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Determinants of Antimicrobial Resistance within a Hospital Setting

Satria Nur SYABAN

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Location of the practicum:
Laboratoire MESuRS, Le CNAM

Professional advisor:
Laura TEMIME, CNAM
Karim AIT BOUZIAD, CNAM

Academic advisor:
Nolwenn LE MEUR - ROUILLARD, EHESP

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List of Acronyms

ESBLE	Extended Spectrum Beta Lactamase Producing Enterobacteriaceae
mrsa	Methicillin Resistant Staphylococcus Aureus
mssa	Methicillin Sensitive Staphylococcus Aureus
c3gs	Third Generation Cephalosporin Sensitive Infections
c3gr	Third Generation Cephalosporin Resistant Infections
cefrpa	Ceftazidime Resistant Pseudomonas Aeruginosa
crab	Carbapenem-resistant Acinetobacter baumannii
pa	Pseudomonas Aeruginosa
crpa	Carbapenem-resistant Pseudomonas aeruginosa
ab	Acinetobacter baumanii
sm	Stenotrophomonas maltophila
bd	1000 BD (1000 bed-days)
sha	Hydroalcoholic solution consumption
pena	Penicilin Type A
penaac	Penicilin - clavulinic acid
pip_taz	Piperacilin Tazobactam
carbapenem	Carbapenem
c3g	Third generation cephalosporins
dial	Number of dialysis procedures conducted
chimio	Number of chemotherapy procedures conducted
urg	Number of patients admitted from the emergency room
diab	Number of patients with diabetes
sej	Number of patients staying in the ward
pat	Number of admitted patients in the ward
cen	Central Measures of Tendency of patient age. Average age (2011-2016) and Median Age (2017-2023)
age75	Number of patients ≥ 75 years of age
age80	Number of patients ≥ 80 years of age
dms	Average duration of stay
covidadm	Number of patients admitted with COVID 19 infection
covidtot	Total number of patients with COVID 19 infection
vvc	Number of central catheters inserted
uri	Duration of urinary catheterization (2011-2016) / Number of urinary catheters

	inserted (2017-2023)
inv	Number of patients with invasive ventilation
invdur	Number of days with invasive ventilation

Abstract

Determinants of Antimicrobial Resistance within a Hospital Setting: A Multimodel Analysis with Hospital Level Aggregated Longitudinal Data

Satria Nur SYABAN[1,2,3], Karim AIT BOUZIAD[3], Nolwenn LE MEUR - ROUILLARD[2], Laura TEMIME[3]

[1] University College Dublin [2] École des Hautes Études de Santé Publique, [3] Conservatoire Nationale des Arts et Métiers

Introduction

Antimicrobial resistance (AMR) poses a major public health challenge globally. Hospital antimicrobial stewardship interventions often rely on large-scale antibiotic consumption and microbiologic surveillance data to inform policy. However, evidence on long-term impacts of specific antibiotic policy changes in real-life hospital settings remains limited. In 2014, a local hospital in Paris implemented a departmental switch from ceftriaxone to cefotaxime across multiple medical wards to mitigate emerging resistance concerns. Later, the COVID-19 pandemic further disrupted antibiotic use and infection control dynamics. This study aims to evaluate the impact of these two major events on antibiotic use and microbiologic resistance across intensive care, medicine, gynecology, and surgical departments over a 13-year period.

Methods

A retrospective longitudinal analysis was conducted using monthly aggregated surveillance data from January 2011 to December 2023. Data sources included PMSI and laboratory surveillance datasets, encompassing monthly antibiotic consumption (DDD/1000 bed-days), resistance profiles of key bacterial pathogens (e.g. Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus), and organizational indicators (length of stay, admissions, procedures). Interrupted time series (ITS) analysis and Poisson GEE regression were used to estimate the effects of the ceftriaxone-to-cefotaxime policy intervention (January 2014) and the COVID-19 pandemic (March 2020) on monthly outcomes. Models were adjusted for department-level heterogeneity and seasonality. COVID-19 burden was introduced as a continuous variable (COVID patients per 1000 bed-days).

Results

The ceftriaxone-to-cefotaxime policy intervention was associated with a significant reduction in ceftriaxone use across both departments (e.g., ICU: −297.38 DDD/1000BD, 95% CI: −394.92 to −199.83; $p < 0.001$), with corresponding increases in cefotaxime. The intervention also coincided with increases in cefepime and 3rd-generation cephalosporin consumption in some departments. In terms of microbiologic outcomes, a reduction in third generation cephalosporin-sensitive isolates was observed, while hypercase-producing and resistant P. aeruginosa strains increased. During the COVID-19 period, antibiotic usage trends varied. In the ICU, ciprofloxacin, penicillin A, and vancomycin consumption decreased significantly, while hydroalcoholic solution use increased by 0.56 DDD/1000BD (95% CI: 0.15 to 0.98; $p = 0.01$) and 141.53 ml/1000BD (95% CI: 50.57 to 232.49; $p = 0.00$) per COVID case. In the medical department, increases were noted for cefepime, total cephalosporins, piperacillin-tazobactam, and SHA usage. Multivariate GEE Poisson models showed that increasing COVID-19 incidence per 1000BD was positively associated with Enterobacterales, MSSA, hypercase-producing organisms, and Pseudomonas aeruginosa in the ICU. In medicine, COVID-19 incidence was associated with higher A. baumannii and hypercase infections but reduced third generation cephalosporin-sensitive and P. aeruginosa incidence.

