Non-Interventional Study Report Template

FINAL Study Report - Cohorts

ICU antimicrobial practices snapshot, bacterial resistance overview and associated risk factors	
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1 ABSTRACT

Title of the Study:	AMR Focus in French ICU: A REA-REZO analysis.
Background/Study Rationale	Antimicrobial resistance (AMR) poses a significant challenge in Intensive Care Units (ICUs), where the heavy use of antibiotics and the presence of multi-resistant bacterial strains necessitate a proactive approach to antibiotic therapy. The practice of administering probabilistic antibiotic treatment in ICUs highlights the critical need for rapid and effective antimicrobial intervention, despite a notable proportion of these treatments being potentially unnecessary. The REA-REZO surveillance network plays a crucial role in monitoring healthcare-associated infections in ICUs, providing essential data for improving antibiotic use and addressing AMR, amidst a backdrop of evolving challenges and the need for enhanced antimicrobial stewardship practices.
Objective(s):	Perform a description on a cohort of mechanically ventilated patients, a cohort of Pseudomonas Aeruginosa infected patients, a cohort of patients with carbapenem infection
Study Design:	The cohort analysis relies on specific data extraction from the REA-REZO database, aiming to produce precise insights by aligning data subsets with the study's objectives on patient outcomes, treatment efficacy, and antibiotic resistance.
Study Population:	The first Cohort will include patients who received mechanical ventilation. This group will be scrutinized for patterns and outcomes specifically associated with ventilator use. The second cohort will consist of patients who were diagnosed with a Pseudomonas aeruginosa infection. The third Cohort will be composed of patients who had a carbapenem-resistant infection.
Exposure & Outcome:	The projected outcome of the cohort analysis is set to include a comprehensive description of each specific patient population within the study: those undergoing mechanical ventilation, those infected with Pseudomonas aeruginosa, and those infected with carbapenem-resistant organisms. The analysis will extend to a comparative evaluation between subgroups, specifically contrasting cases of ventilator-associated pneumonia (VAP) caused by resistant Pseudomonas aeruginosa with those caused by non-resistant strains of the same bacterium. Additionally, a comparison will be conducted between infections caused by carbapenem-resistant and non-resistant organisms. The aim of these comparisons is to delineate the clinical and microbiological distinctions between infections caused by resistant pathogens versus non-resistant ones. This will provide valuable insights into the burden of antimicrobial resistance in the ICU setting and inform future strategies for infection control and antibiotic stewardship.
Study Setting:	The cohort analysis were performed on patients included in Rea-Rezo database from 2018 to 2021. They were recruited in nearly 100 different centers from France participating in Rea-Rezo database reporting.
Statistical Methods:	Categorical data were analyzed using Fisher's exact test or the chi-square test, as appropriate. Continuous data were analyzed using the Wilcoxon test. Attributable mortality of VAP was computed using a multistate model. No inferential analyses were performed.
Results:	Patients facing VAP in the ICU are mainly around 65 years old, predominantly male, and often admitted for medical reasons, with many having been transferred from another hospital and receiving antibiotics upon admission. They experience longer ICU stays, higher mortality rates, and are more likely to need invasive treatments, highlighting the severity and complexity of their condition. Patients with Pseudomonas aeruginosa infections, often admitted for medical reasons and possibly transferred from other hospitals, are typically in their mid-sixties and face complex clinical situations, with those resistant to antibiotics showing longer ICU stays and higher mortality rates. This highlights the challenges of antibiotic resistance, underscoring the importance of infection control and antibiotic stewardship in managing such cases.

	Patients with carbapenem-resistant infections often have a complex clinical profile, are frequently admitted from other hospitals, and face prolonged ICU stays and higher mortality rates, emphasizing the urgent need for improved infection control and antibiotic stewardship.
Conclusions:	In conclusion, our study reaffirms the critical challenge posed by antimicrobial resistance in the ICU. It highlights the need for comprehensive strategies that address the clinical, psychological, and economic dimensions of this issue. As the landscape of antibiotic resistance evolves, so do our approaches to managing these infections, ensuring that patient care remains at the forefront of ICU practice.

List of Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse Event
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
AMR	Antimicrobial resistance
ICU	Intensive Care Units
HAIs	Healthcare Associated Infections
ICP	Infection control practitioner
UPH	University public hospitals
OPH	Other public hospital
PH	Private hospital
Spp	species plurimae: multiple species

2 BACKGROUND

Antimicrobial resistance (AMR) presents a formidable challenge in modern healthcare, particularly within the high-stakes environment of Intensive Care Units (ICUs), where the stakes for patient outcomes are critically high. The pervasive use of antimicrobials in ICUs is a response to the complex interplay of factors inherent to these settings. ICUs are often the epicenter for the convergence of multi-resistant bacterial strains, due to the frequency of infections and hence a use of antibiotics high concentration of patients with compromised health and the extensive utilization of invasive devices. These factors create a breeding ground for nosocomial infections, necessitating a proactive and aggressive approach to antibiotic therapy.

In the context of French ICUs, empirical data reflects a substantial disparity in antibiotic administration when compared to other hospital units. A significant portion—nearly half—of ICU patients are prescribed antibiotics during their stay, a stark contrast to the 15% reported in university and general hospitals, according to the French prevalence survey conducted in 2017(1). This discrepancy can be attributed to the unique pressures exerted by the ICU environment, where the risk of infection is compounded by the presence of resistant bacteria and a high level of invasive device usage.

Probabilistic antibiotic treatment is a common practice within ICUs, stemming from the critical need for the prompt initiation of effective antimicrobial therapy. This preemptive approach often involves the administration of broad-spectrum antibiotics as an interim measure while awaiting definitive microbiological documentation. Yet, studies have indicated that a significant proportion of these interventions—up to one-third—may be unnecessary, as the patients are eventually found to be non-infectious (2). This observation underscores the importance of judicious antibiotic use and the need for rapid and accurate diagnostic capabilities.

The interface between the ICU and the microbiology laboratory is pivotal, with traditional delays in obtaining microbiological results spanning from one to four days. Recent advancements in microbiological techniques have dramatically reduced this turnaround time, facilitating quicker clinical decision-making. However, the level of technological integration, such as computerization of ICUs, varies widely among healthcare facilities and often falls outside the direct control of ICU management. While these developments mark significant progress, they are not without drawbacks. The increased cost of diagnostic procedures, coupled with the complexity of interpreting results—particularly in distinguishing between colonization and infection—pose additional challenges.

Quality antibiotic prescription management is the purview of intensivists but is greatly enhanced by interdisciplinary collaboration with microbiologists, infection control practitioners, infectious disease specialists, and pharmacists. It is a multifaceted endeavor that necessitates a concerted effort from various stakeholders in the healthcare continuum.

The REA-REZO surveillance network plays a crucial role in monitoring Healthcare-Associated Infections (HAIs) in ICU. Covering approximately 20 % of the national ICU bed capacity, healthcare professionals in the network undertake a continuous, year-round inclusion of patients with an ICU length of stay ≥ 48 hours. The network collects data on each patient, encompassing admission and discharge dates, patient demographics, severity of condition upon admission, source of admission, and antimicrobial therapy started within the first 48 hours. Furthermore, details regarding the

insertion and removal of invasive devices and all HAIs, complete with pathogen identification and antimicrobial resistance profiles, are documented.

Through this detailed data collection, the REA-REZO network is equipped to paint an intricate picture of the microbial ecology within individual departments. It enables the identification of the predominant HAIs, whether related to catheter usage or ventilator-associated pneumonia (VAP), and the corresponding microbial resistance patterns.

Despite the established practices, there is a notable paucity of updated information regarding the extent to which French ICUs have integrated antimicrobial stewardship practices, particularly post-2018. The accesses to new antimicrobial drugs and diagnostic tests are critical elements that warrant evaluation within the specialized realm of intensive care. The recent COVID-19 era has further complicated the landscape, with limited data available on patients developing resistant nosocomial pneumonia or infections caused by carbapenem-resistant strains or Pseudomonas aeruginosa.

The forthcoming publication of resistance data and associated risk factors is anticipated to underscore the imperative of enhanced patient screening and the tailored adjustment of empirical antibacterial therapy. This, in turn, is expected to reinforce the prudent use of existing antibiotics and underscore the clinical necessity for the development of new antibacterial agents.

A comprehensive snapshot of ICU practices is invaluable, offering insights into the needs of clinicians, identifying opportunities for enhancing patient care and stewardship, and crafting an informed medical narrative. Utilizing the REA-REZO network's dedicated surveillance of ICU-acquired infections, the study aims to investigate antibiotic use and global antimicrobial resistance at a national scale, with a particular focus on the synergy between microbiology practices and ICU protocols.

The study will be divided in three phases:

- Cohort A: A cohort of mechanically ventilated patients
- Cohort B: A cohort of Pseudomonas Aeruginosa infected patients
- Cohort C: A cohort of patients with carbapenem infection

3 STUDY OBJECTIVES

The cohort analysis has been structured with the following primary objectives:

- **Mechanical Ventilation Cohort (Cohort A):**
  - **Description**: Detailed characterization of patients who underwent mechanical ventilation, including types of admission, patient demographics, and the incidence rate of VAP.
  - **Pathogen Focus**: Identification of the pathogens involved, their resistance profiles, and the associated clinical outcomes.
- **Pseudomonas aeruginosa Infection Cohort (Cohort B):**
  - **Description**: Analysis of patients with Pseudomonas aeruginosa infections, encompassing resistance patterns, duration of treatment, modes of contamination, risk factors, and patient demographics.
  - **Comparative Analysis**: Evaluation of differences between infections caused by resistant versus non-resistant strains of P. aeruginosa, aiming to understand the impact of resistance on clinical decisions and to characterize patient at risk of MDR.
- **Carbapenem-Resistant Infection Cohort (Cohort C):**
  - **Description**: Examination of patients with infections caused by carbapenem-resistant organisms, detailing the associated resistance mechanisms, contamination routes, risk factors, and patient profiles.
  - **Comparative Analysis**: Evaluation of differences between infections caused by Carbapenem resistant versus non-resistant Gram-Negative Bacilli (GNB), aiming to understand the impact of resistance on clinical decisions and to characterize patient at risk of resistant strains.

These objectives have guided the data extraction from the REA-REZO database and the subsequent statistical analysis to address the pertinent research questions. The findings are expected to provide insights into the complexities of treating infections in the ICU, the epidemiology of antimicrobial resistance, and the factors influencing patient outcomes, thereby informing clinical practice and policymaking.

4 RESEARCH METHODS

4.1 Study Design

The analysis of the cohorts is predicated on a pre-existing database, specifically, data will be extracted from the REA-REZO database tailored to each objective of the cohort analysis. This targeted extraction is designed to collate the relevant data necessary to address specific research questions. The methodology ensures that each subset of data is appropriately aligned with the investigative goals, whether they pertain to patient outcomes, the efficacy of treatment protocols, or the prevalence and impact of antibiotic-resistant infections. By utilizing this strategic approach, the analysis aims to yield precise and actionable insights pertinent to the objectives outlined for the cohort study.

4.2 Study Population

The study population includes all patients registered in the REA-REZO database between 2018 and 2021 (4 years).

4.2.1 Inclusion Criteria

The REA-REZO database encompasses data for all patients who were admitted to participating ICUs for a duration exceeding 48 hours over the span of 2018 to 2021.

To facilitate focused analysis, a targeted extraction process will be implemented to delineate three distinct cohorts from this global dataset:

- **Cohort A** will include patients who received mechanical ventilation. This group will be scrutinized for patterns and outcomes specifically associated with ventilator use, including complications like ventilator-associated pneumonia (VAP).
- **Cohort B** will consist of patients who were diagnosed with a Pseudomonas aeruginosa infection.
- **Cohort C** will be composed of patients who had a carbapenem-resistant infection. The data from this cohort will be especially valuable for examining the impact of antibiotic resistance on outcome and the risk factors associated with this antibiotic resistance profile.

4.2.2 Exclusion criteria

There are no exclusion criteria.

4.3 Setting

REA-REZO represents a substantial network of adult Intensive Care Units (ICUs) in France, encompassing close to 100 ICU units, which accounts for approximately a quarter of all ICU beds in the country. The network systematically collects data pertaining to the care received by patients during their stay in the ICU, and these records are maintained in the REA-REZO database. This database acts as a repository of detailed patient care information, enabling analysis and research that can inform and improve ICU practices.

For researchers and stakeholders interested in the specifics of the data collected, a complete description of the variables is accessible in the appendix of the report. This level of detail supports transparency and comprehensiveness, ensuring that the database can be a robust resource for ongoing clinical research and quality improvement initiatives in critical care.

4.4 Outcomes of Interest

The projected outcome of the cohort analysis is set to include a comprehensive description of each specific patient population within the study: those undergoing mechanical ventilation, those infected with Pseudomonas aeruginosa, and those infected with carbapenem-resistant organisms.
The analysis will extend to a comparative evaluation between subgroups, specifically contrasting cases of ventilator-associated pneumonia (VAP) caused by resistant Pseudomonas aeruginosa with those caused by non-resistant strains of the same bacterium. Additionally, a comparison will be conducted between infections caused by carbapenem-resistant and non-resistant organisms.
The aim of these comparisons is to delineate the clinical and microbiological distinctions between infections caused by resistant pathogens versus non-resistant ones. This will provide valuable insights into the burden of antimicrobial resistance in the ICU setting and inform future strategies for infection control and antibiotic stewardship.

4.5 Description of Covariates

The surveillance strategy employed in REA-REZO and hence in this study is centered at the patient level (patient-based surveillance), with data arranged into three distinct subsets.

The different subsets are described in table 1.

