Diagnostic Heterogeneity, Microbial Profiles, and Antimicrobial Resistance in Adult Ventilator-Associated Pneumonia: A Systematic Review and Evidence Synthesis

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Abstract. Ventilator-associated pneumonia (VAP) remains difficult to define because clinical, radiological, microbiological, and molecular criteria vary across studies. This systematic review evaluated diagnostic heterogeneity and synthesized microbial profiles, multidrug resistance (MDR), antimicrobial resistance (AMR), and clinical outcomes in adults receiving invasive mechanical ventilation. Original human studies published from 2020 to 2026 were identified through five bibliographic databases and supplementary evidence methods. Nineteen reports were included. The reconciled evidence set comprised seven reports from the database/master pathway and 12 from a separate other/targeted pathway. Diagnostic definitions, respiratory specimens, culture thresholds, reference standards, and resistance terminology varied substantially. Three compatible patient-level studies contributed 259 MDR cases among 378 patients (68.52%). Random-effects synthesis yielded a pooled MDR prevalence of 70.72% (95% CI, 59.40%-79.96%), with substantial heterogeneity (I^2=77.31%) and a 95% prediction interval of 49.31%-85.71%. *Acinetobacter baumannii* predominated in one patient-level dataset. Specific resistance phenotypes were not pooled because denominators and definitions were incompatible. The findings support standardized VAP definitions, explicit denominator reporting, cautious interpretation of pooled resistance estimates, and context-adapted antimicrobial stewardship. Some historical search dates, exact executed search strings, screening-process details, and report-level provenance for the 12 other/targeted reports remain incompletely documented.

Keywords: Ventilator-associated pneumonia, antimicrobial resistance, multidrug resistance, intensive care.

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1 Introduction

Ventilator-associated pneumonia (VAP) is a major infectious complication of invasive mechanical ventilation. Diagnosis remains difficult because clinical deterioration, radiographic abnormalities, airway colonization, and microbiological detection can overlap with noninfectious pulmonary processes. Studies have used different combinations of clinical, radiological, microbiological, and composite criteria. Such variation can change which patients enter the VAP denominator and influence reported microbial and resistance patterns [1-3].

Microbial epidemiology is also heterogeneous. Gram-negative organisms, particularly non-fermenting gram-negative bacilli and *Enterobacterales*, are frequently reported, while methicilin-resistant *Staphylococcus aureus* remains relevant in selected intensive care settings. Antimicrobial resistance further complicates empirical treatment because multidrug resistance (MDR), extensively drug-resistant phenotypes, organism-specific resistance, and molecular determinants are not uniformly defined or reported [4-8].

Comparability also depends on the units of analysis. The proportion of patients with MDR infection cannot be directly combined with the proportion of resistant isolates, and resistance among MDR isolates cannot be interpreted as the prevalence among all patients with VAP. Therefore, explicit denominator specification is essential when evidence is used to inform empirical treatment or antimicrobial stewardship [9-11].

Therefore, this systematic review evaluated the heterogeneity in VAP definitions, respiratory sampling, microbiological thresholds, resistance terminology, and analytical denominators while synthesizing contemporary evidence on microbial profiles, MDR, AMR, and selected clinical outcomes in adults receiving invasive mechanical ventilation.

2 Methods

2.1 Study design

This study was designed as a systematic review and evidence synthesis of original human research concerning adult VAP. Reporting was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. The review was organized by evidence domain because the included studies differed substantially in design, diagnostic definitions, populations, outcomes, and units of analysis [12,13].

2.2 Eligibility Criteria

Studies were eligible if they were original human research published from January 2020 through the final search period in 2026, included adults aged 18 years or older receiving invasive mechanical ventilation, and reported suspected, probable, or confirmed VAP using a stated clinical, radiological, microbiological, or composite definition. Eligible

designs included prospective and retrospective cohorts, cross-sectional and surveillance studies, diagnostic studies, and randomized trials with extractable VAP data.
Studies were excluded when they involved pediatric or neonatal populations, animals, or in vitro models; addressed community-acquired pneumonia, hospital-acquired pneumonia, or ventilator-associated tracheobronchitis without separable VAP data; or were case reports, reviews, meta-analyses, scoping or umbrella reviews, protocols, editorials, or letters without original data. Duplicate reports and overlapping cohorts that could not be separated were also excluded. Studies conducted in patients with coronavirus disease were eligible when VAP data were separately identifiable.