Conclusion

The intervention to change ceftriaxone to cefotaxime was successful in changing the behaviors and that the effect was sustained. It also positively impacted the resistance profile for ESBLE in the hospital and 3GC resistant strain. COVID 19 was associated with the increase of SHA usage and has had a definitive impact on antibiotic use pattern and the profile of infection in the hospital.

Introduction

Background

Antimicrobial resistance is defined as a condition where microorganisms develop mechanisms to survive, either partially or fully, the substances that were previously able to affect them. (Dadgostar, 2019) This worrying trend is something that has continued to develop over time, impacting the health and economy of nations globally. (Dadgostar, 2019) Many things contribute to the growth of antimicrobial resistance, including its overuse and overprescription, from both the patient and healthcare provider's side, its use in agriculture, increased mobilization of the population, and the internal biological mechanisms of these microorganisms.(Dadgostar, 2019)

Some of the more important broad-spectrum antimicrobials widely used in today's healthcare system are cephalosporins, known for their ability to target both gram-positive and gram-negative bacteria. (Bui, Patel and Preuss, 2024) They are divided into five different generations, each with their own coverage profile against certain bacteria. The third-generation cephalosporins which includes, amongst others, cefotaxime, ceftriaxone, and cefixime, are particularly effective against the gram-negative bacterial family of enterobacteriaceae. (Bui, Patel and Preuss, 2024) This family of bacteria include key intestinal pathogens such as *E.coli, Y. enterocolitica, Salmonella,* and *Shigella.* (Gillespie, 1994) The bactericidal capabilities of cephalosporins stems from their ability to use beta-lactam rings to bind to a specific protein in the cell wall of target bacteria, therefore preventing its ability to synthesize a cell wall. (Bui, Patel and Preuss, 2024) Due to the aforementioned contributing factors to antimicrobial resistance growth, multiple mechanisms of resistance have developed amongst the target bacteria of cephalosporins, including the production of the beta-lactamase enzymes, which breaks down the beta-lactam rings of the drug, and protein structure alteration to prevent the beta-lactam rings from adhering to them, a strategy employed primarily by *S. aureus*. (Bui, Patel and Preuss, 2024)

In order to combat the rise of antimicrobial resistance, many strategies have been employed at different healthcare provision levels, through different political and scientific angles. One such strategy is the policy of switching from ceftriaxone to cefotaxime in order to combat the emergence of resistance towards third generation cephalosporins amongst *enterobacteriales*. Past studies have shown generally that, despite a logistical inconvenience regarding the administration of the drug, replacing ceftriaxone with cefotaxime appear to reduce the selection of enterobacteriaceae that are resistant to third generation cephalosporins (3GC) through all resistance mechanisms. (Grohs *et al.*, 2014; Tan *et al.*, 2018; Bouiller *et al.*, 2024)

COVID 19 was a disruptive element for every aspect of healthcare, including its workforce. Despite the rapid developments in infection control measures and prevention

strategies, the pandemic created a *"..dangerous and psychologically taxing work.."* environment. (McNeill, 2022) Given the close links between policy, operational standards, workforce, and antimicrobial prescriptions, it was apparent that this effect would extend as well into the realms of antimicrobial resistance. Studies have shown that COVID significantly modified the usage patterns of antibiotic and antimicrobial resistance within the French hospital systems. (Layan *et al.*, 2024)

Through this study, we are aiming to understand whether this is the case in the Saint-Joseph Saint-Luc Hospital in Lyon as well, especially when related with the intervention they have applied to prevent antimicrobial resistance in their hospital. Using thirteen year of longitudinal data on antibiotic consumption, microbial resistance, and infection profile in a large tertiary hospital, and evaluating its trend over time should allow us to gather more insight on the matter, hence the importance of the study: it adds to evidence on the efficacy of this intervention and provides additional information on risks that pandemics and a lack of preparedness from institutions can do for the problem of antibiotic resistance.

Aim and Objectives

The study consists of four separate research questions, each with its own group of outcomes and sets of predictors: The first question was aimed at evaluating whether the hospital level policy of substituting ceftriaxone with cefotaxime impacted the prescription patterns of the two antibiotics, and whether its impact persisted over time. The second question was aimed at evaluating whether the same policy impacted the antimicrobial resistance and infection profile within the hospital, and whether the impact persisted over time. The third question aimed to evaluate the impact of the COVID 19 pandemic on the prescription pattern of antibiotics within the hospital, while the fourth and last question aimed to evaluate the impact of the COVID 19 pandemic on microbial infection patterns, both resistant and sensitive, in the hospital.