- The first subset comprises the individual characteristics of the patients, which includes demographic information, date of admission and discharge, vital status at ICU discharge, diagnostic category (medical, surgical trauma), admission from a hospital or from the community, severity (SAPS II) and specific and relevant specific characteristics such as presence of a COVID infection, colonization by a resistant organism, immunodepression and antibiotic treatment within the 2 days around the admission.
- The second subset details the invasive devices that patients are subjected to during their ICU stay, such as intubation and various types of catheters. This information is crucial for understanding potential sources of infection and for correlating the use of invasive devices with infection rates.
- The third subset focuses on ICU-acquired infections, documenting occurrences of pneumonia, catheter-related infections, and bloodstream infections from all sources. This subset is enriched with bacteriological data, which includes the identification of all bacteria involved and their resistance profiles to key antibiotics for a select group of bacteria. The following table summarizes the bacteria species and the key antibiotics collected through surveillance.

	OXA	AMP	GLY	AMC	C3G	PTZ	CAZ	CAR	COL	ESBL	PanR
Staphylococcus aureus	X		X								X
Enterococcus faecalis* and *faecium		X	X								X

Enterobacterales				X	X			X		X	X
Pseudomonas aeruginosa						X	X	X	X		X
Acinetobacter baumannii							X	X	X		X

Table 1: Bacteria species and key antibiotics

OXA: oxacillin (or methicillin), AMP: ampicillin (or amoxicillin), GLY: glycopeptide (vancomycin or teicoplanin), AMC: amoxicillin-clavulanic acid, C3G: 3rd generation cephalosporins (cefotaxime, ceftriaxone), PTZ: piperacillin-tazobactam, CAZ: ceftazidime, CAR: carbapenem (imipenem, doripenem, meropenem), VAN: vancomycin, COL: colistin, ESBL: extended-spectrum beta-lactamase-producing, PanR: non susceptible to all tested agents.

For an exhaustive description of the variables monitored in the network, one can refer to the appendix, which contains all details concerning the data included in the surveillance process.

4.6 Study Procedures

4.6.1 Ethics Review

This retrospective study will not require patient IRB/EC review.

4.6.2 Subject Information and Informed Consent

With respect to the cohort analysis, each participant has provided informed consent for their inclusion in the database and for the research conducted within the scope of the study. This approval is a critical ethical requirement, ensuring that all individuals whose data is included are fully aware of and agree to the nature, purpose, and potential implications of the research. It also implies that the participants have been informed about their rights, including the right to confidentiality and the right to withdraw from the study at any point without any consequences to their medical care or legal status. The participants are informed of all additional analysis on the REA-REZO website (https://rearezo.chu-lyon.fr/etudes.html).

4.7 Data Handling and Validation / Data Management / Data Quality Assurance

The procurement and initial handling of the database for the study has been executed by the designated data manager of the REA-REZO network. This individual is responsible for querying the database to extract relevant data points in alignment with the study's objectives. After this extraction process, the gathered data have been processed and analyzed by the network's statistician. The statistician's role involved applying appropriate statistical methods and analytical tools to interpret the data, test hypotheses, and derive meaningful insights that adhere to the rigorous standards of scientific inquiry.

5 STATISTICAL AND ANALYTICAL METHODS

For each Cohorts analysis, several epidemiological measures have been computed, such as:

- Incidence rate: The overall incidence rate was calculated using the number of VAP (all VAP episodes during the ICU stay) and the sum of ventilation exposure days among all patients. The 95% confidence intervals [95%CI] were estimated using the Ulm method.

- Attributable mortality, Population attributable fraction: To estimate the impact of the group on the mortality attributable to VAP, the method previously reported by von Cube et al (15) was used. Briefly, the attributable mortality of VAP was defined as AM(t) Increase or decrease in death (D) if a patient presents an exposure (E) at the time (t). The population attributable fraction of VAP was defined as Proportion of deaths (D) that would not have occurred if no patient presented the exposure (E) at the time (t). The time-specific AM and PAF were estimated annually at 90 days and their 95% confidence interval were computed using bootstrapping.

- Hazard rate, cumulative risk incidence of VAP: Time dependent hazard rate of VAP was computed daily until the 30th day, using the number of VAP occurring at the specific day and the number of patients still undergoing mechanical ventilation. To estimate the 30th day cumulative incidence of VAP, a model considering extubation and death as competitive risks was fitted using the Aalen Johansen estimator. To estimate the effect of the duration of mechanical ventilation, a daily landmark analysis was performed: the patient still under mechanical ventilation at the t day were included in the analysis and their t+30th day cumulative risk of VAP was computed. In a sensitivity analysis, the same analysis was performed, but the patient that already presented a VAP was excluded from the analysis (to estimate the cumulative incidence for the first VAP).

- Comparison of the cohorts: Concerning the comparison of the cohorts:

Control Group: In the mechanical ventilation, no control group is created. In the cohort of *Pseudomonas aeruginosa*, the control group will be *P. aeruginosa* with no resistance described vs the resistant *P. aeruginosa*. Concerning the patient with carbapenem resistant germ, the control group was an infection in the same localization, with the same germ, with no resistance.

Creation of the control group: The control group was created using matching: the matching was performed using the *Match It package* (R). The matching was performed on exact matching concerning the germ, the site of infection. The matching was also performed on the closest possibility to achieve a standardized mean difference below 0.1 I our cohorts, especially concerning the duration of ventilation before the occurrence of the VAP, and the characteristics of the patients: severity, age, sex, provenance, antimicrobial therapy at the admission of ICU.

Comparison of the cohorts: If the matching did not allow the creation of cohort, classical statistical test was used to compare both groups. In case of adequate matching, the comparison was using pairwise test.

6 RESULTS

The initial patient cohort between the 1st of January 2018 and the 31st of December 2021 has included 161 008 patients.

6.1 Cohort A: Mechanical ventilation cohort

6.1.1 Construction of study sample

From the initial cohort, 98 047 patients benefit from mechanical ventilation. Among them, 12 251 (12.5%) had a VAP.

6.1.2 Main Results

6.1.2.1 Global population.

All results are presented in table A-1. The mean age of the cohort is 66 [55-75] y with a classical male predominance (63.0 %). The SAPS score is 49 [36-63], the rate of fatal issue 24.4 % and the median ICU length of stay 7 [4-15] days. Ventilated patients are more frequently medical (63.0 %) compared to surgical (37.0%). Patients more often come from the community (57.0 %) than from the hospital (43.0%). The percentage of patients receiving antibiotics within 48 hours of admission is very high (57.6 %).

6.1.2.2 Incidence Rate and Cumulative incidence of VAP

In the observed cohort, the incidence rate of ventilator-associated pneumonia (VAP) for 100 ventilated patient was 12.5 % (12 251/98 047), the cumulative incidence rate for 1000 ventilation days was 18.9 cases per 1000 ventilation days, with a 95% confidence interval ranging from 18.6 to 19., indicating a precise estimate with minimal variation (table A-1 below).

Additionally, temporal risk assessment revealed a marked escalation in the incidence of VAP, culminating on the 10th day of ventilation. On this day, the hazard rate, a measure of the instantaneous risk of developing VAP, reached its apex at 29 cases per 1000 ventilation days, with the 95% confidence interval extending from 28 to 31 cases, suggesting a period of heightened vulnerability for patients undergoing mechanical ventilation (Figure A-1 below).

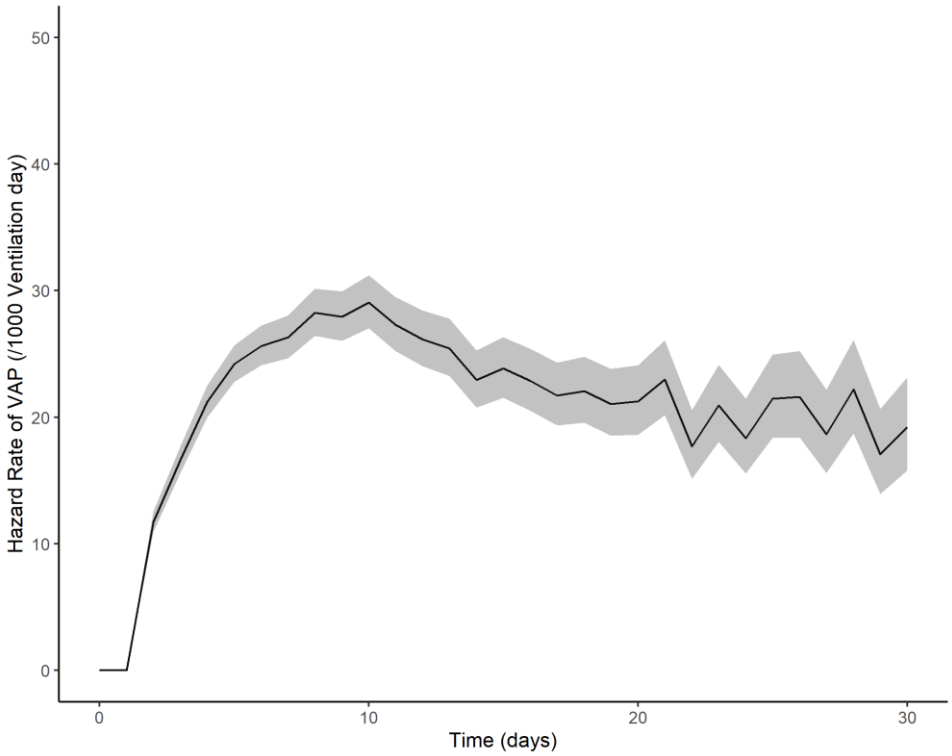

Figure A.1: Time dependent hazard rate of VAP

Upon evaluating the cumulative incidence of ventilator-associated pneumonia (VAP) within the patient population, our findings delineate a progressive increase in incidence over the duration of mechanical ventilation. On the 7th day of ventilation, the cumulative incidence rate was observed to be 11.1%, with a 95% confidence interval narrowly defined between 10.9% and 11.4%, reflecting a consistent risk across the studied cohort. By the 28th day, there was a significant increase in this rate, with the cumulative incidence escalating to 34.7%. The 95% confidence interval for this latter measurement was established between 34.1% and 35.3%, denoting a substantial rise in VAP cases as the duration of ventilation extended, and underscoring the increasing probability of VAP occurrence as the mechanical ventilation period protracted.

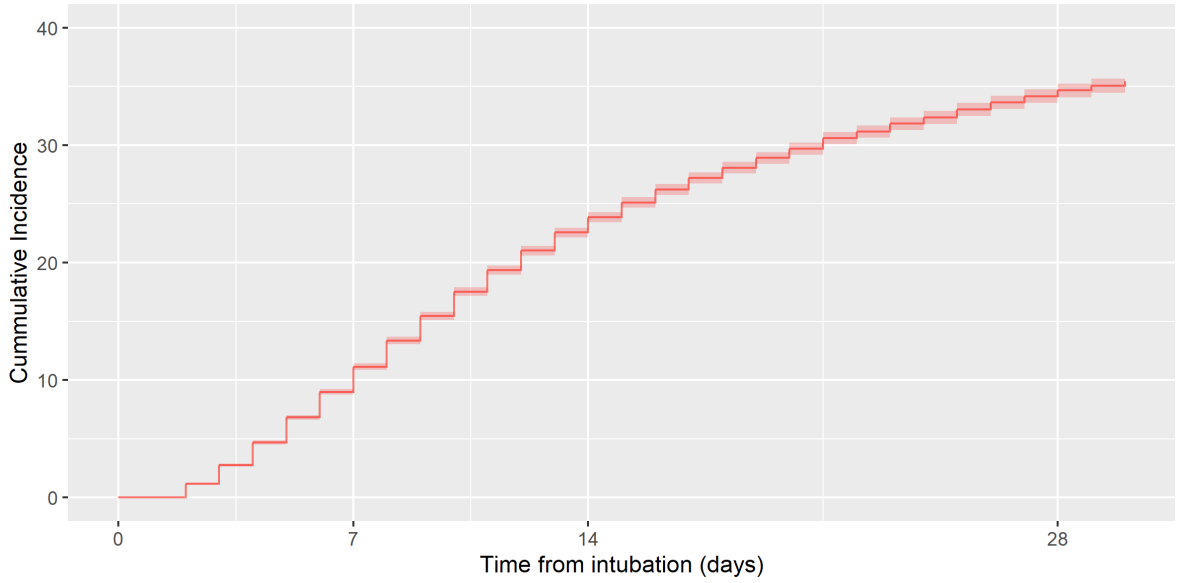

Figure A.2: Cumulative incidence of VAP

6.1.2.3 Attributable mortality of VAP

As the analysis extends to the 30th day of the mechanical ventilation timeline, the attributable mortality associated with ventilator-associated pneumonia (VAP) was estimated at 4.9% (3.7% - 6.2%). This estimation provides an assessment of the mortality directly linked to VAP, distinct from other comorbidities or underlying health issues. Advancing to the 60th day marker, the attributable mortality due to VAP exhibited an increase, calculated to be 7.2% (6.0% - 8.5%). This increment underscores the enhanced risk of mortality as the duration of exposure to mechanical ventilation increases, signifying a prolonged period of susceptibility to adverse outcomes directly ascribed to VAP (Figure A-3)

