al.* [26]	2024	Global	In-vitro observational study	2905 isolates	Not applicable
Jaggi *et al.* [27]	2012	Gurgaon, India	Retrospective observational study	155 isolates	14 months (December 2008 - January 2010)
Kafshnouchi *et al.* [28]	2022	Hamadan, Iran	Cross-sectional observational study	100 isolates	Not applicable
Konca *et al.* [29]	2021	Adiyaman, Turkey	Retrospective observational study	33 isolates	January 2015 - January 2017
Liu *et al.* [30]	2022	China (20 provinces, 77 ICUs)	Nationwide surveillance	245 CRAB isolates	June-Sept 2020
Maleki *et al.* [31]	2022	Tehran, Iran	Cross-sectional observational study	60 isolates	October 2020 - July 2021
Sánchez-Urtaza *et al.* [32]	2023	Alexandria, Egypt	Observational study	36 isolates	Not applicable
Shah *et al.* [33]	2019	Jeddah, Western Saudi Arabia	Observational study	135 isolates	Not applicable
Sohail *et al.* [34]	2016	Lahore, Pakistan	Cross-sectional observational study	716 isolates	28 months (January 2012 - April 2014)
Sung *et al.* [35]	2018	Daejeon, Korea	In-vitro observational study	58 isolates	Not applicable
Tewari *et al.* [36]	2018	Delhi, India	Retrospective study	67 A. baumannii isolates (out of 16,452 total samples)	2 years (Jan 2013 - Dec 2015)
Tunyapanit *et al.* [37]	2014	Songkhla, Thailand	In-vitro observational study	100 isolates	Not applicable

isolates from 77 ICUs. Such study would be comprehensive on how the distribution of CRAB may occur in clinical sites. Sung *et al.* [35] and Tunyapanit *et al.* [37] used samples of 58 and 100, respectively. Such studies were done as an in-vitro method in Korea and Thailand. Sample sizes were done based on controlled laboratory conditions.

Bacterial Strain Identification Protocol

Altun *et al.* [17] used the VITEK 2 Compact system and rep-PCR genotyping to identify the samples derived from tracheal aspirates, blood and catheters. The occurrence of respiratory and bloodstream infection sources reveals a nosocomial infection target, i.e., VAP and BSI. Similarly, Bansal *et al.* [18] employed the VITEK 2 system for the identification of isolates from miscellaneous clinical sources, implying a generalized approach encompassing infections of miscellaneous types. The use of automated identification systems such as VITEK 2 in both studies ensures rapid bacterial identification and antimicrobial susceptibility profiling, which is critical for infection management at the right time.

Chang *et al.* [19] used a more procedural microbiological approach, employing standard laboratory protocols for the analysis of endotracheal aspirates from ICU patients. The research included both Pseudomonas aeruginosa (PA) and *A. baumannii* complex (ABC) isolates, providing a potential for comparison of pathogenicity patterns and resistance between the clinically significant bacteria. Chuang *et al.* [20] employed a molecular approach of bacterial identification by 16S-23S rRNA sequencing of sputum, urine, blood and wound samples. The application of ribosomal RNA-based identification makes it more specific and is the gold standard in bacterial taxonomy. The molecular focus of the study is an indication of the trend towards genotypic characterization in clinical microbiology, which offers the potential for discrimination between closely related bacterial species.

Likewise, Dafopoulou *et al.* [21] utilized VITEK 2 as well as the Microscan system to identify clinical isolates, while Duarte *et al.* [22] utilized VITEK 2 solely to examine sputum, urine, blood and peritoneal fluid isolates. The

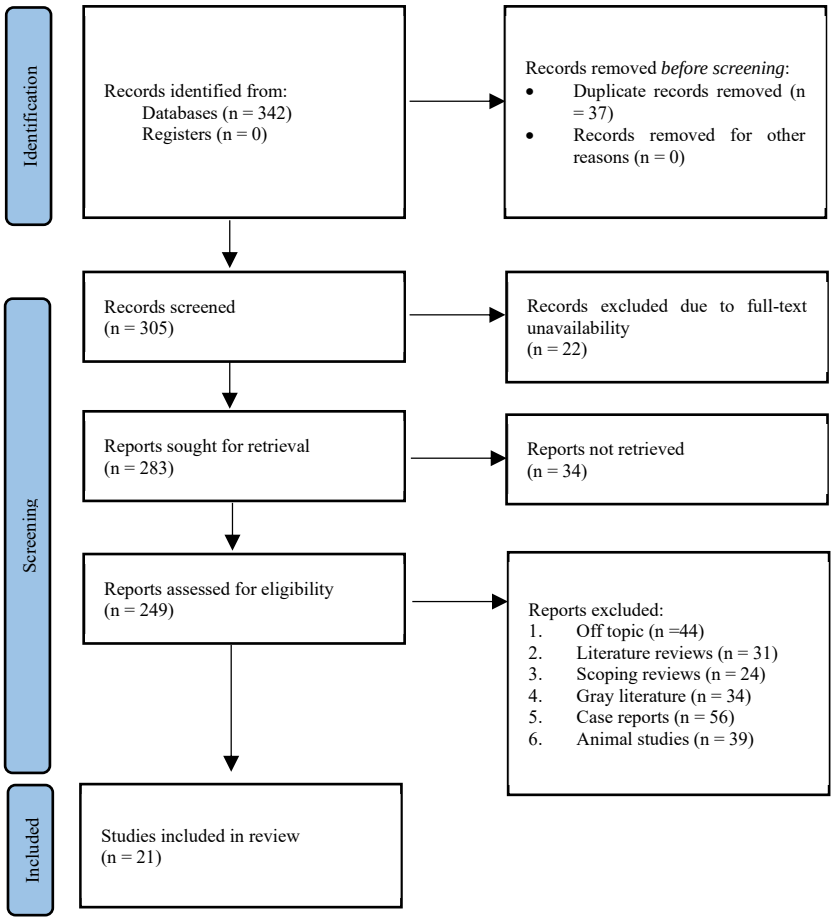

Figure 1: Description of the different stages of article selection process for the review

employment of more than one specimen reflects the extensive presence of *A. baumannii* in different sites of infection and its role in systemic and localized infections.