Methods

Study Design

We conducted a retrospective, single-center, longitudinal study using aggregated monthly longitudinal data of antibiotic consumption, detected microbial infection, as well as hospital administrative and procedural variables from the Saint-Joseph Saint-Luc Hospital in Lyon, France. The study covered a period of 13 years, between January 2011 and December 2023. Multiple units within the hospital were involved in the data collection required to conduct this study, mainly the pharmaceutical unit and the microbiology unit of the hospital. The pharmaceutical unit of the hospital provided the antibiotic consumption data in defined daily doses utilized in each concerned department during a period of one month.

Consumption data of 18 antibiotics were collected for the purpose of this study, three of which are aggregate sums of two or more individual antibiotics within the list. The microbiology unit provided the count of detected microbial infection within the hospital in each concerned department during a particular month. 14 microbial variants were collected for the purpose of this study, which were either targets of the aforementioned antibiotic variables, hypothesized to be impacted by the intervention and COVID 19 based on prior studies, or are related to procedures collected as part of the administrative and procedural variables included in this study. Lastly, the electronic records department of the hospital provided us with administrative and procedural variables conducted or related to the concerned department during a period of one month.

18 administrative and procedural variables are collected for the purpose of this study involving four general groups: comorbidities within the departments, admission and mortality counts, age and patient stay variables, and variables related to procedures performed in each department within the month. This particular variable groups were aligned with the *Programme de Médicalisation des Systèmes d'Information* - Information System Medicalisation Program (PMSI - ISMP) of France, which is the standardized data collection system for French hospital, aimed at aligning the variables being collected by every hospital in the country. This study has been written according to the requirements provided by the École des Hautes Études en Santé Publique, which is generally aligned to the "Strengthening The Reporting of Observational Studies in Epidemiology" (STROBE) guidelines.

Inclusion and Exclusion Criteria

As the dataset we used is an aggregated data of consumption, incidence, or count of the variables for each month, the inclusion and exclusion criteria we have for this study concerns mainly the selection of variables as opposed to the selection of participants. The data we used in this study was collected over two distinct data collection periods: 2011-2016 and 2017 - 2023. For the first period, we included data that was collected and reported in a prior study

done in the hospital, evaluating the impact of the same policy change at only the intensive care unit (ICU) level. The second period included the same antibiotic variables, but included less microbiologic variables due to administrative constraints stemming from a change in data collection system within the hospital. We also attempted to request the same administrative variables as the first period but were unable to obtain some due to a difference in the way some variables were calculated (e.g., bed occupation rate) and other administrative constraints that we were unable to clarify with the partner institution.

During the first period, the dataset included 185 antibiotic, microbiologic, and organizational variables for four different departments, as well as hospital level data, whereas the data collected in the second period included a reduced number of 73 variables. Therefore, for the purpose of this study, we decided to only extract and analyze variables that were collected for both periods for all four departments in the same way, leading us to exclude 112 variables, keeping 73 variables in our joined dataset for both periods. A total of 156 observation "points" were obtained for these 73 variables, representing the number of months between January 2011 and December 2023.