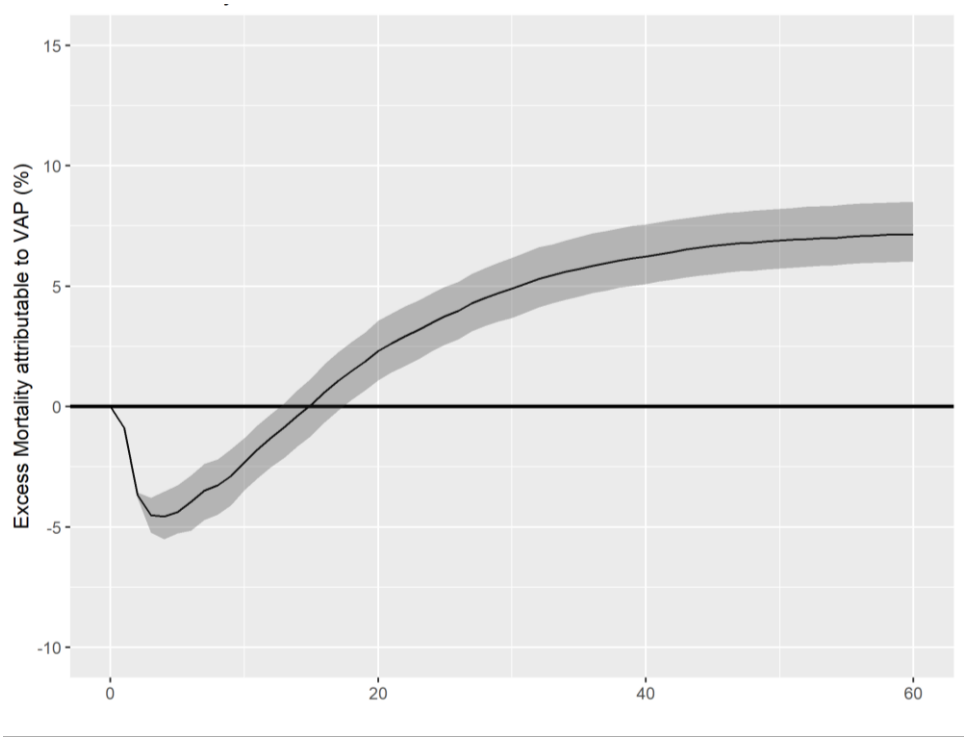

Figure A.3: Time dependent excess mortality of VAP

6.1.3 Description of the population

The table A-1 presents a comparative analysis of patients with and without ventilator-associated pneumonia (VAP) from a sample size of 98,047 mechanically ventilated patients. It reveals a statistically significant difference in age distribution between patients with VAP (median age 65, IQR [55-73] y) and those without VAP (median age 67 [55-75] y), with younger patients more commonly affected by VAP.

Regarding the admission category, a higher proportion of VAP patients were admitted for medical reasons (76.5%) compared to non-VAP patients (61.1%). In contrast, planned and emergency surgical admissions were less common among VAP patients.

A higher percentage of males were affected by VAP (73.5%) compared to those without VAP (64.6%), suggesting a gender disparity in VAP incidence.

Patient provenance also differed significantly; a greater percentage of VAP patients were admitted from other hospitals (45.2%) compared to home admissions (54.8%), whereas non-VAP patients were more likely to be admitted from home (57.2%).

Table A.1: Description of the Cohort Length of ICU stay, and ICU case fatality rates were notably higher for VAP patients, with median ICU stays of 25 days for VAP patients compared to 6 days for non-VAP patients, and ICU case fatality rates of 33.6% for VAP patients compared to 23.1% for non-VAP patients, indicating a more severe clinical course for those with VAP.

All comparisons between VAP and non-VAP patients showed a p-value of less than 0.001, denoting high statistical significance for the differences observed.

	No VAP (n= 85 796)	VAP (n=12 251)	Total (n=98 047)	p value
Age, years	67 [55-75]	65 [55-73]	66 [56-75]	<0.001
<55	20 058 (23.4%)	2 959 (24.2%)	23 017 (23.5%)	<0.001
55-66	21 345 (24.9%)	3 320 (27.1%)	24 665 (25.2%)	
67-76	25 628 (29.9%)	4 075 (33.3%)	29 703 (30.3%)	
>76	18 765 (21.9%)	1 897 (15.5%)	20 662 (21.1%)	
Admission category				<0.001
Medical	52 383 (61.1%)	9 362 (76.5%)	61 745 (63.0%)	
Planned Surgical	14 579 (17.0%)	630 (5.1%)	15 209 (15.5%)	
Emergency Surgical	18 762 (21.9%)	2 253 (18.4%)	21 015 (21.5%)	
Sex, male	55 437 (64.6%)	9 003 (73.5%)	64 440 (65.7%)	<0.001
Patient provenance				<0.001
Home	48 998 (57.2%)	6 705 (54.8%)	5 5703 (56.9%)	
Hospital	36 626 (42.8%)	5 536 (45.2%)	42 162 (43.1%)	
Antibiotics at admission	48 278 (56.7%)	7 833 (64.2%)	56 111 (57.6%)	<0.001
SAPS II	49 [36-63]	50 [38-63]	49 [36-63]	<0.001
<42	30 269 (35.9%)	3 977 (32.7%)	34 246 (35.5%)	<0.001
42-54	20 693 (24.5%)	3 312 (27.3%)	24 005 (24.9%)	
55-67	17 003 (20.1%)	2 551 (21.0%)	19 554 (20.3%)	
>67	16 445 (19.5%)	2 311 (19.0%)	18 756 (19.4%)	
Length of ICU stay, days	6 [3-12]	25 [16-39]	7 [4-15]	<0.001
ICU case fatality	19 779 (23.1%)	4 116 (33.6%)	23 895 (24.4%)	<0.001

Table A.1: Description of the Cohort

For the age : Two test are performed, one for the quantitative value (the patients with no VAP have an higher age, compared to the patient with no VAP (67 [55-75] vs 65 [55-73], p<0.001) and for the qualitative value (i.e. the repartition of the patient with an age <55, between 55-66, between 67-76, and over 76 is different between both groups – p<0.001).

The table A-2 provides data on the timing of mechanical ventilation initiation following ICU admission, the duration of ventilation, the number of VAP episodes, and the time between starting mechanical ventilation and the first episode of VAP.

For the time from ICU admission to the start of mechanical ventilation, most of both non-VAP and VAP patients (85.5% and 75.2%, respectively) were ventilated within 24 hours, which constituted 84.2% of the total patient population. Patients with no VAP were more likely to start mechanical ventilation in the first 24 hours (85.5%) compared to VAP patients (75.2%)

The duration of mechanical ventilation showed a significant disparity: non-VAP patients typically had shorter ventilation periods, with a median of 3 days and an interquartile range of 1 to 7 days. In contrast, VAP patients had a median duration of 20 days, with a much wider interquartile range of 12 to 33 days.

Concerning the number of VAP episodes, the data indicates that among patients who developed VAP, 80% had a single episode, 15% had two episodes, and 5% had more than two episodes of VAP.

The median time between the initiation of mechanical ventilation and the first episode of VAP was 8 days, with an interquartile range from 5 to 13 days, reflecting a consistent period across the VAP patient group.

All listed comparisons between non-VAP and VAP groups show statistically significant differences, with p-values <0.001, suggesting a strong association between these factors and the development of VAP.

	No VAP (n= 85 796)	VAP (n=12 251)	Total (n=98 047)	p value
Time from ICU admission to mechanical ventilation				<0.001
< 24 hours	73 366 (85.5%)	9 217 (75.2%)	82 583 (84.2%)	
24 – 72 hours	8 027 (9.4%)	1 843 (15.0%)	9 870 (10.1%)	
> 72 hours	4 403 (5.1%)	1 191 (9.7%)	5 594 (5.7%)	
Duration of mechanical ventilation, days	3 [1-7]	20 [12-33]	4 [1-10]	<0.001
Number of VAP episodes				
1	-	9 799 (80.0%)	9 799 (10.0%)	
2	-	1 894 (15.5%)	1 894 (1.9%)	
> 2	-	558 (4.6%)	558 (0.6%)	
Time between mechanical ventilation and first VAP, days	-	8 [5-13]	8 [5-13]	

Table A.2: Description of the characteristics of the mechanical ventilation

- Use of medical devices and supportive therapies (table A-3).

The percentage of intubated patients with urinary catheters (97.4 %) and central venous catheter (86.4) is very high. In contrast, the proportion of intubated patients needing an extra-renal epuration or an extracorporeal life support is low (respectively 12.2 % and 2.8 %).

In the non-VAP group (n=85,796), 10.8% underwent extra-renal epuration, whereas a notably higher percentage of patients in the VAP group (n=12 251) required this treatment, at 22.0%. Extra Corporeal Life Support (ECLS) was utilized in 2.5% of non-VAP patients, compared to 5.0% of VAP patients. Again, the difference was statistically significant (p<0.001), suggesting a greater need for ECLS in patients who developed VAP.

The use of urinary catheters was nearly universal across the cohort, with 97.2% in the non-VAP group and 98.9% in the VAP group. The slight increase in the VAP group was statistically significant (p<0.001).

Central venous catheter usage was also higher in the VAP group at 97.2%, compared to 84.8% in the non-VAP group, with a total usage of 86.4% in the entire cohort. This indicates a strong association between central venous catheter usage and the occurrence of VAP (p<0.001).

These results suggest that patients who develop VAP are more likely to have undergone invasive procedures and to require more complex supportive therapies, as evidenced by the higher percentages of device usage and the significant p-values.

	No VAP (n= 85 796)	VAP (n=12 251)	Total (n=98 047)	p value
Extra-renal Epuration	9 231 (10.8%)	2 694 (22.0%)	11 925 (12.2%)	<0.001
Extra Corporeal Life Support	2 136 (2.5%)	607 (5.0%)	2743 (2.8%)	<0.001
Urinary catheter	81 922 (97.2%)	11 950 (98.9%)	93 872 (97.4%)	<0.001
Central venous catheter	72 679 (84.8%)	11 906 (97.2%)	84 585 (86.4%)	<0.001

Table A.3: Description of the Supportive therapies

- Microbial ecology of ventilator-associated pneumonia (VAP).

The incidence of polymicrobial infections (more than one distinct microbe is implicated) was notably substantial. Out of 15,575 diagnosed cases of VAP, there were 4,695 instances of polymicrobial VAP, which constitutes 30.1% of the cases. Overall, 20 270 bacteria were isolated. This high proportion of polymicrobial VAP underscores the complexity of the infection, indicating that a significant number of patients endure infections caused by multiple pathogens concurrently, which can complicate treatment strategies and may affect patient outcomes. Most of the pathogens were Gram-negative bacteria, accounting for 44.3% of cases, with Enterobacterales being the most prevalent at 8 988 cases. Among these, Escherichia coli was identified in 1 733 cases (19.3%), Enterobacter species plurimae (spp) in 2 278 cases (25.3%), and Klebsiella spp in 2 202 cases (24.5%). Other notable Gram-negative bacteria included Proteus spp and Serratia, found in 586 (6.5%) and 852 (9.5%) cases, respectively.

Non-fermenting Gram-negative bacteria were also a significant group, contributing to 25.4% of the VAP cases, with Pseudomonas aeruginosa being the most significant contributor (3 924 cases, 76.2% of non-fermenters), followed by Stenotrophomonas maltophila (800 cases, 15.5%).

Gram-positive bacteria were identified in 21.3% of cases, with Staphylococcus aureus being the predominant organism (2782 cases, 64.3%). Enterococcus spp and Streptococcus spp were also present in 554 (12.8%) and 568 (13.1%) of the cases, respectively.

The category labeled "Other" encompasses various other organisms, including Haemophilus spp (752 cases, 79.7% of the 'Other' category), Candida spp (391 cases, 45.3%), and Aspergillus *spp* (150 cases, 17.4%). Viruses such as CMV and HSV were less commonly detected, found in 78 cases (9.0%).

The data illustrates the diverse microbiological landscape of VAP, with a predominance of Gram-negative organisms, and underscores the significant presence of multi-drug resistant organisms such as Pseudomonas aeruginosa and Acinetobacter baumannii.

	VAP germ (n=20 270)
Gram-negative bacteria	
Enterobacterales	**8 988 (44.3%)**
C3G R	2202 (24.5%)
CAR R	113 (1.3%)
Escherichia coli	1 733 (19.3%)
Enterobacter spp	2 278 (25.3%)
Hafnia spp	354 (3.9%)
Klebsiella spp	2 202 (24.5%)
Morganella spp	273 (3.0%)
Proteus spp	586 (6.5%)
Serratia	852 (9.5%)
Other	710 (7.9%)
Non-fermenting GNB	**5 147 (25.4%)**
CAZ R	1034 (25.3%)
CAR R	920 (17.9%)
Pseudomonas aeruginosa	3924 (76.2%)
Stenotrophomonas maltophilia	800 (15.5%)
Acinetobacter baumannii	373 (7.2%)
Other	50 (1.0%)
Other	**944 (4.7%)**

Haemophilus spp	752 (79.7%)
Other	192 (20.3%)
Gram-positive bacteria	**4 327 (21.3%)**
Enterococcus spp	554 (12.8%)
Staphylococcus aureus	2 782 (64.3%)
Staphylococcus spp	320 (7.4%)
Streptococcus spp	568 (13.1%)
Other	103 (2.4%)
Other	**864 (4.3%)**
Others micro-organism	245 (28.4%)
Candida spp	391 (45.3%)
Aspergillus spp	150 (17.4%)
Virus (CMV, HSV…)	78 (9.0%)

Table A.4: Description of the microbial ecology

6.1.4 Conclusion

The typical patient facing VAP in the ICU is likely to be around 65 years old, with a slightly higher prevalence among males (73.5%), reflecting a gender disparity in VAP incidence. These patients are predominantly admitted for medical reasons (76.5%) rather than surgical, and often have a history of being transferred from another hospital (45.2%). Upon admission, a significant proportion (64.2%) receive antibiotics, indicative of either existing infections or a high-risk profile for infections. The severity of their condition is slightly higher than those without VAP, as suggested by a marginally elevated SAPS II score. They typically experience a longer ICU stay, with a median duration of 25 days, and unfortunately, a higher case fatality rate of 33.6%. These patients are also more likely to require invasive treatments such as extra-renal epuration (22.0%) and extracorporeal life support (5.0%). The development of VAP appears to be associated with an increased use of medical devices, like urinary and central venous catheters, reflecting the complexity and severity of their clinical management.