2.3 Information Sources and Search Strategy

Five bibliographic databases were used: PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL). The eligibility window covered publications from January 2020 through the final search period in 2026. The archived review package preserved the executed PubMed/MEDLINE and Scopus strategies. Exact executed strings for Embase, Web of Science Core Collection, and CENTRAL, and the exact last-search date for each database, were not recoverable from the archived records and were not reconstructed by inference.

Supplementary evidence identification included backward reference screening, forward citation tracking, and targeted supplementary searches. Twelve reports were retained through a separate other/targeted pathway. The reports were R0027 and SUP001-SUP011. Archived records preserve the aggregate pathway but do not reliably preserve the report-level attribution of each report to backward citation screening, forward citation tracking, or targeted searching.

Recoverable search documentation is provided in the accompanying reproducibility materials. The remaining gaps in the search-history metadata and report-level supplementary-search provenance are reported as methodological limitations.

2.4 Study Selection

The final evidence set contained 19 reports. The database/master pathway comprised 445 records, of which 70 duplicates were removed, leaving 375 records for title and abstract screenings. A total of 332 records were excluded at this stage, and 43 reports underwent full-text assessments. Thirty-six reports were excluded after full-text assessment, leaving seven reports from the database/master pathway. A further 12 reports were retained through the separate other/targeted pathway, giving a total of 19 reports. The 12 other/targeted reports were not included in the 445-record database/master count.

The archived screening package contains the 375-record master screening dataset and full-text screening records for the 43 candidate reports. However, the retrieved archive does not reliably document the number of reviewers, whether title/abstract and full-text screening were independently duplicated, or the exact disagreement-resolution procedure. These details were not inferred during the revision. Therefore, the numerical

pathway was reconciled at the aggregate level, while unresolved procedural metadata are reported transparently.

2.5 Data Extraction

The extracted domains included study design and setting, VAP definition, timing after intubation, respiratory specimen type, microbiological method and culture thresholds, organism distribution, MDR or other resistance terminology, organism-specific resistance phenotypes, molecular resistance determinants when available, clinical outcomes, and diagnostic or stewardship interventions. Patient- and isolate-level observations were maintained as separate analytical streams. Resistance terminology was recorded as reported by each study and considered in relation to the established MDR/XDR terminology [8].

2.6 Risk of Bias Assessment

Risk of bias was assessed using RoB 2 for randomized trials and design-appropriate assessment frameworks for non-randomized and diagnostic studies when sufficient signalling information was available. Where the archived evidence was insufficient to support a defensible judgment, the assessment was retained as unresolved rather than inferred. Risk-of-bias judgments were considered alongside study design, population selection, reference-standard limitations, and other methodological concerns when interpreting the evidence.

2.7 Data Synthesis and Statistical Analysis

Evidence was synthesized by domain rather than forcing a single, global estimate. Meta-analysis was performed only when the definitions, populations, units of analysis, and numerator and denominator structures were sufficiently compatible. For MDR prevalence, study proportions were transformed to the logit scale and pooled using a random-effects model with restricted maximum likelihood estimation of between-study variance. Heterogeneity was evaluated using Cochran's Q, I^2, and tau^2 tests, and a 95% prediction interval was calculated.

Only three studies provided compatible patient-level MDR data. Because the number of studies was small, formal small-study or publication bias testing was not performed. Specific resistance phenotypes were not pooled when their denominators or definitions were incompatible. Diagnostic studies with heterogeneous reference standards were synthesized descriptively rather than generating potentially invalid pooled diagnostic accuracy estimates.

2.8 Certainty of Evidence

Certainty was assessed by evidence body using GRADE principles for comparative clinical outcomes and a structured certainty approach for descriptive prevalence and

diagnostic evidence. Risk of bias, inconsistency, indirectness, imprecision, and publication-bias considerations were incorporated where applicable. Given the heterogeneous designs, outcomes, and units of analysis, certainty was interpreted by the evidence domain rather than by assigning a single overall rating to the review [14].

3 Results

3.1 Study Selection

The reconciled database/master pathway contained 445 records. After the removal of 70 duplicates, 375 records underwent title and abstract screening; 332 were excluded, and 43 reports were assessed in full text. Thirty-six full-text reports were excluded, leaving seven included reports from this pathway. A separate other/targeted pathway contributed 12 additional reports, namely R0027 and SUP001-SUP011. These 12 reports were not included in the 445-record database or master count. Thus, the final evidence set comprised 19 studies.