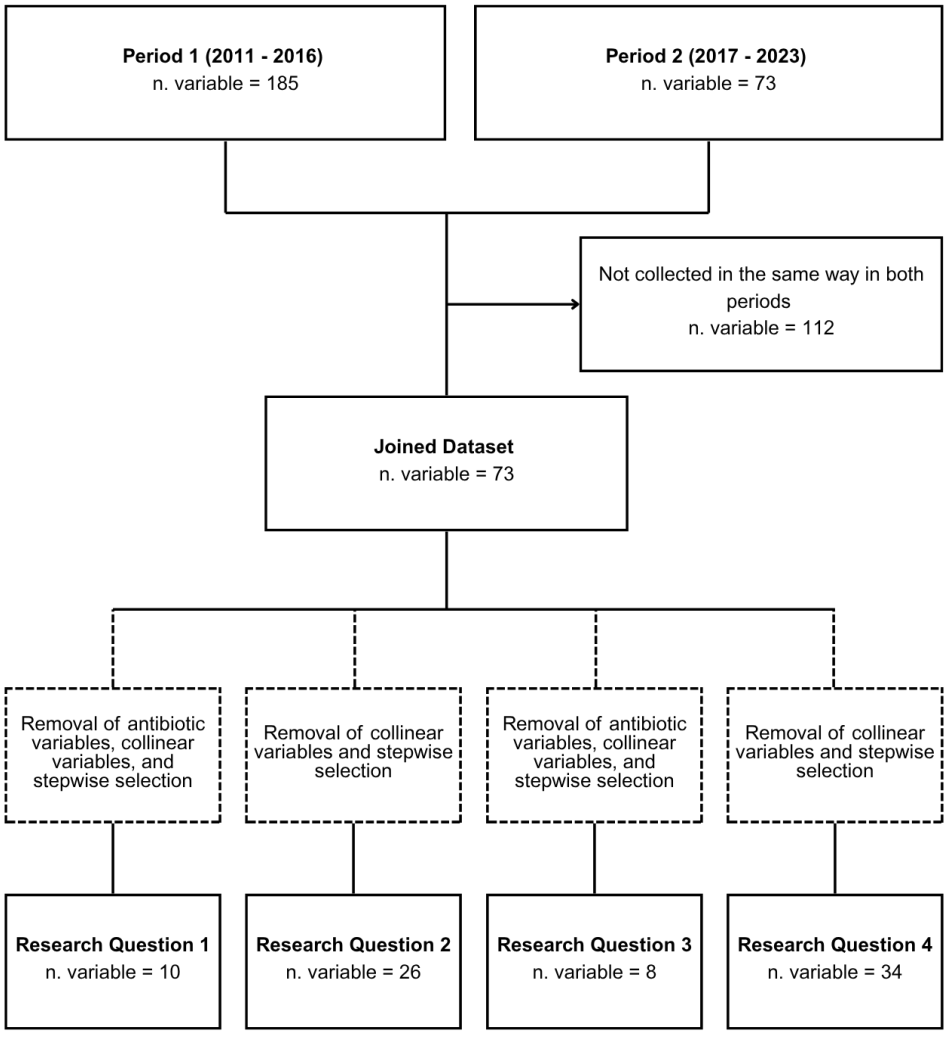

Figure 1. *Variable Exclusion Flowchart for the Study*

Methodology

In order to answer the research questions we have set for the study, multiple methodologies were used based on best practices found in similar prior studies. In general, standard descriptive analyses were performed for the three groups of variables, divided based on the periods of time each research question is concerned by (2011-2019 for the first and second research questions, 2017-2023 for the third and fourth research questions). Proportions were reported as number and percentages, whereas continuous values including antibiotic consumption, microbiologic incidence rates, and administrative variables were reported as average and standard deviation values. Inferential pairwise statistical analysis were also performed once the dataset were stratified for intervention (RQ1 and RQ2) and COVID 19 (RQ3 and RQ4), with wilcoxon rank sum test and fisher's exact test as the statistical methods chosen to evaluate the significance in the difference between the intervention and COVID periods in each variable.

In terms of further statistical analysis and the generation of effect estimates for each outcome, intervention, and predictor groups, several modelling approaches were used. For the first and second research questions, where we aimed to evaluate the impact of a specific intervention, the interrupted time series methodology was used, with a single-level multivariate linear regression as its base and January 2014 as the intervention point. On the other hand, for the third and fourth research questions, where the primary predictor of interest was COVID 19 instead of a particular intervention, a single level multivariable linear regression and poisson regression was used instead, respectively.

Within each of these methodologies, the same general approach was employed, namely beginning with a basic model for each outcome variable and core predictor variable combinations, which was then followed by a univariate regression analysis where we paired the outcome - core variables for each research questions with one predictor variable, after which a multivariate regression were performed containing variables that had a higher than 20% probability value of being significantly correlated with the outcome. Multicollinear predictor variables were also removed prior to running the full model. The final step that was done for each research question was a stepwise exclusion of predictors using the StepAIC() package where the final model(s) were then analyzed and reported in the study.

Results

The results of this study can generally be divided into two distinct periods of time: 2011-2016 for research questions one and two; 2017-2023 for research questions three and four. This separation was designed to help isolate the effect of the main predictor for each of our research question pairs.

Research Period 1 (2011-2019)

Descriptive Analysis

In the first research period, a total number of 108 months were included in the analysis. With the intervention point being set in February 2014, 36 observations are categorized as being within the pre-intervention period and 72 as being within the post-intervention period. In terms of antibiotic consumption, several antibiotics had notable increases or decreases between the two periods, which we subsequently evaluated using pairwise inferential statistics. Within the ICU department, total consumption of third-generation cephalosporin (as well as all cephalosporins), cefepime, cefotaxime, ceftriaxone, ciprofloxacin, floroquinolone, gentamicin, piperacilin-tazobactam and hydroalcoholic solution differs significantly between the pre and post intervention periods. Around half of them generally decreased between the periods, with ceftriaxone (367.52 (185.31) vs 48.44 (87.95) DDD/1000BD; $p < 0.001$), ciprofloxacin (302.02 (185.84) vs 123.06 (110.16); $p < 0.001$), all fluoroquinolones (437.41 (232.81) vs 235.48 (170.17); $p < 0.001$), and gentamicin (227.99 (174.90) vs 141.89 (124.67); $p = 0.015$) showing significant reductions. Within the medical department, total antibiotic use, carbapenems, cefepime, cefotaxime, ceftriaxone, all cephalosporins, all fluoroquinolones, gentamicin, all macrolides, penicillin A, vancomycin, and hydroalcoholic solutions differed significantly between the periods. More than half of these antibiotic types were observed to decrease in consumption, with total antibiotic use (96.30 (20.46) vs 85.39 (21.13); p = 0.018), carbapenems (1.12 (0.82) vs 0.49 (0.44); p < 0.001), ceftriaxone (10.94 (1.90) vs 2.71 (1.95); p < 0.001), fluoroquinolones (9.95 (3.14) vs 6.74 (2.90); p < 0.001), gentamicin (1.97 (1.41) vs 0.73 (0.65); p < 0.001), total macrolides (3.92 (1.32) vs 2.48 (1.25); p < 0.001), penicillin A (22.14 (12.82) vs 14.58 (7.71); p = 0.002), and vancomycin (1.62 (0.94) vs 1.10 (0.66); p = 0.002) showing statistically significant reductions.