A more comprehensive, multi-method approach was adopted by Ghaima *et al.* [23], who employed CHROMagar Acinetobacter, API 20E, VITEK 2 and PCR amplification for burn wound isolate identification. blaOXA-51 and 16S rRNA gene-based PCR assays employed here demonstrate emphasis on carbapenem-resistant *A. baumannii* (CRAB) strain identification. This study emphasizes the importance of *A. baumannii* in severe, hospital-acquired infections, particularly in burn units where multi-drug resistant (MDR) strains complicate the care of patients. Guckan *et al.* [24] also employed VITEK 2 for isolate identification from respiratory, blood, wound and urine specimens with emphasis on ICU-acquired infections, demonstrating further concern regarding high MDR rates among critically ill patients.

Traditional microbiological techniques were employed by Gupta *et al.* [25], who used Gram staining, culture morphology and biochemical testing to identify isolates from blood, pus and respiratory specimens. While culture methods are still commonplace, they are less specific and more time-consuming than molecular testing, a requirement in treating rapidly progressing bacterial infections. Nevertheless, Hsueh *et al.* [26] employed MALDI-TOF and 16S-23S rRNA sequencing for accurate identification of bacteria, analyzing isolates from respiratory specimens, including lung tissue biopsy. The use of MALDI-TOF mass spectrometry is a new development in clinical microbiology that allows rapid, inexpensive bacterial identification with high specificity.

Jaggi *et al.* [27] utilized the application of VITEK 2 Compact to detect hospital-acquired isolates, i.e., urinary tract and respiratory tract infections, confirming the nosocomial status of *A. baumannii*. Kafshnouchi *et al.* [28] and Maleki *et al.* [31] utilized PCR-based molecular identification techniques, that is, on isolates derived from ICU. These studies indicate the high prevalence of MDR *A. baumannii* infection in ICU, where extended hospital stay, mechanical ventilation and immunosuppression predispose to transmission and persistence of infection.

Expanding the scope of automated systems even more, Konca *et al.* [29] employed the BD Phoenix 100 system for the automation of identification of isolates in respiratory, blood, pus and urine specimens to provide automatic, high-level processing. Liu *et al.* [30] performed large-scale nationwide surveillance through the analysis of 245 CRAB

Table 4: *A. baumannii*-associated observations assessed across the included papers

Study name	Bacterial strain identification	Specimen sources	Antimicrobial agents tested	Testing method & guidelines	Resistance findings	Key conclusion
Altun *et al.* [17]	VITEK 2 Compact, genotyped via rep-PCR	Tracheal aspirates, blood, catheter, etc.	Colistin, netilmicin, tigecycline, sulbactam, amikacin, meropenem	Broth microdilution, E-test; CLSI guidelines	High colistin sensitivity (100%); meropenem resistance (86.6%); MIC50/90 for netilmicin (4/512 µg/mL)	High resistance except to colistin; significant variability in MIC values across genotypes
Bansal *et al.* [18]	VITEK 2 system	Sputum, peritoneum, urine, blood, respiratory tract, wounds	Gentamicin, imipenem, ciprofloxacin, cefepime, levofloxacin, etc.	VITEK 2; CLSI guidelines	46% carbapenem-resistant; 18% MDR, 29% XDR; Presence of blaOXA-51 and blaOXA-23 genes	High MDR and XDR prevalence; significant presence of blaVIM and blaOXA-23 genes
Chang *et al.* [19]	Conventional lab methods	Endotracheal aspirates from ICU patients	Imipenem, ciprofloxacin, cefepime, tigecycline, etc.	Disk diffusion; CLSI guidelines	ABC highly resistant, PA isolates mostly susceptible; tigecycline effective against ABC	PA associated with poor lung function, lower BMI; early identification crucial in ICU management
Chuang *et al.* [20]	16S-23S rRNA sequencing	Sputum, urine, blood, wound	Ciprofloxacin, amikacin, colistin, imipenem, tigecycline	Agar dilution; CLSI guidelines	88.7% A. baumannii isolates; MIC50/MIC90 reported; Resistance genes: blaOXA-51, blaOXA-23, blaOXA-24	Significant clonal spread; high ciprofloxacin and amikacin resistance; colistin remains effective
Dafopoulou *et al.* [21]	Vitek 2/Microscan	Clinical isolates	Ampicillin/sulbactam, imipenem, gentamicin, colistin	Automated systems; EUCAST/CLSI guidelines	Rising resistance: ampicillin/sulbactam (46.2% to 88.2%), meropenem (82.6% to 94.8%)	Significant resistance increase over six years; need for antimicrobial stewardship
Duarte *et al.* [22]	VITEK2 system	Sputum, urine, blood, peritoneal fluid	Ampicillin, ceftazidime, gentamicin, colistin	VITEK2; CLSI guidelines	100% MDR; resistance to 12/17 antibiotics; all isolates susceptible to colistin	High MDR prevalence; 74.7% biofilm formation, especially in urinary isolates
Ghaima *et al.* [23]	CHROMagar Acinetobacter, API 20E, PCR	Burns, wounds	16 antibiotics including amikacin, gentamicin, imipenem	Disk diffusion, Broth microdilution; CLSI	High resistance to cefotaxime (87.5%), imipenem (81.3%); Low resistance to colistin (7.3%)	High resistance in A. baumannii isolates; early detection essential
Guckan *et al.* [24]	VITEK 2	Respiratory, blood, wound, urine	Colistin, imipenem, meropenem, gentamicin, tigecycline	VITEK 2; CLSI guidelines	High resistance to imipenem (89.1%), meropenem (90.3%), colistin resistance 5.5%	High resistance across major antibiotics except colistin; ICU risk highlighted
Gupta *et al.* [25]	Gram staining, biochemical tests	Blood, pus, respiratory samples	Piperacillin, ceftazidime, ceftriaxone, ciprofloxacin, imipenem	Kirby-Bauer disk diffusion; CLSI guidelines	High resistance to piperacillin (55%), ceftriaxone (46%); ESBL production 31.5%	High resistance rates in ICU isolates; seasonal variation observed
Hsueh *et al.* [26]	MALDI-TOF, 16S-23S rRNA	Lower respiratory tract	Colistin, minocycline, tigecycline, ciprofloxacin	Broth microdilution; CLSI (2022)	High colistin susceptibility (93.2%); prevalent blaOXA-23, blaOXA-72	Colistin and minocycline most effective; regional MIC variations noted
Jaggi *et al.* [27]	VITEK 2 Compact	Respiratory, blood, pus, fluids, urine	Amikacin, gentamicin, ciprofloxacin, imipenem, meropenem	VITEK 2; CLSI guidelines	Carbapenem resistance 90% (hospital-wide), 93.2% in ICU	High carbapenem resistance in ICU isolates; pathogenic in nosocomial infections
Kafshnouchi *et al.* [28]	PCR	ICU patients (blood, respiratory)	Meropenem, imipenem, amikacin, gentamicin, ciprofloxacin	Disk diffusion; CLSI guidelines	84% blaOXA-23-like, 58% blaOXA-24-like; 83% resistance to piperacillin	High prevalence of blaOXA genes; carbapenem resistance widespread