6.2 Cohort B: Pseudomonas Aeruginosa cohort

6.2.1 Construction of Study Sample

Out of 161,008 patients included in the REA-REZO database from January 1st, 2018, to December 31st, 2021, a total of 4,196 patients developed an infection caused by Pseudomonas aeruginosa. During this period, 5,596 infections involving Pseudomonas aeruginosa were documented, with some patients experiencing more than one infection episode with this organism.

6.2.2 Main Results

6.2.2.1 Frequency of *Pseudomonas Aeruginosa* infection

Pseudomonas aeruginosa is the most frequent germ (table B-1). For the year 2018, *Pseudomonas aeruginosa* accounted for 9.62% of the ICU-acquired infections recorded. In 2019, the proportion of infections attributed to *Pseudomonas aeruginosa* was slightly lower (8.74%). The year 2020 saw a slight increase, with 10.75% of infections being related to *Pseudomonas aeruginosa*. In 2021, the frequency of *Pseudomonas aeruginosa* infections continued to rise, representing 11.41% of the infections. The consistent high rate of *Pseudomonas aeruginosa* across the years is notable as it was the most frequent germ.

	2018	*2019*	*2020*	*2021*
Pseudomonas Spp	1 600 (9.62%)	918 (8.74%)	1 301 (10.75%)	1 777 (11.41%)
Staphylococcus Aureus	1 237 (7.44%)	793 (7.55%)	874 (7.22%)	1 238 (7.95%)
Enterobacter Spp	1 062 (6.39%)	604 (5.75%)	838 (6.92%)	980 (6.29%)
Klebsiella Spp	902 (5.42%)	658 (6.27%)	771 (6.37%)	1 066 (6.85%)
Escherichia coli	857 (5.15%)	545 (5.19%)	542 (4.48%)	752 (4.83%)
Staphylococcus Spp	677 (4.07%)	471 (4.49%)	447 (3.69%)	476 (3.06%)
Enterococcus Spp	472 (2.84%)	287 (2.73%)	419 (3.46%)	477 (3.06%)
Candida Spp	479 (2.88%)	284 (2.70%)	276 (2.28%)	314 (2.02%)
Serratia	384 (2.31%)	233 (2.22%)	259 (2.14%)	351 (2.25%)
Stenotrophomonas maltophilia	293 (1.76%)	176 (1.68%)	210 (1.73%)	304 (1.95%)
Acinetobacter Baumanii	186 (1.12%)	115 (1.10%)	92 (0.76%)	118 (0.76%)

Table B.1: Ten most frequent pathogen per year

Over the span of 2018 to 2021, *Pseudomonas* spp. emerged as the most frequently isolated pathogen in the dataset, reflecting its significant presence in the clinical samples collected from patients. The trend showed a progressive increase; starting at 9.62% of all isolates in 2018, the percentage grew to 11.41% by 2021. This data underscores the prominence of Pseudomonas spp. within the clinical setting and highlights its role as a leading concern in patient management and infection control practices. The resilience and adaptability of Pseudomonas spp., especially its notorious capacity for antibiotic resistance, make it a focal point for monitoring and targeted interventions in healthcare facilities. The slightly highest rate of *Pseudomonas* in the table is related that some infections have been recorded more than once with the identification of *Pseudomonas aeruginosa*, due to the bacterium being identified in multiple time for one infection.

6.2.2.2 Site of infection of *Pseudomonas Aeruginosa*

	2018	*2019*	*2020*	*2021*
Bacteremia	260 (16.25%)	144 (15.69%)	229 (17.6%)	293 (16.49%)
Catheter infection	91 (5.69%)	35 (3.81%)	47 (3.61%)	29 (1.63%)
Pneumonia	1 159 (72.44%)	684 (74.51%)	930 (71.48%)	1 295 (72.88%)
Pneumonia associated with bacteriemia	90 (5.62%)	55 (5.99%)	95 (7.30%)	160 (9.00%)

Figure B.2: Site of infection of Pseudomonas Aeruginosa

The table outlines the distribution of infection sites for *Pseudomonas aeruginosa* from 2018 to 2021, illustrating where the organism was most identified:

- Bacteremia: The incidence of bacteremia showed some variation over the years but remained a significant site of infection, ranging from 15.7% to 17.6%, with the highest occurrence in 2020.

- Catheter Infections: Infections related to catheters decreased markedly over the four years, from 5.7% in 2018 to a low of 1.6% in 2021, indicating a notable decline in these types of infections.

- Pneumonia: Most Pseudomonas aeruginosa infections were identified in patients with pneumonia, with a consistently high prevalence ranging from 71.5% to 74.5%. Pneumonia remained the predominant site of infection throughout the period.

- Pneumonia Associated with Bacteremia: There was an increasing trend in pneumonia cases associated with bacteremia, starting at 5.6% in 2018 and rising to 9.0% in 2021. This indicates a growing concern for more severe infections that involve both the lungs and bloodstream.

These statistics underscore the critical role of Pseudomonas aeruginosa as a pathogen in serious infections, particularly pneumonia, and highlight the need for continued vigilance in monitoring and treating infections caused by this organism. The data also suggests some success in reducing catheter-related infections, a positive sign that could reflect improved infection control practices.

6.2.3 Resistance of *Pseudomonas aeruginosa*

Among the *Pseudomonas*, 1734 (31.0%) were resistant to Piperacillin tazobactam, 1331 (23.8%) were resistant to Ceftazidime, and 1191 (21.3%) were carbapenem resistant.

	First infection n=3187	*Second or more infection n=2409*	*p value*
Pip/Taz resistant	822 (25.8%)	912 (37.9%)	<0.001
Carbapenem resistant	521 (16.3%)	670 (27.8%)	<0.001
Ceftazidime resistant	607 (19.0%)	724 (30.1%)	<0.001
Colistin resistant	85 (2.7%)	86 (3.6%)	0.062
Resistance Group			<0.001
CAZ S – CAR S	2299 (72.1%)	1364 (53.6%)	
CAZ S - CAR R	281 (8.8%)	321 (13.3%)	
CAZ R - CAR S	367 (11.5%)	375 (15.6%)	
CAR R - CAZ R	240 (7.5%)	349 (14.5%)	

Figure B.3: Resistance of Pseudomonas Aeruginosa

CAR: carbapenem, CAZ: ceftazidime

The table B-3 provides a comparative analysis of antibiotic resistance patterns in Pseudomonas aeruginosa between initial and subsequent infections:

- Sensitive group decreased from 72.1% in the first infection to 53.6% in subsequent infections.
- **Pip/Taz Resistance**: Increased significantly from the first to subsequent infections, from 25.8% to 37.9%, indicating a rise in resistance (p<0.001).
- **Carbapenem Resistance**: Resistance to carbapenems also rose markedly from initial to subsequent infections, from 16.3% to 27.8% (p<0.001).
- **Ceftazidime Resistance**: There was a substantial increase in ceftazidime resistance from the first to subsequent infections, from 19.0% to 30.1% (p<0.001).
- **Colistin Resistance**: A slight but not statistically significant increase in colistin resistance was observed, from 2.7% in the first infection to 3.6% in subsequent infections (p=0.062). Resistance Group Comparison:
    - The group with carbapenem resistance alone increased from 8.8% to 13.3%.
    - The group with ceftazidime resistance alone rose from 11.5% to 15.6%.
    - The group with both carbapenem and ceftazidime resistance increased from 7.5% to 14.5%.

The overall p-value for resistance groups was less than 0.001, indicating a statistically significant difference in resistance patterns between the first and subsequent infections. This data suggests a

concerning trend toward increased resistance in recurrent Pseudomonas aeruginosa infections, which has significant implications for treatment options and the importance of antibiotic stewardship.

6.2.4 Resistance of P*seudomonas aeruginosa* depending on the type of infection

The resistance of Pseudomonas aeruginosa to various antibiotics varies depending on the type of infection (table B-4), as indicated by the data from different infection sites. In cases of bacteremia, there is a notable resistance to Pip/Taz at 27.1%, with carbapenem and ceftazidime resistance following closely. Interestingly, the proportion of Pseudomonas aeruginosa showing no resistance in bacteremia cases is 67.6%, suggesting a significant number of strains remain susceptible to commonly used antibiotics.

When examining catheter-related infections, Pip/Taz resistance is marginally higher than in bacteremia at 28.7%, yet the incidence of no resistance remains relatively stable at 65.3%. This could imply that while certain resistances are prevalent, most of the infections might still respond to first-line treatments.

In pneumonia, the resistance to Pip/Taz increases to 32.0%, indicating a more pronounced issue with this antibiotic when dealing with lung infections caused by Pseudomonas aeruginosa. Despite this, the percentage of non-resistant cases only marginally drops to 65.1%, which still reflects a significant proportion of treatable infections within this category.

Pneumonia associated with bacteremia shows similar trends in resistance, with Pip/Taz resistance slightly lower than in pneumonia alone. The data also reflects a minor increase in colistin resistance in these cases. However, like other infection types, most of the strains are not resistant, denoting a substantial segment of the bacterial population could be addressed with standard antimicrobial therapies.

The p-values indicate that except for Pip/Taz, where resistance variance across infection types shows statistical significance, other antibiotic resistances do not demonstrate significant differences. This suggests that while Pip/Taz resistance varies with the type of infection, other resistances such as to carbapenem, ceftazidime, and colistin do not significantly differ between the infection sites analyzed.

	Bacteriemia n=926	*Catheter infection n=202*	*Pneumonia n=4 068*	*Pneumonia associated with bacteriemia n=400*	*p value*
Pip/Taz resistant	251 (27.1%)	58 (28.7%)	1303 (32.0%)	122 (30.5%)	0.028
Carbapenem resistant	186 (20.1%)	38 (18.8%)	878 (21.6%)	89 (22.2%)	0.579
Ceftazidime resistant	195 (21.1%)	54 (26.7%)	985 (24.2%)	97 (242%)	0.156
Colistin resistant	28 (3.0%)	4 (2.0%)	124 (3.0%)	15 (3.8%)	0.695

Group of resistance					0.564
CAZ S – CAR S	626 (67.6%)	132 (65.3%)	2647 (65.1%)	258 (64.5%)	
CAZ S - CAR R	105 (11.3%)	16 (7.9%)	436 (10.7%)	45 (11.2%)	
CAZ R - CAR S	114 (12.3%)	32 (15.8%)	543 (13.3%)	53 (13.2%	
CAR R - CAZ R	81 (8.7%)	22 (10.9%)	442 (10.9%)	44 (11.0%)	

Figure B.4: Resistance of Pseudomonas aeruginosa depending on the type of infection

CAR: carbapenem, CAZ: ceftazidime

6.2.5 Description of the patient with *Pseudomonas aeruginosa* infections.

	No Resistance n=2977	Carbapenem Resistant n=413	Ceftazidime resistant n=469	Carbapenem and ceftazidime resistant n=337	p value
Age, years	67 [58-74]	66 [56-73]	68 [60-75]	65 [55-72]	<0.001
<55	585 (19.7%)	87 (21.1%)	75 (16.0%)	81 (24.0%)	0.006
55-66	797 (26.8%)	112 (27.1%)	130 (27.7%)	105 (31.2%)	
67-76	1074 (36.1%)	149 (36.1%)	161 (34.3%)	112 (33.2%)	
>76	521 (17.5%)	65 (15.7%)	103 (22.0%)	39 (11.6%)	
Admission category					0.329
Medical	2352 (79.0%)	336 (74.8%)	379 (80.8%)	256 (76.2%)	
Planned Surgical	152 (5.1%)	25 (6.1%)	26 (5.5%)	23 (6.8%)	
Emergency Surgical	472 (15.9%)	52 (12.6%)	64 (13.6%)	57 (17.0%)	
Sex, male	2173 (73%)	309 (74.8%)	351 (74.8%)	260 (77.2%)	
Patient provenance					<0.001
Home	1489 (50.1%)	162 (39.3%)	205 (43.8%)	120 (35.6%)	
Hospital	1481 (49.9%)	250 (60.7%)	263 (56.2%)	217 (64.4%)	
Antibiotics at admission	2018 (68.1%)	304 (74.0%)	365 (78.2%)	270 (80.4%)	<0.001
SAPS II	48 [37-62]	49 [38-64]	50 [39-65]	49 [37-61]	0.033
<42	1055 (35.7%)	139 (33.9%)	132 (28.5%)	115 (34.4%)	0.182
42-54	789 (26.7%)	106 (25.9%)	129 (27.9%)	95 (28.4%)	
55-67	582 (19.7%)	80 (19.5%)	101 (21.8%)	67 (20.1%)	
>67	527 (17.8%)	85 (20.7%)	101 (21.8%)	57 (17.1%)	
Length of ICU stay, days	28 [17-45]	35 [22-56]	28 [17-48]	36 [22-56]	<0.001
ICU case fatality	1000 (33.6%)	180 (43.6%)	183 (39.0%)	152 (45.1%)	<0.001

Figure B.5: Description of the patient with Pseudomonas aeruginosa infections

The dataset (table B-5) describes patients with *Pseudomonas aeruginosa* infections categorized by their antibiotic resistance profile. The median age across the groups suggests a slight trend towards younger patients in the carbapenem and ceftazidime resistant category. Statistically significant differences in age distribution among the resistance groups are noted (p<0.001), particularly evident in patients under 55, where 24.0% of those with dual resistance are under this age threshold, compared to 19.7% with no resistance.

Regarding the source of admission, most patients across all categories were admitted for medical reasons, with a relatively lower proportion of planned surgical admissions. No significant difference in admission category is observed among the groups (p=0.329).