Among the microbiologic variables, when stratified by intervention period in the medical department, several indicators differed significantly between the pre- and post-intervention periods. These included total third-generation cephalosporin-sensitive infections (8.23 (1.46) vs 4.70 (2.05); p < 0.001), total extended beta-lactamase-producing enterobacterial strains (0.88 (0.49) vs 0.62 (0.46); p = 0.008), total methicillin-resistant Staphylococcus aureus (0.24 (0.27) vs 0.07 (0.12); p < 0.001), hemoculture-confirmed methicillin-sensitive Staphylococcus aureus (0.24 (0.23) vs 0.13 (0.17); p = 0.007), and total methicillin-sensitive Staphylococcus aureus (0.97 (0.49) vs 0.68 (0.50); p = 0.003). In contrast, within the ICU, significant differences

were observed for hemoculture-confirmed Candida infections (1.21 (2.06) vs 0.66 (1.92); p = 0.048), total extended spectrum beta-lactamase producing enterobacterial strains (5.17 (3.40) vs 3.23 (4.16); p = 0.004), entry-screened (6.34 (5.26) vs 16.30 (8.68); p < 0.001), and hypercase-producing microbial strains (0.00 (0.00) vs 0.68 (1.89); p = 0.014).

Lastly, amongst the organisational variables, when stratified based on intervention period, within the ICU we found that the mean age of patients (64.78 (2.71) vs 66.63 (3.15); p = 0.004), number of central catheters (62.78 (15.89) vs 73.43 (20.96); p = 0.011), number of invasive ventilation procedures (42.26 (14.51) vs 61.55 (20.34); p < 0.001), as well as general stays (136.05 (21.35) vs 151.57 (31.38); p = 0.013) and admission (135.02 (20.99) vs 150.14 (31.52); p = 0.014) differ significantly within the two periods, with all the variables generally increasing. In the medical department, the average age of admitted patients (63.78 (0.68) vs 65.56 (2.19); p < 0.001), average duration of stay, as well as the number of stay (−14.95 (25.11) vs 5.26 (33.46); p < 0.001) and admission (−14.60 (23.03) vs 5.36 (27.78); p < 0.001) differ, with all of them observed as generally increasing other than the average duration of stay (0.18 (0.30) vs −0.09 (0.23); p < 0.001), which shortened significantly.

Subsequent to the descriptive analysis and the creation of line graphs to observe the trends of antibiotic consumption and microbial infection, based on visual observation of the patterns, we found them to be different to the point that a multilevel regression would not be appropriate for the situation, leading to us excluding the gynecology and surgery department from our analysis. Consequently, as the hospital level data are obtained from the sum of the four departments, it was decided that it should also be excluded from our study. Additionally, through the same process, we found what appeared to be an abnormal jump in the values of variables: hydroalcoholic gel consumption, duration of stay, number of patients, and number of admission. After discussing the phenomenon with our liaison within the hospital, it was decided that this shift appeared to be related to problems in the data collection process. We therefore decided to normalize these variables by centering their values around their mean values in each data collection period, which allowed us to ensure the comparability of the data between the two periods. This step was deemed to be important as the aforementioned variables were found to be significant predictors in other similar studies done in the past.

Specific Results

Research Question 1

Intervention effect on Cefotaxime and Ceftriaxone Prescription

We began our analysis by plotting the consumption values of both cefotaxime and ceftriaxone (i.e., the primary target of the intervention we are evaluating) in a time-series graph (see figure 2). Based on the visual observation we performed on these graphs we were able to note an immediate change in consumption value of both medications in the medical department, in line with the direction of the intervention. On the other hand, in the ICU, there was a slight delay of around two months before a stable increased usage for cefotaxime and decreased consumption of ceftriaxone was observed. This trend was also confirmed by the pairwise inferential statistic we performed (see: Research Period 1 (2011-2019), General Results), where a significant increase in cefotaxime consumption and a significant decrease in ceftriaxone consumption was observed in both departments before and after the intervention point.