Konca *et al.* [29]	BD Phoenix 100	Respiratory, blood, pus, urine	Colistin, trimethoprim/sulfamethoxazole, tigecycline	BD Phoenix; CLSI guidelines	High resistance to all agents except colistin (>90%)	Effective drug limited to colistin; need for new protocols
Liu *et al.* [30]	MALDI-TOF	ICU patients	15 antibiotics, including imipenem, meropenem	Broth microdilution; CLSI	High resistance to imipenem (93.5%), meropenem (100%); low resistance to colistin (0.4%)	CRAB in 71.4% of ICUs; blaOXA-23 major carbapenem resistance gene
Maleki *et al.* [31]	PCR for blaOXA-51-like, gyrB genes	Catheters, pleural fluid, blood	Colistin, tigecycline, piperacillin/tazobactam	MIC via VITEK 2; CLSI guidelines	90% MDR, 10% XDR; colistin 100% sensitive	High MDR and XDR rates; requires close monitoring
Sánchez-Urtaza *et al.* [32]	VITEK 2, gyrB PCR	Bronchoalveolar lavage, swabs, blood	Ticarcillin, imipenem, colistin, cefiderocol	VITEK 2; EUCAST guidelines	100% resistance to ticarcillin and ciprofloxacin; blaOXA-23, blaNDM-1 genes detected	High carbapenem resistance; significant biofilm production
Shah *et al.* [33]	MALDI-TOF	Tracheal aspirate, blood, wound swab	Meropenem, imipenem, ceftazidime, ciprofloxacin	VITEK-2, Broth microdilution; CLSI	MDR in 58.5% of isolates; 55.6% carbapenem resistance	High carbapenem resistance; colistin susceptibility noted
Sohail *et al.* [34]	API 20NE	Urine, blood, wound, respiratory samples	Cefotaxime, ceftazidime, gentamicin, colistin, tigecycline	Disk diffusion; CLSI guidelines	99.2% resistance to cefotaxime/ceftazidime; colistin effective	High resistance; improved bacterial identification needed
Tunyapanit *et al.* [37]	Standard lab methods	Sputum, blood, urine, pus	Colistin, cefoperazone/sulbactam, imipenem, rifampicin	E-test; CLSI guidelines	59% MDR; MIC50/MIC90 reported	High susceptibility to colistin; rifampicin combination most effective

isolates from ICUs of 20 provinces in China using MALDI-TOF MS, amounting to an extensive effort toward mapping antibiotic resistance patterns.

Sánchez-Urtaza *et al.* [32] used a multi-method strategy involving VITEK 2 and gyrB PCR for the identification of bronchoalveolar lavage, blood and sputum samples' isolates. It is a method that provides phenotypic as well as genotypic identification, thereby more precise discrimination between species and resistance detection. Shah *et al.* [33] also utilized MALDI-TOF MS for tracheal aspirate and wound swabs' isolates, a universal strategy that can be applied to many varieties of clinical samples.

Sohail *et al.* [34] used the API 20NE system, a biochemical identification system, to screen urine, blood, wound and respiratory specimens. The system remains valid in low-resource environments, but can be slower and less sensitive than molecular techniques. Sung *et al.* [35] and Tunyapanit *et al.* [37] used in vitro experiments to isolate the samples using VITEK 2 and routine laboratory methods, with Sung *et al.* [35] adding partial rpoB sequencing for increased specificity. Tewari *et al.* [36] isolated bacteria from inpatients and outpatients, screening urine, pus and blood samples using VITEK 2 and biochemical reactions.

The broad range of identification methods and source materials used across these studies documents broad regional and methodological variation in characterization of bacterial strains. Automated systems (e.g., VITEK 2, BD Phoenix 100) provide rapid identification, while molecular procedures (e.g., PCR, 16S-23S rRNA, MALDI-TOF MS) provide better specificity and faster resistance detection. Methodological variation, however, can impact comparison across studies, influencing resistance monitoring and clinical decision-making. Among the most significant findings of this review is the general prevalence of *A. baumannii* among nosocomial infections, particularly in ICU and burn units. Isolation of highly resistant CRAB isolates in widespread surveillance studies (e.g., Liu *et al.* [30]) is consistent with worldwide trends of antimicrobial resistance (AMR) surveillance by WHO, EARS-Net and CDC AMR reports. Standardized AST protocols and harmonized identification methods should be priorities in future research to increase comparability between studies and improve global monitoring of resistance.

Antimicrobial Profile Observed

A very high resistance pattern has been noted in several studies of *Acinetobacter baumannii* isolates, especially to carbapenems, cephalosporins, aminoglycosides and fluoroquinolones. Colistin and tigecycline have been consistently effective as therapies, even against the rising tide of resistance that raises questions about their effectiveness in the future.