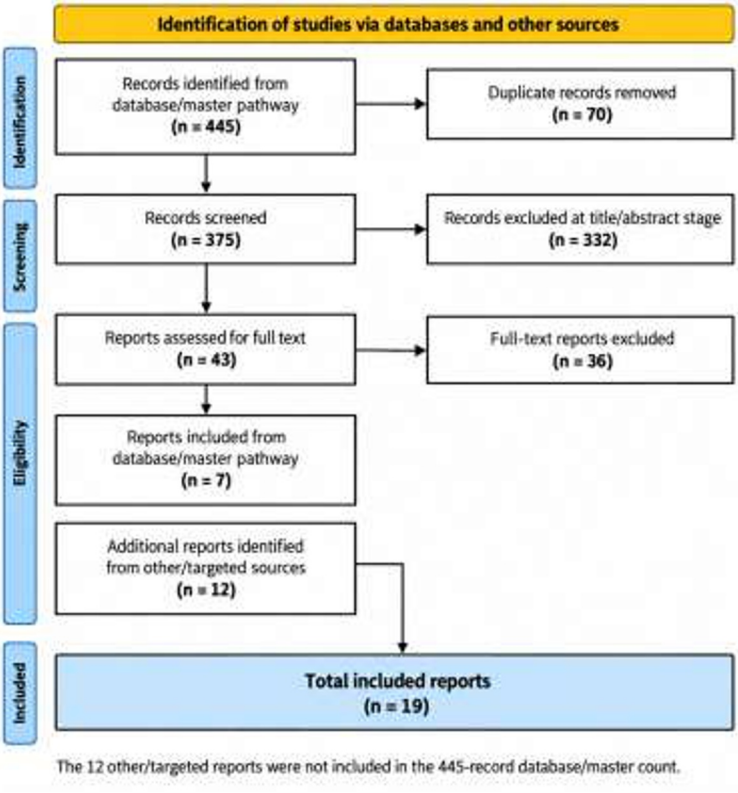


Fig. 1. PRISMA 2020 flow diagram of evidence identification and study selection.

3.2 Study Characteristics

The 19 included reports comprised randomized trials, diagnostic investigations, observational microbiology and AMR studies, stewardship research, coronavirus disease-associated VAP studies, and exploratory biofilm evidence. The populations, VAP definitions, specimen types, reference standards, and analytical denominators varied substantially.

Table 1. Characteristics and principal contributions of the included reports.

ID	Study	Design	Population/VAP subset	Primary contribution	Identification pathway
R0014	REGARD-VAP [16]	RCT	VAP	Antibiotic duration	Database/master
R0017	iDIAPASON [17]	RCT	Pseudomonas VAP	Antibiotic duration	Database/master
R0050	ANTHARTIC biomarker [3]	Observational diagnostic	VAP subgroup	Biomarkers	Database/master
R0109	Vitamin D study [21]	RCT	VAP/sepsis subgroup	Adjunctive intervention	Database/master
R0027	RESTORE-IMI 2 [18]	RCT	VABP subgroup	Antimicrobial treatment	Other/targeted
R0102	Clinical pharmacist-led ASP [19]	RCT	VAP subgroup	Antimicrobial stewardship	Database/master
SUP001	Syria 2025 [9]	Cross-sectional	Suspected/culture-positive VAP	MDR	Other/targeted
SUP002	Oman 2025 [10]	Cohort	VAP/MDR-VAP	MDR	Other/targeted
SUP003	Korea 2021 [11]	Cohort	VAP	Microbial profile/MDR	Other/targeted
SUP004	India 2021 [2]	Observational	VAP-related bacterial isolates	Isolate-level AMR	Other/targeted
SUP005	India 2023 [1]	Prospective cohort	Adult VAP	Clinical/microbiology	Other/targeted
SUP006	Egypt 2021 [4]	COVID-19 cohort	Adult COVID ICU VAP	Microbiology/AMR	Other/targeted
SUP007	Iran 2021 [6]	Isolate study	COVID ICU VAP; K. pneumoniae	Biofilm/AMR	Other/targeted
SUP008	Thailand 2022 [20]	Diagnostic/cross-sectional	HAP/VAP	Rapid diagnostics	Other/targeted
SUP009	China 2025 [7]	Diagnostic	Suspected/clinical VAP	tNGS	Other/targeted