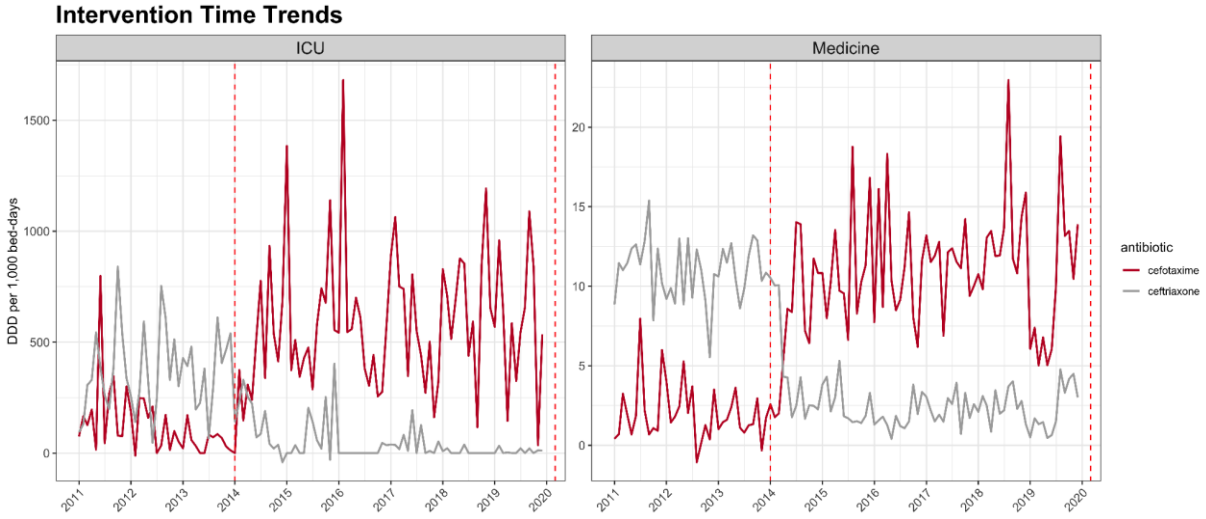

Figure 2. *Time Graph of Cefotaxime and Ceftriaxone Consumption (DDD/1000BD) in the ICU and medical department*

In order to confirm the results we obtained through our descriptive and inferential statistical analysis, we attempted to fit the observations we have into several interrupted time series (ITS) models, beginning with a base model containing only the outcome variables of cefotaxime and ceftriaxone in both the ICU and Medicine. In this base ITS model, we found that the intervention was significantly associated with an immediate change in cefotaxime and ceftriaxone consumption for both departments. The ICU experienced a step change of +495.06 DDD/1000BD (95% CI: 284.40 to 705.73; $p < 0.001$) in cefotaxime consumption and -297.08 DDD/1000BD (95% CI: -396.58 to -197.58; $p < 0.001$) in ceftriaxone consumption, whereas the medical department had a step change of +7.42 DDD/1000BD (95%CI: 4.76 to 10.07; p =

0.000) in cefotaxime consumption and −7.01 DDD/1000BD (95% CI: −8.52 to −5.50; p = 0.00) in ceftriaxone consumption. Other than Ceftriaxone consumption in the ICU, which showed a significant sustained decrease of −4.74 DDD/1000BD (95% CI: −8.93 to −0.56; p = 0.03) after the intervention point, the two target antibiotics maintained their increased or decreased consumption until the end of the study period, showing that the intervention effect was maintained over time.

Following this first model, we fitted sixteen univariate models, with the two target antibiotics as the outcome variables and all non-multicollinear organization variables as outcome variables. Setting the threshold probability value as less than 20%, we extracted the significant predictors and included them in our multivariate ITS regression and engaged the resulting models in a stepwise regression process to produce the most parsimonious model possible for each outcome within each department. A total of four final models were obtained. In analyzing the results of these for models we saw that in the ICU, after adjusting for dialysis, total number of stays, and average duration of stays, the intervention was still associated with a +442.04 DDD/1000BD (95%CI 246.37 to 637.71; p = 0.00) immediate increase in cefotaxime consumption, as well as an immediate decrease of −297.38 DDD/1000BD (95% CI: −394.92 to −199.83; p = 0.00) in ceftriaxone consumption after adjusting for incidence of patients older than 80 years old, duration of invasive ventilation, and hydroalcoholic solution usage. Similarly, in the medical department, an immediate increase of 8.14 DDD/1000BD (95% CI: 5.54 to 10.74; p < 0.001) was observed after adjusting for number of stays, along with an immediate decrease of −6.39 DDD/1000BD (95% CI: −7.97 to −4.81; p = 0.00) in ceftriaxone consumption after adjusting for average duration of stays.

Some additional covariates in the final model were also associated with cefotaxime and ceftriaxone consumption for both departments. In the ICU, number of patient stays and average duration of stay were positively correlated with cefotaxime use, where each additional hospital stay was linked to an increase of 4.28 DDD/1000BD (95% CI: 2.48 to 6.08; p < 0.001), and each additional death was associated with an increase of 28.72 DDD/1000BD (95% CI: 1.56 to 55.89; p = 0.04). Everything else held constant, within the medical department, each additional stay was associated with a reduction of −0.03 DDD/1000BD (95% CI: −0.05 to −0.01; p = 0.00) in cefotaxime consumption, while each additional incidence unit of death was associated with an increase of 1.62 DDD/1000BD (95% CI: 0.19 to 3.05; p = 0.03) of ceftriaxone consumption.