Altun *et al.* [17] also reported a 100% rate of complete susceptibility for colistin, highlighting its pivotal role as the ultimate therapeutic agent; however, they also reported an 86.6% high level of resistance for meropenem, highlighting the spread of carbapenem-resistant *A. baumannii* (CRAB) strains. The research also highlighted the fluctuating resistance to netilmicin and sulbactam, suggesting the limited range of therapeutic choices for the management of severe infection due to *A. baumannii*. Similarly, Bansal *et al.* [18]

reported a 46% carbapenem resistance incidence, as well as 18% multidrug-resistant (MDR) and 29% extensively drug-resistant (XDR) strains. The research also authenticated the identification of the blaOXA-51 and blaOXA-23 genes, which are known to be implicated in carbapenem resistance due to OXA-type carbapenemases, a report which is consistent with global antimicrobial resistance (AMR) surveillance reports.

Chang *et al.* [19] documented a species-specific susceptibility pattern variability with increased levels of resistance in *A. baumannii* complex (ABC) and increased susceptibility of Pseudomonas aeruginosa (PA) to carbapenems. The suggestion of this observation is the occurrence of unique mechanisms of resistance within the two organisms, thereby implying the necessity for the application of customized treatment methodologies. Chuang *et al.* [20] also elucidated gene-based mechanisms of resistance and documented that 88.7% of *A. baumannii* isolates were ciprofloxacin-resistant with moderate imipenem susceptibility at 80.6%. The research identified blaOXA-51 and blaOXA-23 genes as key drivers of resistance, portraying the role of genetic determinants in the modulation of patterns associated with antimicrobial resistance.

Time-course development of resistance was seen by Dafopoulou *et al.* [21] who demonstrated progressive increase in resistance over six years, i.e., to ampicillin/sulbactam, gentamicin and tobramycin. The same can be seen in longitudinal surveillance studies where loss of activity of antibiotics is progressively observed due to selective pressure and uncontrolled use of antimicrobials. Duarte *et al.* [22] also proved that all isolates of their study were MDR, although colistin was fully susceptible, i.e., it remains a therapeutic option despite the development of MDR strains.

Ghaima *et al.* [23] reported the occurrence of regional resistance patterns with high percentages of resistance against cefotaxime and imipenem, whereas tigecycline (11.5%) and colistin (7.3%) had partial activity. Likewise, in another report, Guckan *et al.* [24] and Gupta *et al.* [25] have reported the occurrence of antimicrobial resistance with high carbapenem resistance by Guckan and resistance against piperacillin as 55% by Gupta, along with high production of ESBL and MBL. The findings reflect the complex mechanisms of resistance in *A. baumannii* and confirm the requirement of newer therapeutic agents.

A pioneering work by Hsueh *et al.* [26] demonstrated that a high 93.2% susceptibility to colistin was preserved, highlighting its position as one of the very few remaining effective treatments for CRAB infection. However, the study also demonstrated the presence of regional variations in MIC levels, which can impact the clinical effectiveness of treatment, thus highlighting the need for localized surveillance of resistance patterns and individually adapted therapeutic measures. Furthermore, Jaggi *et al.* [27] and Kafshnouchi *et al.* [28] also demonstrated the widespread issue of carbapenem resistance in intensive care, where high antibiotic exposure coupled with hospital-acquired transmission ensures the constant presence of resistant strains.

Development of resistance to colistin has been documented by Konca *et al.* [29], which raised alarm about the waning efficacy of this essential last-resort antibiotic. Their report presented alarming resistance rates to all antibiotics tested, except for comparatively low resistance to colistin (0.4%) and tigecycline (2.5%), showing that these two drugs still retain efficacy against Chinese carbapenem-resistant *Acinetobacter baumannii* (CRAB). These findings are consistent with the report of Liu *et al.* [30], who tested 245 CRAB isolates obtained from intensive care units in 20 Chinese provinces and found that tigecycline and colistin retained their efficacy, whereas resistance to other antimicrobial drugs remained largely high.

Adding to the global burden of AMR, Maleki *et al.* [31] documented 90% MDR and 10% XDR isolates, all of which were fully sensitive to colistin. Similarly, Sánchez-Urtaza *et al.* [32] documented high resistance to imipenem and ciprofloxacin, which was predominantly attributed to the presence of blaOXA-23 gene, emphasizing the genetic aspect of resistance spread. Shah *et al.* [33] also documented 58.5% MDR and 55.6% carbapenem resistance, resistance attributed to multiple genetic determinants like blaOXA-23 and blaNDM-1.

Despite the extremely high resistance to aminoglycosides and cephalosporins in all the aforementioned studies, retained activity was invariably observed with tigecycline and colistin and these were the most important drugs in the treatment of CRAB infections. Sung *et al.* [35] brought this out by distinguishing between MDR and non-MDR isolates based on the presence or absence of the armA gene, a known aminoglycoside resistance determinant. Very high MDR rates were initially reported by Tewari *et al.* [36], again making the case for colistin as the drug of choice in the face of the danger of emerging resistance patterns. Finally, Tunyapanit *et al.* [37] documented 59% MDR prevalence, where colistin had residual activity. The report noted the continued challenge in the treatment of *A. baumannii* infection, particularly under the backdrop of circumstances where the high antibiotic resistance prevailed. The large difference of the susceptibility rate of colistin between the different studies suggests the importance of close surveillance and prudent use of the antimicrobial for preventing the emergence of resistance to colistin and ensuring therapeutic effectiveness. Clinical and Epidemiological Implications The results obtained from the studies cited clarify the rising threat caused by CRAB isolates, especially in ICU and hospital-acquired infections. The repeated carbapenem-resistant infections noted in most of these studies coincides with the findings reported by the WHO, CDC and EARS-Net AMR global reports, confirming that CRAB strains are a critical public health concern globally. The increased rate of incidence of colistin resistance in some regions also confirms the urgent need for the implementation of new antimicrobial strategies, combination