A notable difference is seen in the patient provenance, with a higher proportion of those with resistance coming from other hospitals compared to those coming from home, suggesting that hospital transfer may be a risk factor for acquiring resistant strains (p<0.001).

Antibiotic use at admission was highest in the group with dual resistance to carbapenem and ceftazidime which is likely reflective of the more complex medical needs and possibly prior exposure to antibiotics in this group (p<0.001).

In terms of severity at admission measured by SAPS II, there is a slight variation among the groups, but it remains statistically significant (p=0.033), potentially indicating more severe illness in patients with resistant strains.

The length of ICU stay was longer for patients with carbapenem resistance alone or in combination with ceftazidime resistance, which may reflect the more complicated and difficult-to-treat nature of these infections (p<0.001).

ICU case fatality rates were notably higher in the resistant groups, particularly for those with dual resistance (45.1%), suggesting that resistance contributes to poorer outcomes (p<0.001).

Overall, the data illustrates that resistance to antibiotics in *Pseudomonas aeruginosa* infections is associated with specific demographic profiles, more complex medical histories, longer ICU stays, and higher mortality rates. This underlines the critical challenges posed by resistant strains in the clinical management of infected patients.

	No Resistance n=2977	Carbapenem Resistant n=413	Ceftazidime resistant n=469	Carbapenem and ceftazidime resistant n=337	p value

Extra-renal Epuration	724 (24.3%)	141 (34.1%)	152 (32.4%)	136 (40.4%)	<0.001
Extra Corporeal Life Support	145 (4.9%)	21 (5.1%)	21 (4.5%)	25 (7.4%)	0.216
Mechanical ventilation	2897 (97.4%)	404 (97.8%)	454 (97.0%)	328 (97.3%)	0.901
Urinary catheter	2896 (98.3%)	400 (98.3%)	462 (98.7%)	322 (98.8%)	0.830
Central venous catheter	2864 (96.3%)	399 (96.6%)	458 (97.9%)	334 (99.4%)	0.009

Figure B.6: Description of the supportive therapies for the patient with Pseudomonas aeruginosa infections

The table B-6 presents a breakdown of the use of various medical interventions in patients with *Pseudomonas aeruginosa* infections, differentiated by their antibiotic resistance profiles.

Extra-renal epuration was used more frequently in patients with resistant strains, with 40.4% in the carbapenem and ceftazidime resistant group undergoing this procedure, a significant increase compared to 24.3% in the non-resistant group ($p<0.001$). This suggests a correlation between the severity of infection and the need for such advanced supportive treatments in cases with resistance.

The use of Extra Corporeal Life Support (ECLS) did not vary significantly across the groups, though the highest usage was seen in patients with dual resistance to carbapenem and ceftazidime at 7.4%. This may indicate the necessity of ECLS in more severe cases which often may coincide with higher resistance ($p=0.216$).

The urinary catheter usage was similarly high across all groups, indicating its standard application in ICU care for patients with these infections, without significant variation linked to antibiotic resistance ($p=0.830$).

Central venous catheter usage was statistically different across groups, with the highest usage at 99.4% in the dual-resistant group ($p=0.009$). This could reflect more intensive management and monitoring requirements in patients with more resistant infections.

Overall, the data suggests that while certain interventions like extra-renal epuration and central venous catheter usage are more common in patients with resistant *Pseudomonas aeruginosa* infections, other supportive treatments such as ECLS, mechanical ventilation, and urinary catheterization are consistently used regardless of the resistance profile, highlighting their role as standard practices in the care of critically ill patients.

	No Resistance n=2897	Carbapenem Resistant n=404	Ceftazidime resistant n=454	Carbapenem and ceftazidime resistant n=328	p value
Time from ICU admission to mechanical ventilation					0.163
< 24 hours	2022 (69.8%)	285 (70.5%)	330 (72.7%)	247 (75.3%)	
24 – 72 hours	501 (17.3%)	60 (14.9%)	68 (15.0%)	39 (11.9%)	
> 72 hours	374 (12.9%)	59 (14.6%)	56 (12.3%)	42 (12.8%)	
Duration of mechanical ventilation, days	22 [13-38]	30 [16-48]	22 [13-40]	27 [17-45]	<0.001
Number of VAP episodes					<0.001
0	530 (18.3%)	50 (12.4%)	79 (17.4%)	56 (17.1%)	
1	1594 (55.0%)	220 (54.5%)	265 (58.4%)	184 (56.1%)	
2	546 (18.8%)	79 (19.6%)	68 (15.0%)	67 (20.4%)	
> 2	227 (7.8%)	55 (13.6%)	42 (9.3%)	21 (6.4%)	
Time between mechanical ventilation and first VAP, days	8 [5-14]	11 [7-19]	9 [6-15]	12 [7-20]	<0.001

Figure B.7: Description of the mechanical ventilation for the patient with Pseudomonas aeruginosa infections

The table B-7 presents characteristics of patients undergoing mechanical ventilation who were infected with *Pseudomonas aeruginosa*, categorized by their resistance to antibiotics.

Most patients in each resistance category were put on mechanical ventilation within the first 24 hours of ICU admission, and the differences between groups were not statistically significant (p=0.163). However, the median duration of mechanical ventilation differed significantly across groups. Patients with carbapenem-resistant and dual-resistant infections experienced longer periods of ventilation, suggesting that antibiotic resistance is associated with more extended mechanical support needs (p<0.001). Globally, the level of resistance is compatible with classical rates between 20 and 40 % published in the literature for France (3–6). The number of ventilator-associated pneumonia (VAP) episodes also varied significantly with resistance. The proportion of patients with more than two VAP episodes was higher in the carbapenem-resistant group, indicating a potential link between resistance and the likelihood of recurrent VAP (p<0.001).

The time between initiation of mechanical ventilation and the first VAP episode was also longer in patients with any form of resistance, particularly in the dual-resistance group, with a median of 12

days. This extended period could reflect the complexity of managing infections with resistant organisms, possibly due to a limited number of effective antibiotics and the challenge of eradicating the infection ($p<0.001$).

Overall, these characteristics highlight the additional burdens placed on healthcare resources when treating *Pseudomonas aeruginosa* infections with resistance to key antibiotics, including longer durations of mechanical ventilation and increased frequency of VAP episodes. This further underlines the importance of antibiotic stewardship and infection prevention strategies in the ICU.

6.2.6 Conclusion

Statistically significant differences in age distribution among the resistance groups are noted ($p<0.001$), particularly evident in patients under 55, where 24.0% of those with dual resistance are under this age threshold, compared to 19.7% with no resistance. The severity of their condition at admission can be inferred from the SAPS II scores, with those harboring resistant strains exhibiting marginally higher scores. The duration of ICU stay is longer for those with resistant strains, suggesting more challenging infections. We noticed a higher resistance rate for the second infection, irrespective of the type of resistance studied. The mortality rate also tends to be higher among these patients, particularly in those with dual resistance. This patient profile underscores the challenges that antibiotic resistance poses in clinical management, the need for robust infection control practices, and the importance of antibiotic stewardship. Physician should consider in their empirical antimicrobial therapy the SAPS II score, the late-onset VAP, and the origin of the patient.

6.3 Cohort C: Carbapenem Resistant cohort

6.3.1 Construction of Study Sample

To begin the patient matching process, we selected all patients suffering with at least one Carbapenem-resistant infection. Then, for the first infection encountered, we matched a 1:1 patient based on the exact matching technique. This strategy ensured a one-to-one correspondence between the groups, aligning them based on the type of germ, the number of infections, and the infection site. From the pool of 11,799 germs devoid of Carbapenem resistance and 1,122 germs exhibiting Carbapenem resistance, we successfully grouped 958 patients into each category for further comparative analysis.

6.3.2 Main Results

6.3.2.1 Prematching characteristics

	No Carbapenem resistance n=11799	*Carbapenem resistance n=1122*	*p value*
Number of infections			<0.001
1	10 572 (89.6%)	678 (60.4%)	
2	1 037 (8.8%)	221 (19.7%)	
3	158 (1.3%)	125 (11.1%)	
4	28 (0.2%)	58 (5.2%)	
>4	4 (0%)	40 (3.6%)	
Germ			<0.001
Gram-negative bacteria			
Enterobacterales			
Citrobacter Spp	565 (4.8%)	10 (0.9%)	
Escherichia coli	1892 (16.0%)	8 (0.7%)	
Enterobacter Spp	2 135 (18.1%)	57 (5.1%)	
Hafnia Spp	314 (2.7%)	3 (0.3%)	
Klebsiella Spp	2002 (17.0%)	51 (4.5%)	
Morganella Spp	240 (2.0%)	11 (1.0%)	
Proteus Spp	474 (4.0%)	17 (1.5%)	
Serratia	717 (6.1%)	5 (0.4%)	
Other	66 (0.6%)	0 (0.0%)	
Total		**162**	
Non-fermenting GNB			
Pseudomonas Spp	2620 (22.2%)	900 (80.2%)	
Stenotrophomonas maltophilia	491 (4.2%)	0 (0.0%)	
Acinetobacter Spp	252 (2.1%)	60 (5.3%)	
Other	31 (0.3%)	0 (0.0%)	
Total		**960**	
Site of infection			0.006
Pneumonia	9067 (76.8%)	864 (77.0%)	
Pneumonia with Bacteriemia	550 (4.7%)	62 (5.5%)	
Infection of Catheter	380 (3.2%)	51 (4.5%)	
Bacteriemia			
Digestive	312 (2.6%)	25 (2.2%)	
Urinary	235 (2.0%)	12 (1.1%)	
Catheter	176 (1.5%)	16 (1.4%)	
Soft tissue and skin	55 (0.5%)	5 (0.4%)	
Pulmonary	318 (2.7%)	42 (3.7%)	
Other	246 (2.1%)	15 (1.3%)	
Undetermined	460 (3.9%)	30 (2.7%)	

Table C.1: Prematching characteristics

This table C-1 outlines the incidence of infections and identifies the specific pathogens in patients with and without carbapenem resistance.

For patients without carbapenem resistance, the vast majority (89.6%) had only one infection. In contrast, in the carbapenem-resistant group, a lower percentage (60.4%) had a single infection, with progressively more patients experiencing multiple infections. Notably, 3.6% of carbapenem-resistant patients had more than four infections, indicating a trend where resistance is associated with higher infection rates.

Pseudomonas spp. is significantly more prevalent in the carbapenem-resistant group, constituting 80.2% of the germs identified, compared to 22.2% in the non-resistant group. This stark contrast is statistically significant and underscores the challenge of treating infections caused by carbapenem-resistant *Pseudomonas*.

The distribution of infections across different sites is relatively similar between the two groups, with pneumonia being the most common site. However, there is a slight but statistically significant variation in the distribution of infection sites, with pneumonia with bacteremia and catheter infections being slightly more common in the carbapenem-resistant group.

The presence of *Acinetobacter* spp. is also higher in the carbapenem-resistant group. This data suggests that carbapenem resistance is not isolated to a single pathogen but is seen across a range of bacterial species.

Overall, the table reveals a significant association between carbapenem resistance and an increased frequency of infections, as well as a variation in the type of pathogens and infection sites, which highlights the complexity of managing infections in carbapenem-resistant patients.

	No Carbapenem resistance n=11799	Carbapenem resistance n=1122	p value
Age, years	66 [57-74]	65 [56-73]	0.011
<55	2518 (21.3%)	251 (22.4%)	
55-66	3144 (26.6%)	328 (29.2%)	
67-76	4022 (34.1%)	385 (34.3%)	
>76	2115 (17.9%)	158 (14.1%)	
Admission category			0.025
Medical	8831 (74.9%)	880 (78.5%)	
Planned Surgical	798 (6.8%)	61 (5.4%)	
Emergency Surgical	2162 (18.3%)	180 (16.1%)	
Sex, male	8746 (74.1%)	851 (75.8%)	0.221
Patient provenance			
Home	5578 (47.3%)	678 (60.5%)	<0.001

Hospital	6204 (52.7%)	443 (39.5%)	
Antibiotics at admission	7631 (65.0%)	842 (75.3%)	<0.001
SAPS II	50 [38-63]	48 [37-63]	0.280
<42	3841 (32.9%)	381 (34.3%)	0.706
42-54	3168 (27.1%)	301 (27.1%)	
55-67	2449 (20.9%)	219 (19.7%)	
>67	2232 (19.1%)	210 (18.9%)	
Length of ICU stay, days	24 [15-38]	37 [22-58]	0.001
ICU case fatality	3844 (32.6%)	476 (42.4%)	< 0.001

Table C.2: Description of the pre-matching patients

This table delineates the demographics and clinical characteristics of patients with infections, comparing those with no carbapenem resistance to those with carbapenem resistance.

A slight difference in median age between the two groups indicates that carbapenem-resistant infections are not confined to an older population, which is often more susceptible to infections due to a variety of factors including comorbid conditions.

The distribution of patients in the admission categories reveals a higher percentage of medical admissions in the carbapenem-resistant group, suggesting that these infections may be more prevalent among patients admitted for medical reasons rather than surgical.

The difference in patient provenance is notable, with a significantly higher proportion of carbapenem-resistant infections found in patients coming from home compared to the hospital. This could suggest a community-associated trend for these resistant infections, or it might reflect the transfer of patients from home due to the severity of their condition.

Antibiotic administration at the time of admission was significantly higher in the carbapenem-resistant group, pointing towards a more aggressive initial treatment approach, possibly due to the anticipated difficulties in treating these infections.

The Severity of Acute Physiology Score (SAPS II) did not show a significant difference between the groups, indicating that the overall severity of illness at admission was comparable.

The length of ICU stays, and ICU case fatality rates were both significantly higher in the carbapenem-resistant group, underscoring the serious impact of antibiotic resistance on patient outcomes. Longer ICU stays can contribute to a higher risk of adverse events and increased healthcare costs, while the higher fatality rate reflects the critical nature and challenge of managing these infections.