All four models performed well, with adjusted R^2 ranging from 0.51 - 0.82, showing that the models were able to explain approximately 50 - 80% of variance in the data, indicating a moderate to good fit for all of them. Additionally, based on AIC score comparison, the stepwise regression managed to produce models with more parsimonious fit for all ward - antibiotic combinations, leading to our decision to keep and report on all four.

outcome	ward	formula
cefotaxime	ICU	cefotaxime ~ time.id + intervention + time.post.int + dial + sej + dms
cefotaxime	Medicine	cefotaxime ~ time.id + intervention + time.post.int + sej
ceftriaxone	ICU	ceftriaxone ~ time.id + intervention + time.post.int + age80 + invdur + sha.norm
ceftriaxone	Medicine	ceftriaxone ~ time.id + intervention + time.post.int + dms

***Table 1**. Final Model Formula for Research Question 1*

Research Question 2

Intervention effect on Microbiologic Profile in the Hospital

Following the completion of the general descriptive and pairwise inferential statistics on microbiologic variables, we performed a base interrupted time series model to evaluate the association between each microbiologic variable with the intervention and assess its effect on the trends in the infection profile within the hospital. 12 ITS models were fitted in this first step with relatively few significant associations found. In the ICU, only Methicilin-Resistant S.aureus (MRSA) and Methicilin-Sensitive S.aureus (MSSA) incidence (infection / 1000BD) were found to be significantly associated with the core interrupted time series variable. Entry-screened MRSA incidence were found to have a significant trend of increase before the intervention +0.16 (95% CI: 0.06 to 0.26; p = 0.00) and a significant trend of decrease after it −0.18 (95% CI: −0.29 to −0.08; p = 0.00); No significant associations were found with the intervention itself. On the other hand, hemoculture confirmed MSSA was found to be significantly associated with the intervention, with it showing a step-change of −1.28 (95% CI: −2.46 to −0.10; p = 0.03) after the intervention. In the medical department, we found no microbiologic variables that are correlated significantly with the intervention. However, hemoculture confirmed total third generation cephalosporin sensitive infections and total ESBL producing enterobacteriaceae infections were found to have a significant decreasing post-intervention trend, showing a reduction of −0.05 (95% CI: −0.09 to 0.00; p = 0.05) and −0.02 (95% CI: −0.03 to 0.00; p = 0.03) respectively.

We subsequently ran 1045 univariate regressions, combining every permutation of microbiologic strains as outcome variable, with antibiotic, microbiologic, and organizational variables. Unlike the previous research question, we set the threshold probability value as less than 30% and extracted the significant predictors to include in our stepwise regression fitting. A total of 20 multivariate models were fitted with the selected variables, with 13 models being produced in the end as we have decided not to include any variables that were not available for the whole period of the study and exclude those with significant multicollinearity.

Out of the thirteen models we ran, in the ICU department, we found that three microbiologic variables were significantly associated with the intervention. A significant step

decrease of −3.81 (95% CI: −6.75 to −0.88; *p* = 0.01) was observed in total incidence (per 1000BD) of ESBLE infection after controlling for entry screening of ESBLE, consumption of ciprofloxacin, penicillin type A, carbapenem, and ciprofloxacin, as well as duration of invasive ventilation. A borderline significant effect was observed for total C3Gr infections, with a step decrease of -4.57 (95% CI: -9.21 to 0.07, p = 0.05) after controlling for entry ESBLE screening, invasive ventilation duration, and carbapenem, ciprofloxacin, and penicillin type A consumption in the ward. Lastly, a step decrease of −1.42 (95% CI: −2.57 to −0.27; p = 0.02) in hemoculture confirmed MSSA incidence was observed after controlling for community level of ESBLE and Metronidazole consumption. Another interesting correlation was noted with hemoculture confirmed MRSA infection in the ICU, where a significant increase of 0.04 (95% CI: 0.01 to 0.07; p = 0.01) was observed for every time unit elapsed prior to the intervention and a significantly decreasing trend of −0.05 (95% CI: −0.08 to −0.02; p = 0.00) for every unit time elapsed was observed afterwards. On the other hand, within the medical department, only total hypercase producing strains were observed as experiencing a significant step change of +0.24 (95% CI: 0.04 to 0.45; p = 0.02) after controlling for carbapenem and piperacilin-tazobactam consumption in the ward.

It is worth noting, however, that only the performance of the total EBLSE ICU model had sufficiently strong performance, capable of explaining approximately 20% of the variance in the data. The other models, even those with significant results, while improved through the stepwise regression model, had relatively weak performances, which may be due to unexplained variability represented by clinician adherence and other variables that were not captured through our data collection activity.

***Table 2**. Final Model Formula for Research Question 2*

	ICU
c3gr_all	c3gr_all ~ time.id + intervention + time.post.int + eblse_screening + carbapenem + ciprofloxacin + pena + invdur
eblse_all	eblse_all ~ time.id + intervention + time.post.int + eblse_screening + carbapenem + ciprofloxacin + pena + invdur
hypercase_all	hypercase_all ~ time.id + intervention + time.post.int + carbapenem + dial
hypercase_blood	hypercase_blood ~ time.id + intervention + time.post.int + cephalosporin + sha.norm
mrsa_all	mrsa_all ~ time.id + intervention + time.post.int + amikacin + vancomycin
mrsa_blood	mrsa_blood ~ time.id + intervention + time.post.int + mrsa_screening + carbapenem
mssa_blood	mssa_blood ~ time.id + intervention + time.post.int + eblse_screening + metronidazole
	Medicine
c3gs_all	c3gs_all ~ time.id + intervention + time.post.int + fluoroquinolone
eblse_all	eblse_all ~ time.id + intervention + time.post.int + amikacin + carbapenem + gentamicin

hypercase_all	hypercase_all ~ time.id + intervention + time.post.int + carbapenem + pip_taz
hypercase_blood	hypercase_blood ~ time.id + intervention + time.post.int + amikacin
mrsa_all	mrsa_all ~ time.id + intervention + time.post.int + carbapenem + cefepime + gentamicin + pena
mrsa_blood	mrsa_blood ~ time.id + intervention + time.post.int + carbapenem