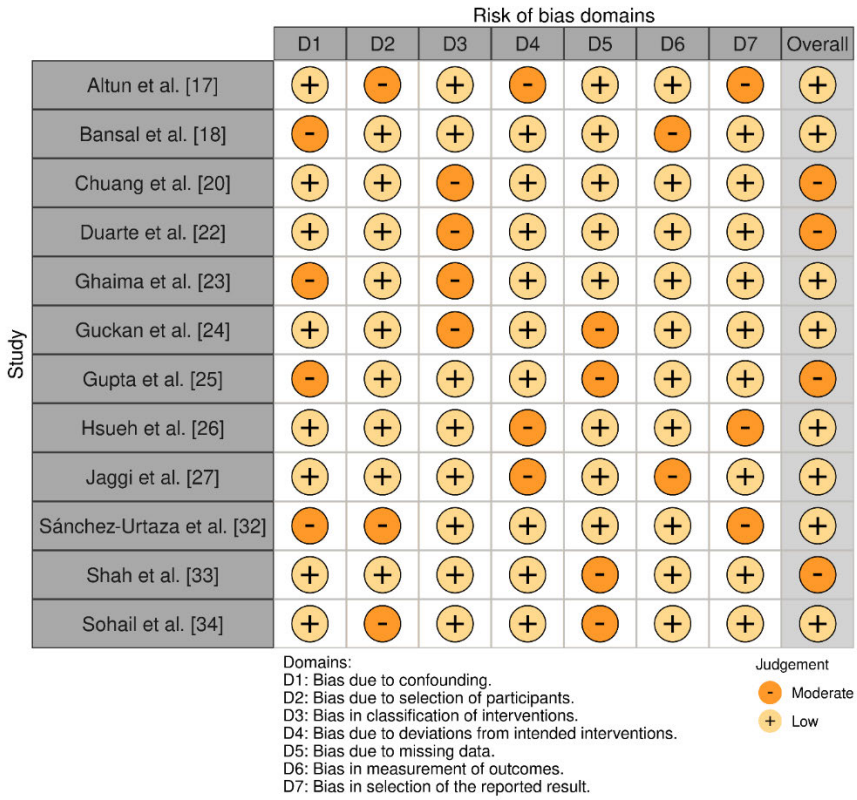

Figure 2: Bias assessment using the ROBINS-I tool

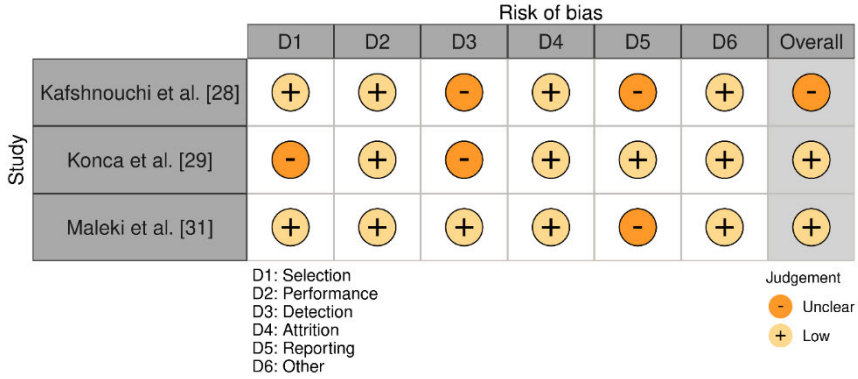

Figure 3: Bias assessment using the AXIS tool

therapy and the discovery of new drugs. Though tigecycline and colistin are the most potent drugs at the moment, the difference in the MIC values and the resistance pattern noted in different regions confirms that therapeutic efficacy might not always be consistent across different locations. Future studies need to concentrate on genotypic surveillance, studies on alternative therapeutic agents and enhanced knowledge of resistance mechanisms against the development of multidrug-resistant infections caused by *A. baumannii*.

Quality Assessment Observations

Altun *et al.* [17], Duarte *et al.* [22] and Shah *et al.* [33] score lower generally on the overall bias using the ROBINS-I tool as shown in Figure 2 with occasional ratings on specific domains as a moderate rating as seen with D2, Confounding on Altun *et al.* [17] while a "Moderate" rating on D6, Bias due to missing data of Hsueh *et al.* [26]. Others also presented a moderate risk for various domains. IThere were some issues of limitations in the studies such as Gupta *et al.* [25] and Sánchez-Urtaza *et al.* [32]. There was a problem related to the study design or handling data.

The AXIS tool (Figure 3) applied to studies by Kafshnouchi *et al.* [28], Konca *et al.* [29] and Maleki *et al.* [31], revealed moderate bias in performance and detection domains. Kafshnouchi *et al.* also exhibited moderate bias in reporting, which indicates a possible issue in transparency and completeness of reporting. Konca *et al.* [29] showed low bias in most domains but moderate bias in selection, which indicates areas for improvement in sample representativeness.