SUP010	DELAVAP 2024 [22]	Quasi-experimental	First non-severe VAP	Antibiotic strategy	Other/targeted
SUP011	Türkiye 2024 [5]	Cohort	VAP	COVID-era AMR	Other/targeted
R0112	Hakamifard et al. 2023 [15]	Open-label RCT	XDR A. baumannii VAP	Adjunctive inhaled therapy	Database/master
R0113	Razzazzadeh et al. 2022 [23]	RCT	VAP with augmented renal clearance	Meropenem PK/clinical outcome	Database/master

3.3 Diagnostic Heterogeneity

Diagnostic definitions differed in clinical signs, radiological findings, timing after intubation, microbiological confirmation, specimen type, and culture thresholds. Approaches included clinical and radiological adjudication with microbiological confirmation, Clinical Pulmonary Infection Score-based assessment, and quantitative or semi-quantitative culture thresholds. In a multicenter Korean cohort, the thresholds were at least 10^4 colony-forming units/mL for bronchoalveolar lavage, at least 10^5 for bronchoscopic aspirates, and at least 10^5 for endotracheal aspirates. Other studies used different or less explicitly standardized approaches [6].

Rapid syndromic molecular testing and metagenomic sequencing were also performed. The Thai multiplex pneumonia panel study reported high sensitivity and negative predictive value, whereas the Chinese metagenomic study reported high sensitivity against a comprehensive clinical diagnosis. Because the reference standards were not equivalent, these diagnostic studies were synthesized descriptively rather than pooled [20,3].

3.4 Microbial Profiles

In the verified 176-patient VAP dataset, Acinetobacter baumannii was identified in 81 patients (46.02%), Staphylococcus aureus in 39 (22.16%), Pseudomonas aeruginosa in 14 (7.95%), and Stenotrophomonas maltophilia in 12 (6.82%). These values are patient-level findings from one study and were not pooled with isolate-level estimates. Other reports also showed prominent Gram-negative organisms, particularly Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae [9-11,16-19].

The prominence of non-fermenting Gram-negative organisms supports the clinical importance of the local ICU ecology. At the same time, differences in denominators and sampling frames mean that cross-study pathogen proportions should not be interpreted as directly comparable prevalence estimates.

3.5 Multidrug Resistance

Three patient-level studies provided compatible MDR outcomes. The Syrian study reported 55 MDR cases among 69 culture-positive VAP patients, the Oman cohort reported 96 among 133 VAP patients, and the Korean cohort reported 108 cases among

176 VAP patients. Together, these studies contributed 259 MDR cases among 378 VAP patients, corresponding to a crude proportion of 68.52% [6,16,17].

The random-effects meta-analysis yielded a pooled MDR prevalence of 70.72% (95% CI, 59.40%-79.96%), with substantial heterogeneity (I^2=77.31%; tau^2=0.1498; Q=8.82, df=2; p=0.012). The 95% prediction interval was 49.31%-85.71%. The leave-one-out analyses produced pooled estimates ranging from 66.69% to 74.99%, indicating that the pooled estimate was not driven by a single study.

3.6 Biomarkers and Molecular Diagnostics

The ANTHARTIC exploratory study included 161 cardiac-arrest patients, of whom 33 formed the VAP subgroup. CRP and procalcitonin showed moderate discrimination, whereas combined biomarker models achieved higher reported area under the curve values. The small and highly selected VAP subgroup and reference-standard considerations limit generalizability [2].

A Thai molecular diagnostic study reported a sensitivity of 98%, specificity of 81%, positive predictive value of 60%, and negative predictive value of 99% for the overall hospital-acquired or VAP cohort. A Chinese metagenomic study included 199 suspected VAP patients and 196 clinically diagnosed cases; metagenomic sequencing detected pathogens with 98.98% sensitivity compared with 66.84% for culture and had a shorter reported turnaround time. These findings are clinically promising but remain subject to reference-standard and applicability concerns [20,3].

3.7 Clinical Outcomes and Antimicrobial Stewardship

Clinical outcome evidence was intervention-specific. REGARD-VAP enrolled 461 patients with VAP and compared individualized short-course treatment with usual-duration treatment. The primary composite of 60-day death or pneumonia recurrence was approximately 41% versus 44%, while median antibiotic exposure was 6 versus 14 days. iDIAPASON randomized 186 adults with Pseudomonas aeruginosa VAP to 8 versus 15 days of therapy and reported a composite failure of 25.5% versus 35.2%, with recurrence of 9.2% versus 17% [1,4].