In summary, the presence of carbapenem resistance in infections is associated with a distinct clinical profile, characterized by longer ICU stays, higher case fatality, and a higher likelihood of antibiotic administration at admission, all of which contribute to the complexity of care for these patients.

	No Carbapenem resistance n=11799	Carbapenem resistance n=1122	p value
Extra-renal Epuration	2642 (22.4%)	423 (37.7%)	<0.001
Extra Corporeal Life Support	550 (4.7%)	72 (6.4%)	0.011
Mechanical ventilation	11365 (96.4%)	1100 (98.0%)	0.006
Urinary catheter	11406 (98.0%)	1090 (98.7%)	0.127
Central venous catheter	11371 (96.5%)	1101 (98.2%)	0.003

Table C-3: Description of the pre matching supportive therapies

The table C-3 provides a comparative analysis of the medical interventions and devices used in patients with and without carbapenem resistance.
Patients with carbapenem resistance have a significantly higher rate of undergoing extra-renal epuration, with 37.7% compared to 22.4% in the non-resistant group. This substantial difference ($p<0.001$) suggests that carbapenem-resistant infections may be associated with a greater incidence of renal complications or a higher severity of illness, necessitating renal supportive therapy.
The use of Extra Corporeal Life Support (ECLS) is also more frequent in patients with carbapenem resistance, 6.4% versus 4.7% in non-resistant patients, indicating a potential for more severe disease in this population that requires advanced life-sustaining treatments ($p=0.011$).
A small but statistically significant difference is observed in the use of mechanical ventilation, with 98.0% of carbapenem-resistant patients receiving mechanical ventilation compared to 96.4% in the non-resistant group ($p=0.006$). This could reflect the higher respiratory support needs in patients with resistant infections.
The use of urinary catheters is high in both groups, exceeding 98%, and shows no significant difference ($p=0.127$). This high usage rate is likely due to the common practice of catheterization in critically ill ICU patients.
There is also a statistically higher use of central venous catheters in the carbapenem-resistant group ($p=0.003$). Central venous catheters are essential for administering medications, fluids, and for hemodynamic monitoring in severe infections, suggesting that resistant infections may require more intensive monitoring and treatment delivery.
In summary, the data indicates that carbapenem resistance in infections is linked with an increased use of certain medical interventions, which may be indicative of more complex and severe clinical scenarios requiring extensive medical support.

	No Carbapenem resistance n=11 799	Carbapenem resistance n=1 122	p value
Time from ICU admission to mechanical ventilation			0.036
< 24 hours	8 290 (72.9%)	776 (70.5%)	
24 – 72 hours	1 732 (15.2%)	165 (15.0%)	
> 72 hours	1 343 (11.8%)	159 (14.5%)	
Duration of mechanical ventilation, days	19 [11-31]	30 [17-50]	<0.001
Number of VAP episodes			
0	2 935 (24.9%)	182 (16.2%)	< 0.001
1	6 980 (59.2%)	533 (47.5%)	
2	1 498 (12.7%)	250 (22.3%)	
> 2	386 (3.3%)	157 (14.0%)	
Time between mechanical ventilation and first VAP, days	8 [5-13]	10 [6-18]	<0.001

Table C.4: Description of the pre matching mechanical ventilation

The table provides insight into the timeframe from ICU admission to mechanical ventilation initiation, the duration of mechanical ventilation, the number of VAP episodes, and the time between mechanical ventilation and the first VAP episode in patients with and without carbapenem resistance.

The timing of mechanical ventilation after ICU admission shows a slight but statistically significant difference between the two groups, with a smaller proportion of carbapenem-resistant patients receiving mechanical ventilation within the first 24 hours compared to those without resistance. The difference suggests that patients with carbapenem resistance are more likely to be mechanically ventilated later in their ICU stay.

The duration of mechanical ventilation is considerably longer in patients with carbapenem resistance, with a median of 30 days compared to 19 days in non-resistant patients. This significant prolongation ($p<0.001$) could reflect the complexity and severity of care required for infections with resistant bacteria.

There is a notable difference in the number of VAP episodes, with a higher incidence of multiple episodes in the carbapenem-resistant group. Not only are single episodes of VAP less common among these patients, but also the rate of experiencing more than two episodes is considerably higher (14.0% vs. 3.3%), indicating a potential association between carbapenem resistance and recurrent VAP.

Furthermore, the time from mechanical ventilation to the first episode of VAP is longer in the resistant group, with a median of 10 days versus 8 days in the non-resistant group. The extended time to the first VAP episode (p<0.001) might suggest a persistent vulnerability to infection or difficulties in early infection control among patients with resistant strains.

Collectively, these findings underscore the increased burden of care in managing carbapenem-resistant infections, manifested by extended mechanical ventilation, higher rates of VAP, and delayed onset of VAP, all of which highlight the clinical challenges posed by antibiotic resistance.

	No Carbapenem resistance n=5852	Carbapenem resistance n=588	p value
Carriage BLSE admission	1 027 (17.5%)	186 (31.6%)	<0.001
Carriage EPC admission	53 (0.9%)	84 (14.3%)	<0.001
Carriage ABRI admission	7 (0.1%)	12 (2.0%)	<0.001
Carriage PARC admission	369 (6.3%)	308 (52.4%)	<0.001
Carriage SARM admission	130 (2.2%)	13 (2.2%)	1
Carriage BLSE acquired	748 (12.8%)	133 (22.6%)	<0.001
Carriage EPC acquired	41 (0.7%)	55 (9.4%)	<0.001
Carriage ABRI acquired	7 (0.1%)	6 (1.0%)	<0.001
Carriage PARC acquired	303 (5.2%)	247 (42.0%)	<0.001
Carriage SARM acquired	72 (1.2%)	6 (1.0%)	0.937

Table C.5: Description of the pre matching carriage of the patient

The cohort is made up of patients from the initial cohort (patients with at least one infection carbapenem sensitive or resistant) who have been screened for colonization by carbapenem-resistant bacteria, either on admission or during their stay in the intensive care unit. The table compares the prevalence of various drug-resistant organisms carried by patients without carbapenem resistance and patients with carbapenem resistance.
Carriers of Extended Spectrum Beta-Lactamase (ESBL) at admission are significantly more prevalent in the carbapenem-resistant group at 31.6%, nearly twice as much as in the non-resistant group at 17.5%. This trend continues with the acquisition rates, where 22.6% of the carbapenem-resistant group acquired BLSE during their stay compared to 12.8% in the non-resistant group.
For Extended Spectrum Beta-lactamase-producing Enterobacteriaceae (EPC), the carbapenem-resistant group shows a notably higher carriage at admission, 14.3% versus 0.9%, and acquisition, 9.4% versus 0.7%, pointing to a strong association between carbapenem resistance and the presence of EPC.
The data also reveals a higher prevalence of Acinetobacter baumannii resistant to imipenem (ABRI) in the carbapenem-resistant group both at admission and acquired during the stay.
The most significant difference is observed with Pseudomonas aeruginosa resistant to carbapenems (PARC), with 52.4% of the carbapenem-resistant group carrying this organism at admission and 42.0% acquiring it during their stay, compared to 6.3% and 5.2%, respectively, in the non-resistant group.

Interestingly, the carriage and acquisition rates of Staphylococcus aureus resistant to methicillin (SARM) show no significant difference between the two groups, suggesting that SARM is not preferentially associated with carbapenem resistance.
These findings suggest that carbapenem resistance is a marker for multiple drug resistance, as indicated by the higher rates of carriage and acquisition of various resistant organisms, especially ESBL, EPC, ABRI, and PARC. This reflects the challenges in controlling the spread of multidrug-resistant organisms in the healthcare setting and underscores the need for stringent infection control measures.

6.3.2.2 Post matching characteristics

	No Carbapenem resistance n= 958	*Carbapenem resistance n=958*
Number of infections		
1	677 (70.7%)	677 (70.7%)
2	216 (22.5%)	216 (22.5%)
3	53 (5.5%)	53 (5.5%)
4	10 (1.0%)	10 (1.0%)
>4	2 (0.2%)	2 (0.2%)
Germ		
Gram-negative bacteria		
Enterobacterales		
Citrobacter Spp	10 (1.0%)	10 (1.0%)
Escherichia coli	8 (0.8%)	8 (0.8%)
Enterobacter Spp	54 (5.6%)	54 (5.6%)
Hafnia Spp	3 (0.3%)	3 (0.3%)
Klebsiella Spp	50 (5.2%)	50 (5.2%)
Morganella Spp	9 (0.9%)	9 (0.9%)
Proteus Spp	16 (1.7%)	16 (1.7%)
Serratia	5 (0.5%)	5 (0.5%)
Non-fermenting GNB		
Pseudomonas Spp	748 (78.1%)	748 (78.1%)
Acinetobacter Spp	55 (5.7%)	55 (5.7%)
Other		
Site of infection		
Pneumonia	755 (78.8%)	755 (78.8%)
Pneumonia with bacteriemia	46 (4.8%)	46 (4.8%)
Infection of Catheter	43 (4.5%)	43 (4.5%)
Bacteriemia		
Digestive	23 (2.4%)	23 (2.4%)
Urinary	10 (1.0%)	10 (1.0%)

Catheter	11 (1.1%)	11 (1.1%)
Soft tissue and skin	3 (0.3%)	3 (0.3%)
Pulmonary	33 (3.4%)	33 (3.4%)
Other	10 (1.0%)	10 (1.0%)
Undetermined	24 (2.5%)	24 (2.5%)

Table C.6: Post matching characteristics.

The provided table showcases the results of a 1:1 exact matching process for patients with infections, comparing those with no Carbapenem resistance to those with Carbapenem resistance, each group containing 958 patients.

In both groups, most patients had only one infection, representing 70.7% of each cohort. The consistency extends to patients with two infections at 22.5%, three infections at 5.5%, and so on, down to those with more than four infections, which accounts for 0.2% in each group. This equal distribution post-matching indicates a successful matching process based on the number of infections.

The matching also achieved parity in terms of the germs present. Pseudomonas spp. is the predominant germ, making up 78.1% of the infections in both groups. Other germs such as Acinetobacter spp., Enterobacter spp., and Klebsiella spp. show identical frequencies in both cohorts, further confirming the efficacy of the matching.

Infection sites were also meticulously matched. Pneumonia was the most common site of infection, comprising 78.8% of cases in both groups. Other sites of infection such as pneumonia with bacteremia, catheter infections, and various other sites including digestive, urinary, and soft tissue and skin, display the same proportion in both the non-resistant and resistant groups.

This table thus reflects a well-matched comparison cohort, setting the stage for subsequent analyses that can accurately assess the impact of Carbapenem resistance on clinical outcomes without confounding due to differences in the number of infections, the type of germs, or the site of infection.

	No Carbapenem resistance n= 958	Carbapenem resistance n= 958	p value
Non-fermenting GNB (n=803)			
Pip/Taz Resistance	138 (17.2%)	451 (56.2%)	<0.001
Ceftazidime resistance	110 (14.5%)	390 (48.8%)	<0.001
Colistin resistance	19 (2.4%)	41 (5.1%)	0.006
Enterobacterales (n=155)			

Resistance C3G	49 (31.6%)	115 (74.2%)	<0.001
BLSE	23 (14.8%)	61 (39.4%)	<0.001

Table C.7: Associated resistance in both groups

This new table presents a comparative analysis of antibiotic resistance: those with no Carbapenem resistance and those with Carbapenem resistance. The data is stratified into two categories of germs: non-fermenting Gram-negative bacteria (GNB) and Enterobacterales.

For *non-fermenting GNB* (803 germ):

- Piperacillin/Tazobactam (Pip/Taz) Resistance: There is a significant difference between the two groups, with a resistance rate of 17.2% in the non-resistant group compared to 56.2% in the resistant group (p<0.001).
- Ceftazidime Resistance: A similar pattern is observed, with 14.5% resistance in the non-resistant group and 48.8% in the resistant group (p<0.001).
- Colistin Resistance: The resistance is more than double in the Carbapenem-resistant group (5.1%) compared to the non-resistant group (2.4%), with a statistically significant difference (p=0.006).

For *Enterobacterales* (155 instances):

- C3G Resistance: 31.6% of the non-resistant group versus a much higher 74.2% of the resistant group exhibit resistance (p<0.001).
- BLSE (Beta-Lactamase): Resistance is significantly higher in the Carbapenem-resistant group (39.4%) compared to the non-resistant group (14.8%) (p<0.001).

This table C-8 compares the demographic and clinical characteristics of patients grouped by their infection's carbapenem resistance status.

	No Carbapenem resistance n=958	Carbapenem resistance n= 958	p value
Age, years	66 [57-74]	65 [56-72]	0.065
<55	212 (22.1%)	221 (23.1%)	0.060
55-66	256 (26.7%)	277 (28.9%)	
67-76	309 (32.3%)	323 (33.7%)	
>76	181 (18.9%)	137 (14.3%)	
Admission category			0.120
Medical	698 (72.9%)	737 (77.0%)	
Planned Surgical	67 (7.0%)	57 (6.0%)	
Emergency Surgical	192 (20.1%)	163 (17.0%)	

Sex, male	685 (71.5%)	713 (74.4%)	0.165
Patient provenance			<0.001
Home	504 (52.6%)	367 (38.3%)	
Hospital	454 (47.4%)	590 (61.7%)	
Antibiotics at admission	658 (69.2%)	737 (77.3%)	<0.001
SAPS II	51 [39-64]	49 [38-64]	0.146
<42	285 (30.0%)	314 (33.1%)	0.518
42-54	258 (27.1%)	252 (26.5%)	
55-67	211 (22.2%)	195 (20.5%)	
>67	197 (20.7%)	189 (19.9%)	
Length of ICU stay, days	27 [17-43]	33 [20-54]	<0.001
ICU case fatality	300 (31.3%)	415 (43.3%)	<0.001

Table C.8: Characteristics of the post matching patients

The median age of patients is similar between the two groups, with a slightly younger median age in the carbapenem-resistant group. There is a marginally higher percentage of younger patients (<55) in the carbapenem-resistant group, but the difference is not statistically significant (p=0.060).