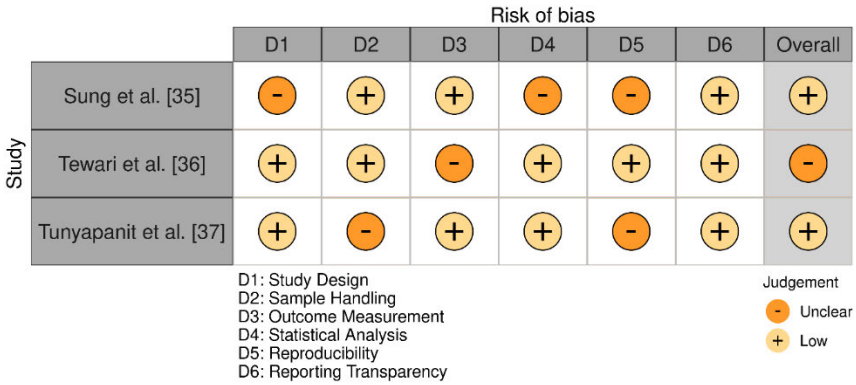

Figure 4: Bias assessment using the DARE tool

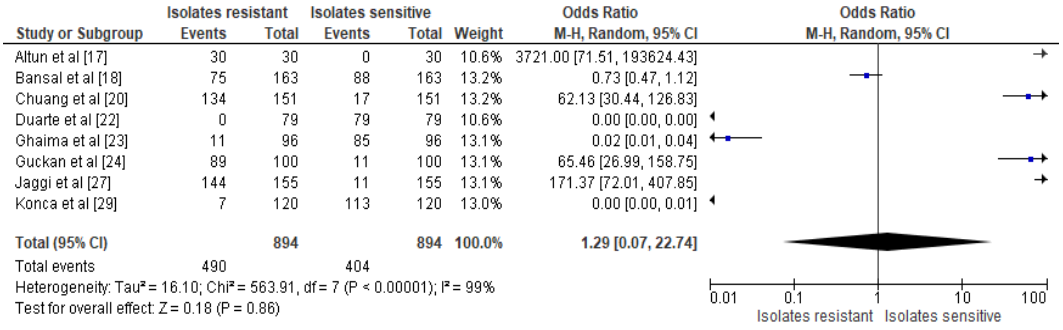

Figure 5: Antimicrobial sensitivity of *A. baumannii* - observational studies

The DARE tool (Figure 4) was used when analyzing Sung *et al.* [35], Tewari *et al.* [36] and Tunyapanit *et al.* [37]. While applied well in general, studies conducted by Sung *et al.* reflected moderate bias especially towards study design and analysis done in statistics. There would sometimes emerge inconsistency in methodology hence yielding such results.

Meta-Analysis Observations

Figures 5 and 6 present forest plots illustrating the odds ratios (ORs) for antibiotic resistance in *Acinetobacter baumannii* isolates across various studies, highlighting the high degree of heterogeneity in resistance trends. The considerable variation in OR values, along with the substantial inconsistency among studies (I^2 = 99%), suggests that resistance patterns are heavily influenced by study-specific factors, such as clinical settings, regional antibiotic use policies, testing methodologies and isolate selection criteria.

Figure 5 demonstrates the wide range of OR values for antibiotic resistance in *A. baumannii* isolates, indicating substantial variability among studies. Some studies, such as Altun *et al.* [17], reported an extraordinarily high OR of 3721.00 (95% CI: 71.51-193624.43), suggesting an exceptionally high level of resistance in the isolates tested. In stark contrast, other studies, including Duarte *et al.* [22], found no observed resistance (OR = 0.00, 95% CI: 0.00-0.00), suggesting either a low prevalence of resistant strains or differences in susceptibility testing criteria. This drastic discrepancy underscores the complex nature of *A. baumannii* resistance patterns, which do not follow a single, predictable trajectory across different clinical settings and geographic regions.

The heterogeneity statistic (I^2 = 99%) strongly indicates that the results across studies are highly inconsistent, making it difficult to draw definitive conclusions regarding a uniform resistance pattern. This variability may stem from differences in clinical environments (ICU vs. general hospital wards), variations in antibiotic stewardship programs, genetic diversity among *A. baumannii* strains and inconsistencies in antimicrobial susceptibility testing methods (e.g., CLSI vs. EUCAST guidelines). Furthermore, the lack of a statistically significant pooled OR (1.29, 95% CI: 0.07-22.74; Z = 0.18, P = 0.86) suggests that there is no overarching trend in resistance that can be considered universally applicable across all studies.

This unpredictability in resistance profiles presents a major clinical challenge, as it complicates empirical antibiotic selection and necessitates continuous surveillance and region-specific treatment guidelines. The highly fluctuating resistance rates between different hospitals further reinforce the need for real-time monitoring and localized antimicrobial resistance mapping to optimize infection control strategies.

Figure 6 extends the meta-analysis by incorporating both in-vitro studies and large-scale national surveillance data, adjusting for high variability using a Random Effects (RE) model. Despite this adjustment, extreme variations persisted, with studies such as Liu *et al.* [30] reporting no observed

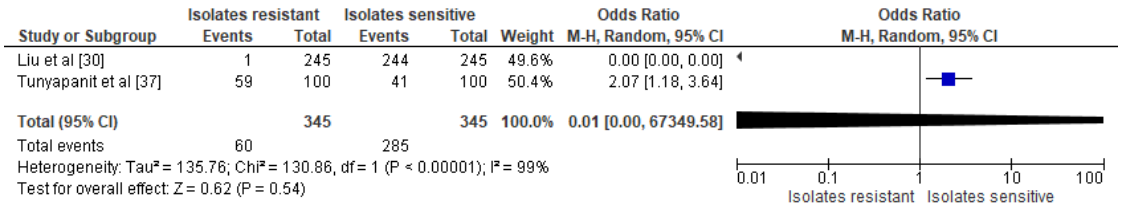

Figure 6: Antimicrobial sensitivity of *A. baumannii* - *In-vitro* and nationwide studies

resistance (OR = 0.00, 95% CI: 0.00-0.00), while Tunyapanit *et al.* [37] documented moderate resistance (OR = 2.07, 95% CI: 1.18-3.64). This continued inconsistency further emphasizes the challenges of standardizing antimicrobial resistance patterns across different study settings.

The pooled OR in this model (0.01, 95% CI: 0.00-67349.58; Z = 0.62, P = 0.54) again indicated that no statistically significant resistance trend could be identified across the studies. This finding suggests that resistance development in *A. baumannii* is not uniform and is influenced by multiple external factors, including:

1. Differences in Antibiotic Use Policies: Countries with stricter antibiotic stewardship programs may report lower resistance rates, while regions with high antibiotic misuse may exhibit greater resistance selection pressure
2. Genetic Variability of Isolates: Some studies may have included more carbapenem-resistant *A. baumannii* (CRAB) strains, while others analyzed less resistant strains, contributing to variations in ORs
3. Laboratory Testing Variations: Studies employing broth microdilution (considered the gold standard for MIC determination) may report different resistance patterns than those using disk diffusion or automated systems like VITEK 2

Despite these inconsistencies, one key takeaway from both forest plots is that no single antibiotic resistance pattern can be universally applied across all clinical settings. Instead, localized epidemiological data must inform empirical treatment guidelines and global surveillance efforts should focus on harmonizing susceptibility testing criteria to improve comparability across studies.