The 2026 vitamin D trial enrolled 80 adult patients in the ICU with severe traumatic lung contusion who subsequently developed VAP and sepsis; high-dose vitamin D was associated with shorter mechanical ventilation and ICU stay and lower mortality, but the highly selected population limits generalizability. Hakamifard et al. randomized 60 adults with XDR Acinetobacter baumannii VAP to inhaled colistin versus inhaled tobramycin/fosfomycin as adjunctive therapy; the open-label design and physician-determined treatment discontinuation introduced important risk-of-bias concerns. Razzazzadeh et al. randomized 45 patients with VAP and augmented renal clearance to different meropenem regimens and reported pharmacokinetic/pharmacodynamic differences without a clear corresponding between-group clinical-improvement difference. DELAVAP provided non-randomized comparative evidence on immediate versus conservative antibiotic initiation in suspected non-severe VAP and was interpreted separately because of temporal and clinical selection confounding [7,21-23] [21].

RESTORE-IMI 2 contributed to the VABP subgroup within a broader hospital-acquired or ventilator-associated bacterial pneumonia trial. In the prespecified modified microbiological intent-to-treat VABP subgroup, day-28 mortality was 18.6% versus 30.8% for imipenem/cilastatin/relebactam versus piperacillin/tazobactam. The pharmacist-led stewardship trial reported improved VAP-specific antibiotic appropriateness and clinical cure; however, internal inconsistencies in broader HAP/VAP denominators prompted the retention of only explicitly stratified VAP data [18,19].

3.8 Coronavirus-Disease-Associated VAP and Exploratory Biofilm Evidence

Coronavirus disease-associated VAP studies have demonstrated context-specific microbial and resistance patterns, including selected studies of Klebsiella pneumoniae isolates and biofilm formation. These studies were retained as contextual evidence and were not combined with the main patient-level MDR estimate. Exploratory biofilm evidence remains insufficiently standardized to support a pooled quantitative relationship between endotracheal tube biofilm, resistance, and clinical outcomes [9-11].

3.9 Risk of Bias and Certainty

The audit identified methodological concerns in selected studies, including subgroup selection, internal denominator inconsistencies, heterogeneous reference standards, narrow isolate populations, and temporal confounding in non-randomized comparative designs. These limitations contributed to very low certainty for MDR prevalence, microbial profile, diagnostic heterogeneity, biomarker evidence, rapid molecular diagnostics, and coronavirus disease-associated resistance evidence. Evidence concerning antibiotic duration and treatment strategies was assessed separately and retained as moderate certainty, whereas the pharmacist-led stewardship evidence was judged to be of low certainty.

4 Discussion

4.1 Principal findings

This review indicates that contemporary adult VAP evidence is better understood as a set of context-dependent evidence domains rather than a single homogeneous epidemiological dataset. The principal methodological finding was the extent of heterogeneity in case definitions, specimen strategies, microbiological thresholds, resistance terminology, and analytical denominators. Within the compatible patient-level evidence, the crude MDR proportion was 68.52%, and the pooled prevalence was 70.72%, but the high heterogeneity limits the transportability of this estimate across ICUs.

4.2 Diagnostic Heterogeneity and Epidemiological Interpretation

Diagnostic heterogeneity is not merely a reporting issue. It can change the population classified as having VAP and therefore change the organisms and resistance phenotypes entering the denominator. A definition based on clinical and radiological criteria with selective culture confirmation is not analytically interchangeable with one requiring a quantitative culture threshold or a molecular reference standard. Consequently, differences in reported VAP microbiology may reflect differences in case ascertainment as well as genuine geographic or temporal variation [2,3,7,20].

This has direct implications for evidence synthesis. A pooled pathogen or resistance estimate can become misleading when studies differ in whom they classify as VAP, the specimen they test, and the threshold they use. The inability to pool several diagnostic studies in this review therefore reflects an important methodological constraint rather than a failure of the analysis.

4.3 Interpretation of the MDR Estimate

The pooled MDR prevalence of 70.72% indicates a substantial resistance burden within the three contributing patient-level populations, but it should not be interpreted as a universal empirical probability for all ICUs. The 95% prediction interval of 49.31%–85.71% and I^2 of 77.31% indicate clinically meaningful between-study variation. Therefore, local ICU ecology, prior antimicrobial exposure, duration of ventilation, patient-level risk factors, and local antibiograms remain more relevant to empirical therapy than the pooled estimate alone [9-11].