In terms of admission categories, a higher percentage of patients with carbapenem-resistant infections were admitted for medical reasons compared to those without resistance, although this difference is not statistically significant (p=0.120).

A significant difference is observed in the patient provenance, with a higher percentage of carbapenem-resistant infections occurring in patients admitted from hospitals rather than from home (p<0.001). The matching process allowed to find a more reliable constatation, with nosocomial patient being more at risk of carbapenem resistance.

There is also a notably higher percentage of carbapenem-resistant patients who received antibiotics at the time of admission, indicating a possible predisposition or awareness of their resistant infection status (p<0.001).

Severity at admission, as indicated by SAPS II scores, shows no significant difference between the groups, suggesting that the initial illness severity is comparable.

However, the length of ICU stay is significantly longer for patients with carbapenem resistance, and these patients also have a higher ICU case fatality rate, highlighting the severe impact of carbapenem-resistant infections on patient outcomes (p<0.001 for both length of stay and fatality rate).

These findings illustrate the clinical burden associated with carbapenem-resistant infections, including longer ICU stays and increased mortality, and emphasize the importance of targeted interventions to manage and prevent these challenging infections.

The table compares the utilization of medical interventions in matched patient cohorts with and without Carbapenem resistance.
A significant difference is observed in the use of extra-renal epuration, with 36.2% of patients with Carbapenem resistance requiring this treatment, compared to 26.3% in the non-resistant group. This indicates a higher need for renal support therapies in patients with resistant infections (p<0.001).
The need for Extra Corporeal Life Support (ECLS) is also higher in the Carbapenem-resistant group at 5.9%, as opposed to 3.1% in the non-resistant group, suggesting that more severe cases requiring advanced life support are present in the resistant cohort (p=0.004).
Mechanical ventilation is broadly used in both groups, with no significant difference between them, indicating that this intervention is a standard treatment regardless of the resistance status of the infection (p=0.658).

	No Carbapenem resistance n= 958	Carbapenem resistance n= 958	p value
Extra-renal Epuration	252 (26.3%)	347 (36.2%)	<0.001
Extra Corporeal Life Support	30 (3.1%)	57 (5.9%)	0.004
Mechanical ventilation	931 (97.3%)	936 (97.7%)	0.658
Urinary catheter	926 (97.6%)	926 (98.5%)	0.194
Central venous catheter	917 (95.7%)	938 (98.0%)	0.006

Table C.9: Supportive therapies of the post matching patients

The use of urinary catheters is similarly high across both cohorts, with a slightly higher, but not statistically significant, prevalence in the Carbapenem-resistant group (p=0.194).
A statistically significant difference is noted in the use of central venous catheters, used in 98.0% of the Carbapenem-resistant group compared to 95.7% in the non-resistant group (p=0.006). This suggests that patients with Carbapenem resistance may require more frequent central access for medication administration or monitoring.
Overall, the data reflects that while certain interventions like extra-renal epuration and central venous catheterization are more common among patients with Carbapenem-resistant infections, other interventions such as mechanical ventilation and urinary catheterization are consistently high in ICU patients regardless of their infection's resistance profile.

The table provides a detailed comparison between patients with and without Carbapenem resistance regarding their mechanical ventilation timeline, the duration of ventilation, the number of ventilator-associated pneumonia (VAP) episodes, and the interval from the start of mechanical ventilation to the first episode of VAP.

The initiation of mechanical ventilation after ICU admission shows a marginal, non-significant difference between the two groups, with a slightly higher percentage of patients without Carbapenem resistance starting ventilation within 24 hours.

The median duration of mechanical ventilation is 21 days for the non-resistant group and 27 days for the resistant group, but this difference is not statistically significant, indicating that the length of mechanical ventilation may not be directly influenced by the resistance status of the pathogen causing the infection.

However, there is a significant difference in the number of VAP episodes, with a higher incidence in the Carbapenem-resistant group, particularly notable in those with more than two episodes (6.9% vs. 4.6%). This suggests that Carbapenem resistance is associated with a higher risk of recurrent VAP (p=0.002).

	No Carbapenem resistance n= 958	Carbapenem resistance n= 958	p value
Time from ICU admission to mechanical ventilation			0.084
< 24 hours	690 (74.1%)	684 (73.1%)	
24 – 72 hours	143 (15.4%)	125 (13.4%)	
> 72 hours	98 (10.5%)	127 (13.6%)	
Duration of mechanical ventilation, days	21 [12-35]	27 [16-44]	<0.001
Number of VAP episodes			0.002
0	226 (23.6%)	172 (18.0%)	
1	534 (55.7%)	518 (54.1%)	
2	154 (16.1%)	202 (21.1%)	
> 2	44 (4.6%)	66 (6.9%)	
Time between mechanical ventilation and first VAP, days	9 [5-15]	10 [6-18]	<0.001

Table C.10: Mechanical ventilation in the post matching patients

The time to the first VAP episode after the onset of mechanical ventilation is also significantly different, with patients with Carbapenem resistance experiencing their first VAP episode later than those without resistance. This extended interval (median of 10 days vs. 9 days) is statistically significant and may reflect the complex nature of managing infections that are resistant to antibiotics (p<0.001).

These findings highlight the challenges posed by Carbapenem resistance in the clinical management of ICU patients, particularly concerning the prevention and treatment of VAP. The data underscores the need for vigilant monitoring and proactive measures to reduce the incidence of VAP in this vulnerable patient population.

The table C-11 compares the carriage of various antibiotic-resistant organisms upon admission and those acquired during the hospital stay between patients with no Carbapenem resistance and those with Carbapenem resistance.

For both groups, the carriage of Extended Spectrum Beta-Lactamase (BLSE) producing organisms on admission is significantly higher in the Carbapenem-resistant group (30.2%) compared to the non-resistant group (13.9%). Similarly, the acquisition of BLSE during the hospital stay is higher in the Carbapenem-resistant group, although the difference is not statistically significant (p=0.085).

Carriage of Extended Spectrum Beta-lactamase-producing Enterobacteriaceae (EPC) upon admission is notably absent in the non-resistant group but present in 17.2% of the Carbapenem-resistant group. The acquisition of EPC is also significantly higher in the Carbapenem-resistant group during the hospital stay (10.8%).

	No Carbapenem resistance n=112	Carbapenem resistance n=454	p value
Carriage BLSE admission	17 (13.9%)	137 (30.2%)	<0.001
Carriage EPC admission	0 (0.0%)	78 (17.2%)	<0.001
Carriage ABRI admission	0 (0.0%)	12 (2.6%)	0.080
Carriage PARC admission	25 (20.5%)	226 (49.8%)	<0.001
Carriage SARM admission	2 (1.6%)	11 (2.4%)	1
Carriage BLSE acquired	15 (12.3%)	93 (20.5%)	0.085
Carriage EPC acquired	0 (0.0%)	49 (10.8%)	<0.001
Carriage ABRI acquired	0 (0.0%)	6 (1.3%)	0.482
Carriage PARC acquired	21 (17.2%)	173 (38.1%)	<0.001
Carriage SARM acquired	2 (1.6%)	5 (1.1%)	0.651

Table C.11: Carriage of the post matching patients

Carriage of *Acinetobacter baumannii* resistant to imipenem (ABRI) is not observed in the non-resistant group on admission, and although there is a low incidence in the Carbapenem-resistant group, the difference is not statistically significant.

The carriage of *Pseudomonas aeruginosa* resistant to carbapenems (PARC) upon admission and acquisition is substantially higher in the Carbapenem-resistant group (49.8% and 38.1%, respectively), indicating a strong association with Carbapenem resistance.

The carriage and acquisition of *Staphylococcus aureus* resistant to methicillin (SARM) do not show a significant difference between the two groups.

These findings illustrate a significant correlation between Carbapenem resistance and the carriage and acquisition of multiple drug-resistant organisms, especially BLSE, EPC, and PARC, underscoring the complex challenge of managing such infections in the healthcare setting.

6.3.2.3 Conclusion

Patients grappling with carbapenem-resistant infections typically present with a complex clinical profile. These individuals are often admitted for medical reasons, and a significant number come directly from other hospital settings, highlighting the transmissible nature of such resistant strains. Upon admission, they are likely to receive antibiotics, reflecting either a pre-emptive approach to infection management or a response to existing infections. These patients tend to have a longer duration of ICU stays, suggesting more complicated and difficult-to-treat infections. Mortality rates are notably higher in this group, underscoring the severe impact of carbapenem resistance on patient outcomes. The data emphasizes the critical need for enhanced infection control measures and tailored antibiotic stewardship to manage the risks associated with these resistant infections effectively.

7 DISCUSSION

The imperative to understand and address the challenges of antimicrobial resistance in the intensive care environment is underscored by our findings within the Mechanical Ventilation Cohort. The incidence of ventilator-associated pneumonia (VAP) is a critical indicator for intensive care units, reflecting both the susceptibility of the mechanically ventilated patient to opportunistic pathogens and the efficacy of the infection control practices within the care environment.

7.1 Discussion among the 3 types of cohorts.

7.1.1 VAP among ICU patient:

The typical patient facing VAP in the ICU is likely to be around 65 years old, with a slightly higher prevalence among males (73.5%), reflecting a gender disparity in VAP incidence. These patients are predominantly admitted for medical reasons (76.5%) rather than surgical, and often have a history of being transferred from another hospital (45.2%). Upon admission, a significant proportion (64.2%) receive antibiotics, indicative of either existing infections or a high-risk profile for infections. The severity of their condition is slightly higher than those without VAP, as suggested by a marginally elevated SAPS II score. They typically experience a longer ICU stay, with a median duration of 25 days, and unfortunately, a higher case fatality rate of 33.6%. These patients are also more likely to require invasive treatments such as extra-renal epuration (22.0%) and extracorporeal life support (5.0%). The development of VAP appears to be associated with an increased use of medical devices, like urinary and central venous catheters, reflecting the complexity and severity of their clinical management.

Our study draws from a robust dataset covering 20 % of ICU beds in France, offering a comprehensive view of the epidemiological landscape over a four-year period. VAP are the first ICU-acquired infections in France (7). The cumulative incidence rate for 1000 ventilation days was 18.9 cases per 1000 ventilation days, close to European ICUs, underscoring the persistent nature of this complication despite advancements in care practices (8).

Notably, the direct correlation between the duration of mechanical ventilation and the occurrence of VAP suggests that efforts to reduce the duration of mechanical support could be a pivotal strategy in reducing the burden of VAP. The maximum instantaneous risk peaks around 10 days which is also close to the figures found in other European study. Therefore, the description of the duration of ventilation is a critical data in each unit. The management of sedation and weaning procedures are of major importance. Of course, this must be balanced against the clinical needs of each patient, as premature weaning could lead to adverse outcomes. This is far from the results reported in US ICUs, which are around 1–2.5 cases per 1000 ventilation days. This certainly due to different surveillance system.

VAP mortality should be considered by more sophisticated statistical approaches, such as competing risks models. The attributable mortality in our cohort has been calculated to be 7.2 % (6.0% - 8.5%). Since the picture is very large, it should be studied to ascertain that the repartition is homogenous in all types of VAP.

The picture of a patient with a VAP is typically a man, at any age, but usually under 75 years. Medical patients are more prone to VAP than surgical patients. The mean duration of mechanical ventilation is usually high, around 20 days. Another aspect of the data is the numbers of cases (30.1) with more than one bacterial type by infection. The characteristics of France from a microbiological point of view

is a significant drop in S. aureus associated with an increase of Gram-Negative bacilli (GNB), enterobacteria (E coli, Enterobacter and Klebsiella) and non-fermenting GNB, with Pseudomonas aeruginosa in the first place. It is thus important to be certain to cover all involved bacteria in the VAP.

7.1.2 Pseudomonas aeruginosa and ICU acquired infection:

Pseudomonas aeruginosa remain the most frequent germ isolated among ICU-acquired infection. The main infection site is pneumoniae, regularly associated with bacteriemia. The resistance to piperacillin tazobactam, carbapenem and ceftazidime were frequent, however the colistin resistance remained scarce. Theses resistances were more frequently observed for patient with medical admission, among male patient, and for more severe patients. They were also associated with a higher mortality.

The identification of Pseudomonas aeruginosa as a leading cause of VAP within our cohort aligns with the pathogen's known propensity for thriving in moist environments (9). Early-onset VAP (within the first 4 days of hospitalization) in previously healthy patients not receiving antibiotics usually involves normal oropharyngeal flora, whereas late-onset VAP (after the 5th days of hospitalization) and VAP in patients with risk factors for multidrug resistant (MDR) pathogens are more likely to be due to MDR pathogens (7).The bacterium's adaptive mechanisms and intrinsic resistance to multiple drug classes makes it a formidable pathogen in the ICU setting. In this context, our study's insights into the resistance profiles of Pseudomonas aeruginosa are particularly concerning, revealing a high proportion of strains resistant to frontline antibiotics such as Pip/Taz and carbapenems.

Transitioning to the Pseudomonas aeruginosa Infection Cohort, our findings provide a stark illustration of the clinical quandaries posed by antibiotic resistance. The high rate of carbapenem resistance observed requires attention, as it not only complicates therapeutic decision-making, but also has significant implications for patient morbidity and mortality.