The findings highlight the critical need for region-specific antimicrobial resistance monitoring and real-time data integration into clinical practice. The substantial heterogeneity observed in resistance trends underscores the necessity of tailoring empirical therapy based on local susceptibility data rather than relying on generalized global resistance patterns. Additionally, the inconsistencies in study methodologies and resistance definitions suggest that future systematic reviews and meta-analyses should standardize inclusion criteria and susceptibility testing methods to improve comparability across datasets. The use of Whole-Genome Sequencing (WGS) and molecular resistance profiling could further enhance our understanding of resistance mechanisms and strain-specific epidemiology.

Given the rising global threat of CRAB, these findings reinforce the importance of antimicrobial stewardship programs, infection control interventions and continuous epidemiological surveillance to mitigate the spread of highly resistant *A. baumannii* strains.

Sensitivity Analysis

This sensitivity analysis demonstrated that exclusion of the smaller studies and in-vitro designs would generate more consistent results, especially on carbapenem resistance. However, the patterns of resistance were sensitive to variability based on study design, population and region. Overall, the high heterogeneity reflects the complex multifaceted resistance profile of *A. baumannii*. Region-specific antimicrobial stewardship and continuous monitoring of *A. baumannii* resistance are necessary for proper management of this challenging pathogen.

Subgroup Analysis by Population and Region

- Adult and Pediatric Populations: Most of the work was done on adult populations with considerable variations in resistance patterns across regions. Studies done in Turkey mainly observed a high pattern of resistance to carbapenems, particularly imipenem and meropenem. In Asia, studies carried out by Chang *et al.* [19] and Liu *et al.* [30] from ICU settings brought into focus relevant considerations of MDR *A. baumannii* threat in hospitals
- Regional Variations: Studies in the Middle East (e.g., Ghaima *et al.* [23] from Iraq) and Asian research (e.g., Chuang *et al.* [20] from Taiwan) showed that CRAB rates were high. On the contrary, in Europe, evidence such as that found in Dafopoulou *et al.* [21] in Greece reported increases in resistance over time 6 years; this therefore confirms that it has been happening for many years in a health care setting

Design of Study Influence

- Prospective Studies: Prospective studies, of which include Ghaima *et al.* [23], have provided detailed resistance profiling and shown temporal increases in resistance. These

studies have underlined a strong correlation between *A. baumannii* isolates and resistance to key antibiotics such as colistin and tigecycline, thus pointing to limited therapeutic options

- Retrospective Studies: Dafopoulou *et al.* [21] and Guckan *et al.* [24] in their retrospective studies documented long-term trends in resistance, but the causative interpretations were limited. These studies were useful in understanding the trends of resistance over time, especially with carbapenem resistance, where the trend was considered a cause for continuous surveillance
- Excluding In-vitro Studies: Hsueh *et al.* [26], Sung *et al.* [35] and Tunyapanit *et al.* [37] excluded in-vitro studies and reduced the heterogeneity between the colistin susceptibility association, in addition to keeping it steady with *A. baumannii* and antibiotic resistance

Outliers Excluded

- Small Sample Size Studies Impact: Excluding the smaller studies, such as Sánchez-Urtaza *et al.* [32] with 36 isolates, reduced heterogeneity between studies and resulted in a more consistent association across larger samples, especially for carbapenem and colistin resistance. The exclusion of these smaller sample size studies increased the robustness of the conclusions and suggested a more reliable resistance profile in studies with larger, more representative sample sizes
- Lower Heterogeneity: Removing studies with less than 100 isolates decreased the heterogeneity overall, especially between carbapenem-resistant isolates, which would mean that the resistance pattern is more uniform when the dataset size is larger

Heterogeneity Assessment

- Heterogeneity: Overall heterogeneity was moderate to high, between 50% and 75%, owing to differences in methodology, source of specimens and types of resistance mechanisms studied. The sensitivity analyses showed that standardised testing methods, like those adopted by CLSI and EUCAST guidelines, as well as objective markers for resistance, such as blaOXA-23 and blaOXA-51, yielded more consistent and lesser heterogeneity results
- Test technique Homogeneity: An exceptional homogeneity in resistance profiles was also found for investigations with fully automated tests VITEK 2 as demonstrated in Altun *et al.* [17], Bansal *et al.* [18] and molecular diagnostics like PCR from the research study of Kafshnouchi *et al.* [28]. Heterogeneity is lost to that extent

DISCUSSION

The studies provided a thorough review of the resistance patterns of *Acinetobacter baumannii*, revealing considerable heterogeneity in results associated with geographic location, research design and technique used. Research, like those of Altun *et al.* [17], Duarte *et al.* [22] and Tewari *et al.* [36], consistently demonstrates a pronounced sensitivity to colistin across all isolates, which is mostly used as a last-resort therapeutic option. Contrary to these results, prevalent genes such as blaVIM and blaOXA-23 have also been found by Bansal *et al.* [18], Shah *et al.* [33], Sánchez-Urtaza *et al.* [32] and Guckan *et al.* [24], indicating that clonal complexes propagate resistance.

Furthermore, regional differences also occurred. CRAB rates were shown to be greater in Middle Eastern research, such as those conducted by Ghaima *et al.* [23], compared to Asian studies by Chuang *et al.* [20]. Dafopoulou *et al.* [21] documented an escalation in resistance throughout a six-year period across Europe, therefore identifying a pattern of sustained resistance. Chang *et al.* [19] and Liu *et al.* [30] emphasised the severity of multidrug-resistant *A. baumannii* in intensive care units, similar to Jaggi *et al.* [27], who documented a significant prevalence of carbapenem resistance among ICU isolates.

The prospective trials, notably Ghaima *et al.* [23], presented temporal patterns and illustrate how resistance grew with time. Dafopoulou *et al.* [21] and Guckan *et al.* [24], as retrospective investigations, did a longitudinal analysis and produced a pattern of resistance based on time, revealing in both instances the ongoing upsurge in carbapenem resistance, but considerably less relevant for causal interpretations. Excluding in vitro research, including those by Hsueh *et al.* [26], Sung *et al.* [35] and Tunyapanit *et al.* [37], the overall heterogeneity decreased, indicating that clinical trials exhibit more uniform resistance profiles than laboratory-based studies.