The consistency of the leave-one-out analysis suggests that the pooled result was not driven by one study. However, this does not remove uncertainty arising from the small number of contributing studies, their observational designs, and differences in population and setting. Therefore, the appropriate interpretation is that MDR is common in the contributing VAP populations, not that approximately seven in ten patients with VAP will have MDR infection in every clinical setting.

4.4 Gram-Negative Organisms and Local ICU Ecology

Acinetobacter baumannii was prominent in the verified patient-level microbiological dataset and also appeared repeatedly in isolate-level evidence. This pattern is clinically relevant because resistant non-fermenting gram-negative organisms can substantially constrain empirical treatment options. However, the review also demonstrates why isolate-level resistance should not be converted into patient-level prevalence without compatible denominators. The practical implication is that local microbiological surveillance should report both the organism distribution and the analytical denominator used to derive it [2,6,9-11].

4.5 Implications for Antimicrobial Stewardship

The evidence supports an approach that combines early empirical treatment with subsequent microbiology-guided refinement rather than relying on a single pooled resistance estimate. Shorter antibiotic strategies have shown encouraging results in selected VAP populations, but their applicability depends on diagnostic certainty, organism profile, clinical response, and the population studied. Similarly, adjunctive and pharmacokinetic interventions address specific clinical contexts and should not be generalized across all patients with VAP [1,4,7,22,23].

The pharmacist-led stewardship evidence suggests a potential benefit, but internal denominator inconsistencies reduce certainty. Future intervention studies should prespecify VAP-specific denominators and outcomes so that stewardship effects can be separated from broader HAP/VAP populations [19].

4.6 Implications of Rapid Molecular Diagnostics

Rapid molecular diagnostics and metagenomic approaches may improve the speed of pathogen detection; however, analytical performance alone does not establish clinical utility. The included diagnostic studies used different reference standards, creating uncertainty about the degree to which reported sensitivity reflects true diagnostic accuracy. Future studies should use transparent reference standards, clearly report patient selection and flow, and evaluate whether faster pathogen identification changes antimicrobial decisions or clinical outcomes [3,7,20].

4.7 Implications for Future VAP Research

This review identified several reporting priorities. Future VAP studies should define the case ascertainment framework, specify the respiratory specimen and microbiological threshold, state whether the denominator represents all enrolled patients, culture-positive patients, all isolates, or organism-specific isolates, and use explicit definitions for MDR and other resistance phenotypes. These elements would improve cross-study comparability and strengthen future quantitative synthesis.

Supplementary searches also require a reproducible audit trail. The present review could reconcile the aggregate numerical pathway and identify the 12 other/targeted reports, but it could not recover all historical search metadata or report-level attribution of those 12 reports to individual supplementary-search methods. Future reviews should preserve database histories, exact search strings, search dates, deduplication logs, screening decisions, and report-level provenance throughout the review process.

4.8 Strengths and Limitations

The strengths include the contemporary evidence window, multiple major bibliographic databases, explicit separation of diagnostic, microbiological, AMR, clinical-outcome, and exploratory biofilm domains, strict separation of patient-level and isolate-

level denominators, and selective quantitative synthesis only when data were sufficiently compatible.

Limitations include the small number of studies contributing to the MDR meta-analysis, substantial heterogeneity, incompatible denominators for specific resistance phenotypes, heterogeneous diagnostic reference standards, and methodological concerns in the selected studies. In addition, the aggregate PRISMA pathway is reconciled, but the exact last-search dates, exact executed Embase, Web of Science, and CENTRAL strings, detailed screening-procedure metadata, and report-level attribution of the 12 other/targeted reports to individual supplementary-search methods remain incompletely documented. These limitations concern the review audit trail and should be considered when interpreting the completeness and reproducibility of the evidence identification process.

5 Conclusion

Contemporary adult VAP evidence is characterized by marked heterogeneity in diagnostic definitions, respiratory sampling, microbiological thresholds, AMR terminology, and analytical denominators. Among three compatible patient-level studies, MDR was present in 259 of 378 patients (68.52%), with a random effects pooled prevalence of 70.72% (95% CI, 59.40%-79.96%) and substantial heterogeneity. The pooled estimate should not be treated as a universal ICU-level probability. Specific resistance phenotypes could not be pooled reliably because denominators and definitions were incompatible. The findings support standardized VAP case definitions and microbiological reporting, explicit denominator specification, local resistance surveillance, and context-specific antimicrobial stewardship. The final numerical evidence-identification pathway was reconciled as 7 database/master reports plus 12 other/targeted reports, while remaining search-history, screening-process, and report-level provenance gaps are reported transparently.

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