Patients infected with carbapenem-resistant Pseudomonas aeruginosa faced a longer duration of ICU stay and increased ICU case fatality, a reflection of both the virulence of the pathogen and the limited treatment options available. The significant use of antibiotics at the time of admission in this group may suggest a pre-existing recognition of the risk of resistant pathogens, yet it also raises concerns about the potential for driving further resistance through selective pressure.

The challenges associated with treating these infections are multifaceted. They necessitate not only the development of new antimicrobials but also a more judicious application of existing antibiotic therapies. Antibiotic stewardship programs must be dynamic, informed by real-time surveillance data, to optimize the use of antimicrobials and minimize the collateral damage of resistance development.

7.1.3 Challenge related to Carbapenem resistance:

Patients grappling with carbapenem-resistant infections typically present with a complex clinical profile. These individuals are often admitted for medical reasons, and a significant number come directly from other hospital settings, highlighting the transmissible nature of such resistant strains. Upon admission, they are likely to receive antibiotics, reflecting either a pre-emptive approach to infection management or a response to existing infections. These patients tend to have a longer duration of ICU stays, suggesting more complicated and difficult-to-treat infections. Mortality rates

are notably higher in this group, underscoring the severe impact of carbapenem resistance on patient outcomes. The data emphasizes the critical need for enhanced infection control measures and tailored antibiotic stewardship to manage the risks associated with these resistant infections effectively.

The problem posed by carbapenem-resistant infections is even more complex, since it covers a range of different situations: the mechanism of carbapenem resistance may be very different in nature. This resistance may be linked to a carbapenemase or to a non-enzymatic mechanism in different bacteria, namely enterobacteria (e.g., *E coli* and *Klebsiella* sp.) and non-fermenting Gram-negatives (*Pseudomonas aeruginosa* and *Acinetobacter baumanii*). The Carbapenem-Resistant Infection Cohort analysis further amplifies the critical concerns raised by the previous cohorts. The stark differences in the use of medical interventions, such as extra-renal epuration and central venous catheters, point to the complex clinical course encountered with carbapenem-resistant infections. The elevated need for such interventions may reflect both the direct impact of the resistant infections and the indirect effects of the aggressive treatments employed to combat them.

The longer time to first VAP episode in the carbapenem-resistant group suggests a protracted vulnerability for these patients, potentially related to the persistence of the resistant organisms in the ICU environment or their ability to evade early detection and treatment. This finding underscores the need for heightened surveillance and early intervention strategies specifically tailored to this high-risk population.

The study's observation of increased carriage and acquisition of multiple drug-resistant organisms in the carbapenem-resistant group further underscores the interconnected nature of antibiotic resistance. Patients with carbapenem-resistant infections are not only at risk from the primary pathogen but also from a broader spectrum of resistant organisms, complicating infection control and treatment efforts.

The persistence of such resistance patterns points to the necessity for a comprehensive approach to infection control that goes beyond the individual patient and addresses the systemic factors that contribute to the spread of resistance within the ICU. This includes but is not limited to environmental hygiene, hand hygiene compliance, and the judicious use of invasive devices and antibiotics.

The implications of our study for clinical practice are profound. The association between carbapenem resistance and increased morbidity necessitates an escalated response from healthcare systems. In the ICU, where patients are already at their most vulnerable, the emergence of such resistant infections can significantly alter the trajectory of recovery and increase the demands on healthcare resources.

In the face of rising antimicrobial resistance, ICUs must adapt their protocols and practices. Our findings advocate for the implementation of aggressive infection control measures, including the isolation of patients with resistant infections and the meticulous disinfection of the ICU environment. Furthermore, antimicrobial stewardship programs must be refined to ensure that the empirical use of broad-spectrum antibiotics does not contribute to the escalation of resistance rates.

In summary, the presence of carbapenem resistance in infections is associated with a distinct clinical profile, characterized by longer ICU stays, a higher medical admission rate, surprisingly a higher proportion of home admission, and of antibiotic administration at admission, all of which contribute

to the complexity of care for these patients. This is in line with recent published data among ICU patients (10,11)

The financial impact of managing carbapenem-resistant infections is substantial, as longer ICU stays and increased interventions translate directly into higher costs. It is not only the direct costs of treatment but also the indirect costs associated with extended hospital stays, such as the opportunity cost of occupied beds that could be used for other patients, that need to be considered.

7.2 Biases or Limitations

Firstly, the study's observational design inherently limits the ability to establish causality. While associations between carbapenem resistance and patient outcomes can be observed, it is not possible to conclusively determine whether the observed resistance is the cause of the worse outcomes, or if it is a marker for other confounding factors. Surveillance is limited by the workload of recovering data from the patient files. REA-REZO is a network based on voluntary participation of units. The presence of unmeasured variables, such as individual patient comorbidities, variations in ICU protocols, and differences in the administration of antibiotic therapies, could all influence the outcomes attributed to antimicrobial resistance.

Secondly, the study draws upon data exclusively from the REA-REZO surveillance network, which, despite its comprehensive coverage, does not capture the entirety of the ICU patient stay. Regional differences in antibiotic prescribing habits, local epidemiology of resistant organisms, and variations in infection control practices could affect the applicability of these findings to other settings, both within and outside of France.

Another limitation is the potential for selection bias. Patients included in the study were those admitted to ICUs for more than 48 hours, which may inadvertently exclude a subset of patients who either succumbed to their infections rapidly or recovered quickly without the need for prolonged ICU care. This selection could skew the severity spectrum of the study population, possibly overestimating the prevalence of resistance in less severe cases or underestimating it in the most severe cases.

Furthermore, the reliance on cultured organisms to identify infections may not account for the full scope of antimicrobial resistance. Culture-negative infections, which may still be significant, are not represented, potentially leading to an underrepresentation of the true burden of resistant infections.

Lastly, the post-matching analysis, although robust, does not account for all variables that could influence the outcomes. The matching was based on the type of germ, number of infections, and site of infection, but other factors like prior antibiotic exposure, time to appropriate therapy, and underlying health status were not included in the matching criteria.

In summary, while this study provides valuable insights into the prevalence and impact of antimicrobial resistance in ICU settings, these limitations must be considered when interpreting the results. They also highlight areas for further research, particularly in enhancing the design of observational studies to better control confounding variables and in expanding the data sources to provide a more holistic view of the issue at hand.

8 CONCLUSION

The battle against antimicrobial resistance in ICUs requires a concerted effort that encompasses policy changes, research, and clinical practice. Policies that incentivize the development of new antibiotics and diagnostic tools are essential. Furthermore, there is a need for global cooperation in surveillance and reporting of resistance patterns to inform clinical guidelines and policy decisions.

In conclusion, our study reaffirms the critical challenge posed by antimicrobial resistance in the ICU. It highlights the need for comprehensive strategies that address the clinical, psychological, and economic dimensions of this issue. As the landscape of antibiotic resistance evolves, so do our approaches to managing these infections, ensuring that patient care remains at the forefront of ICU practice.

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11 APPENDICES

DICTIONARY OF VARIABLES

Patient's Characteristics	
Age of the patient at the time of entrance	Natural Number
Patient’s sex (different de ‘gender’)	1=M, 2=F
Admission date in ICU	dd/mm/yy
Discharge date from ICU	dd/mm/yy
Length of Stay	Whole number
Origin of the patient at the time of admission	See details below
Patient's SAPS II (Simplified Acute Physiology Score II) on admission (first 24h of ICU stay)	Natural Number <= 163
Type of admission as defined in SAPS II score: (medical: no surgery within one week of admission to ICU)"	1=medical, 2=urgent surgery,3= Scheduled surgery, 9=unknown
Traumatology on admission	1=yes, 2=no
Immunodepression on admission	1= <500 PN, 2=other ID, 3=ID number, 9=unknown
Antibiotics on admission	1=yes, 2=no
Deceased during ICU stay	
Exposure to Devices	
Intubation or tracheostomy	1=yes, 2=no
Beginning of the intubation / tracheostomy	dd/mm/yyyy
Duration of intubation / tracheostomy	In days
End date of intubation	dd/mm/yy
Re-intubation during the stay	1=yes, 2=no
Date of reintubation	dd/mm/yy
Indwelling Urinary Catheter during the stay in ICU	1=yes, 2= no
Indwelling Urinary Catheter date	dd/mm/yy
Duration of Indwelling Urinary Catheter	Whole number

End of Indwelling Urinary Catheter	dd/mm/yy
Central Venous Catheter during the stay	1=yes, 2= no
Number of CVC during the stay	Whole number
extracorporeal membrane oxygenation	1=veno-arterial, 2=veno-venous, 3=No,
Infections	
NI during the stay	1=yes, 2= no
Number of NIs during the stay	Whole number
Colonization of CVC during the stay	1=yes, 2= no
Number of CVC colonization during the stay	Whole number
Nosocomial bacteremia during the stay	1=yes, 2= no
Number of Nosocomial bacteremia during the stay	Whole number
Nosocomial lung disease during the stay	1=yes, 2=no
Number of lung diseases during the stay	Whole number
Urinary tract infection during the stay (yes/no)	1=yes, 2= no
Number of urinary tract infections during the stay	Whole number
Venous Catheter Related Infection	1=yes, 2= no
Number of CRI during the stay	Whole number
Facility & ICU identifiers	
Healthcare Facility Code (unique)	
ICU Code (unique)	
C.CLIN	

INFECTION DATASET

This dataset contains information on the infection date, site, micro-organisms (MOs) and their resistances to antibiotics.

Establishment code	See codes
Service code	See codes

Number of the Infection	Natural number
Infection Date	dd/mm/YYYY
MO1	See MO subsection
Sensitivity of MO1 to oxacillin	0= sensible, 1= Resistant
Sensitivity of MO1 to ampicillin	0= sensible, 1= Resistant
See 'Resistance' subsection	
..	
MO 2	See MO subsection
Sensitivity of MO2 to oxacillin	0= Sensible, 1= Resistant
Sensitivity of MO2 to ampicillin	0= Sensible, 1= Resistant
Diagnostic Criterion of PNE (if PNE)	Detailed description below
Source of the Blood Stream Infection	Detailed description below
Site of the infection (PNE, URI, BAC, CVC)	PNE, URI, BAC or CVC
Catheter related infection information	Detailed description below

Microorganisms (MO)

Prior to 2003, MO were encoded through 3 digits numbers. Afterwards MO were encoded through 6 letter-codes, which can be found in the MO dictionary below. In the former encoding way, some MOs were gathered and are therefore not perfectly matched to a specific MO in the latter.

Thus, there is an added variable in the dictionary for these MO, with the name of the group in 3 letters and 'NSP' (not specified), in order to make it possible to use MO data on a wider time period, with lesser information loss.

The full Micro-Organisms list is put as annex.

Resistances

Resistances are encoded as a Boolean for each antibiotic amongst the ones tested for each MO. The table below presents each MO and the antibiotic for which the resistance is to be tested.

Intermediate resistance is assimilated to resistance for the purpose of simplification.

	OXA	AMP	GLY	AMC	C3G	PTZ	CAZ	CAR	COL	ESBL	PanR
Staphylococcus Aureus	X		X								X
Enterococcus Faecalis & Faecium		X	X								X
Enterobacteriaceae				X	X			X		X	X
Pseudomonas Aeruginosa						X	X	X	X		X
Acinetobacter Baumannii							X	X	X		X

- OXA: oxacillin (or methicillin)
- AMP: ampicillin (or amoxicillin)
- GLY: glycopeptide (vancomycin or teicoplanin)
- AMC: amoxicillin/clavulanic acid
- C3G: 3rd generation cephalosporine: cefotaxime (or ceftriaxone)
- PTZ: piperacillin/tazobactam
- CAZ: ceftazidime
- CAR: carbapenem: imipenem or doripenem or meropenem
- COL: colistin
- BLSE: extended-spectrum beta-lactamases-producing
- PANR: Pan-resistant stem

Pan Drug resistant micro-organisms are defined as follows:

- 0: not PDR: susceptible to at least one antimicrobial agent tested
- 1: possible PDR: non-susceptible (intermediate or resistant) to all antimicrobial agents tested in the hospital
- 2: confirmed PDR: non-susceptible (intermediate or resistant) to all agents in all antimicrobial categories, confirmed by a reference or other clinical microbiology laboratory testing a supplemental panel of antimicrobial agents beyond those routinely tested.

Catheter dataset

Structure

Catheter Dataset	
Healthcare Facility identifiers	
ICU identifier	
Order number of the Central Catheter (CC)	Natural number
CC Type	1=CVC, 2= Haemodialysis Catheter 3=Picc
Catheter site	1= subclavian 2 = internal jugular 3= femoral 4= peripheral 5= other

Date of catheterisation / date of entry if patient entered ICU with a catheter in place.	dd/mm/YYYY
Removal date of the CVC/ Discharge date if the patient left ICU with the catheter in place	dd/mm/YYYY
Length of Catheterisation	Natural number
Accuracy on presence of Colonisation, CRI, or CLABSI	0=no COL/CRI/CLABSI, 1=COL, 2=Local Infection, 3=General Infection, 4=CLABSI, 5= Not specified infection 9=unknown
Date of colonisation, CRI or BLC	dd/mm/YYYY
MO1 of COL/CRI/CLABSI	See MO codes in the 'Infection' section
MO2 of COL/CRI/CLABSI	See MO codes
CVC sent to the laboratory for further analysis	1= sent (to the laboratory) for culture; 2 = not cultured; 3= not removed in ICU.
Sensitivity to oxacillin of MO1	0=sensible, 1=Intermediate or Resistant
Sensitivity to oxacillin of MO2	0=sensible, 1=I or R
..	0=sensible, 1=I or R
	0=sensible, 1=I or R
	0=sensible, 1=I or R
…	0=sensible, 1=I or R
…	0=sensible, 1=I or R