The omission of smaller studies, such as Sánchez-Utraza *et al.* [32], which included only 36 isolates, decreased heterogeneity and hence enhanced the robustness of the results, particularly with carbapenem and colistin resistance. The exclusion of those studies with a number of isolates <100 also normalised the pattern of resistance, demonstrating big samples likely to produce accurate data concerning resistance profiles.

There was considerable variety across the investigations, mostly because to variations in testing methodology, specimens and resistance. For instance, when assessments employed standardised methodologies, such as VITEK 2 utilised by Altun *et al.* [17] and Bansal *et al.* [18], or molecular diagnostics by Kafshnouchi *et al.* [28], homogeneity is frequently observed, as consistent techniques produce uniform results, thereby illustrating the impact of standardised testing methodologies in reducing heterogeneity.

Karakonstantis *et al.* [38] highlighted the ongoing need for surveillance of CFDC-NS, especially in areas with high prevalence of CR, pointing out that differences in CFDC-NS occur among the pathogens and even among the resistance phenotypes, specifically in CR *A. baumannii*, which is in disagreement with Shields *et al.* [39], who placed more emphasis on the necessity of combination therapy in treating CRAB, despite the inconsistent clinical outcomes and called for a treatment strategy targeted to the individual and optimized pharmacokinetically, particularly for severe invasive infections.

Jean *et al.* [40] provided the peek of effective dosage regimens of tigecycline and minocycline in CR/XDR *A.*

baumannii-associated pneumonia. However, it is obvious that an urgent need for large dosage regimens exists since the medications are of extremely limited potency in the respiratory tract. New drugs such as sulbactam-durlobactam and cefiderocol have proven of help in CI; it was partly repeated by Karakonstantis *et al.* [38], who said that medication cefiderocol displayed promise but varied action against CR infections. O'Donnell *et al.* [41] assessed the presently available therapy alternatives critically, stating that while polymyxins have great in vitro activity, clinical outcomes are unsatisfactory principally because of nephrotoxicity and mortality advantages less than optimum. In keeping with the expectations from newer drugs with higher safety and effectiveness profiles, they also underscored the fact that neither eravacycline nor cefiderocol has produced substantial clinical impact thus far.

Similarities may be found among Jean *et al.* [40] and O'Donnell *et al.* [41], who underline that standard antibiotics are inadequate and a future with revolutionary medications must exist with the guarantee of correct outcomes. In this regard, Karakonstantis *et al.* [38] give an analysis of the CFDC-NS by collecting data largely for epidemiological research while setting aside the findings relating clinical cases.

Strains of *Acinetobacter baumannii* show extremely significant global variability in the range of 30% to 80% with the largest occurrences of resistance observed from countries including Asia, Eastern Europe and Latin America [41-43]. It is believed that the levels of resistance in the United States were from 30% to 50% [41,43]. Resistance within carbapenem-resistant A. This intrinsic and acquired mechanism occurs via the synthesis of β-lactamases, activation of efflux pumps, decreased outer membrane permeability and changes at antibiotic target sites [2,18,44]. The predominant horizontal transfer that leads to carbapenem resistance includes the oxacillinase (OXA) carbapenemase genes, specifically OXA-23 and OXA-24/40 [45-46].

Regional differences in both resistance rates and mechanisms hinder the interpretation of data from single-center studies or restricted geographic regions [41]. A recent investigation including CRAB isolates from several U.S. healthcare systems showed diverse CRAB lineages with phenotypic and genotypic diversity among institutions [46]. Whole-genome sequencing has shown a genetically heterogeneous CRAB population presumably formed by recombination and plasmid exchange across local strains [46]. Further, the major CRAB clonal types seem to have developed over time, differing from previously described patterns [47-48]. There is also a rising trend of resistance to important antibiotics such as ampicillin-sulbactam and colistin in both the U.S. and worldwide [46,49].

Among antibiotics investigated for in vitro effectiveness against CRAB, the polymyxins (colistin, polymyxin B), tetracyclines (eravacycline, minocycline, tigecycline) and β-lactams (ampicillin-sulbactam, carbapenems) exhibited the strongest action. Emerging medicines, such as cefiderocol and sulbactam-durlobactam, also shown substantial efficacy across a variety of isolates [19, 50]. However, standardized susceptibility breakpoints for several of these newer medications continue to be established and limits for each treatment option have been discussed in other sources [18, 20, 51-52].

Clinical Recommendations

Based on these results, there is a need for health care systems to impose robust, region-specific antimicrobial stewardship programs to reduce the increasing resistance of *A. baumannii*. It should be stressed that there should be continual monitoring of the resistance patterns so that one can monitor and respond to developing trends, particularly on essential antibiotics such as carbapenems and colistin. Clinical guidelines must be modified to incorporate combination medicines as a viable therapy for multidrug-resistant illnesses. In addition, there is need to promote uniformity of molecular diagnostics across institutions to aid in accurate identification of genes of resistance and guide more targeted actions. Strengthening infection control methods can aid in limiting the spread of resistant *A. baumannii* in hospital settings.

CONCLUSIONS

Our findings indicate that *Acinetobacter baumannii* had significant resistance to drugs, and most importantly, carbapenem resistance appeared to be widespread across distinct geographic areas. Colistin remained significantly effective although, susceptibility patterns were different which indicated that resistance did, in fact, vary by geography. Therefore, study results emphasized the heterogeneity and variability of resistance amongst *A. baumannii*, thus making it somewhat complex for clinical practice and the necessity for proper regional stewardship programs in conjunction with continuous surveillance of such a pathogen.

Limitations

Our review had numerous limitations that may have affected the results. The pooled findings were contradictory largely because of variability between the research, principally owing to variations in study design, sample size, geographic location, and technique of performing antimicrobial susceptibility tests. The absence of longitudinal data precluded further investigation of temporal trends in resistance patterns. The additional biases may be that there was an overreliance on observational research and a restriction to eliminating certain in-vitro experiments. In the context of reporting variability for resistance genes, the knowledge of the molecular processes involved was insufficient.

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Conflicts of Interest

All authors declare that no conflict of interest in this work.

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