Research Period 2 (2017-2023)

Descriptive Analysis

In the second research period, relevant for research questions three and four, the primary predictor of interest is COVID-19. The period covers 84 months of observation points—46 months without the COVID pandemic (i.e., before March 2020 and after June 2023) and 38 months during the declared COVID pandemic in France (between March 2020 and June 2023). In terms of antibiotic variables, within the ICU, we observed significant decreases between COVID and non-COVID periods for ciprofloxacin (102.69 (141.38) vs 45.03 (86.50); $p = 0.012$), penicillin A (201.14 (313.14) vs 129.47 (169.82); $p = 0.043$), and vancomycin (179.92 (157.50) vs 125.55 (146.62); $p = 0.047$). A significant increase was also noted in hydroalcoholic solution use (76,975.71 (44,553.92) vs 129,456.64 (56,262.47); $p < 0.001$). On the other hand, within the medical department, amongst the variables with significant changes, a trend of increasing usage was observed for cefepime (0.94 (0.93) vs 1.87 (1.55); $p = 0.005$), total cephalosporins (22.52 (6.97) vs 26.86 (7.31); $p = 0.018$), piperacillin/tazobactam (2.31 (1.00) vs 2.97 (1.18); $p = 0.004$), and hydroalcoholic solution use (25,115.99 (12,863.41) vs 32,801.01 (12,995.66); $p = 0.004$). Ceftriaxone (2.26 (1.11) vs 1.76 (1.03); $p = 0.027$) showed the only significant decrease in this setting.

Amongst the microbiologic variables, several interesting patterns were observed in terms of significant differences. In the ICU, total detected third-generation cephalosporin-sensitive infections (13.93 (19.56) vs 16.35 (10.69); $p = 0.019$), cephalosporin-resistant Pseudomonas aeruginosa infections (0.65 (1.44) vs 2.32 (2.82); $p = 0.002$), carbapenem-resistant Pseudomonas aeruginosa infections (0.95 (2.80) vs 2.91 (4.28); $p = 0.002$), entry-screened extended beta-lactamase-producing enterobacterial strains (17.81 (9.42) vs 12.19 (8.82); $p = 0.004$), total Pseudomonas aeruginosa infections (17.81 (9.42) vs 12.19 (8.82); $p = 0.004$), and hemoculture-confirmed Pseudomonas aeruginosa (1.01 (2.48) vs 1.68 (2.54); $p = 0.039$) were found to differ significantly. For the medical department, we found significant differences only for hemoculture (0.11 (0.15) vs 0.26 (0.28); $p = 0.008$) and total methicillin-sensitive Staphylococcus aureus infections (0.44 (0.33) vs 0.63 (0.41); $p = 0.039$).

Lastly, amongst the organisational variables for the ICU, we found a reduction in cancer cases (7.78 (2.93) vs 6.34 (2.99); $p = 0.037$), a decrease in median age (68.49 (2.78) vs 66.29 (3.39); $p = 0.003$), and a reduction in the number of patients aged 80 or older (9.50 (3.34) vs 7.21 (2.98); $p = 0.001$). In contrast, COVID admissions increased (0.22 (0.66) vs 8.84 (8.72);

p < 0.001), as did the total number of COVID patients (5.83 (16.57) vs 66.13 (48.98); p < 0.001). For the medical department, we observed a decrease in cancer patients (134.57 (13.28) vs 120.66 (11.23); p < 0.001), while the number of stays increased (2,447.13 (290.91) vs 2,596.89 (247.40); p = 0.002), along with the average duration of stay (4.49 (0.45) vs 5.15 (0.43); p < 0.001) and the number of deaths (27.63 (6.63) vs 32.11 (8.88); p = 0.030). Similarly, both COVID admissions (5.61 (16.05) vs 57.74 (44.50); p < 0.001) and total COVID patients (5.83 (16.57) vs 66.13 (48.98); p < 0.001) increased significantly. It is however, important to note, that these differences do not imply causation as these significant differences were inferred only from pairwise analysis with minimal regards for time continuity, which will be taken into account in the regression models we subsequently performed for these variables.

Specific Results

Research Question 3

COVID 19 Effect on the Profile of Antibiotic Prescription in the Hospital

A slightly different approach was taken in the analysis performed to answer this research question. As there were no target antibiotics in the response of this question and the purpose of this question was to build a profile of antibiotic prescription in the target departments, we began directly by running all 20 antibiotic variables in a base linear regression model against COVID total, as a proxy variable for the COVID 19 pandemic period, as we judged COVID patient load as a more reliable representation of the pandemic in the hospital's specific setting than a period-based categorical COVID 19 variable. Through our base models, we found some antibiotic types that were correlated significantly with COVID 19. In the ICU, only the consumption of hydroalcoholic solution is significantly associated with the pandemic, with every unit increase in COVID patient incidence leading to an increased consumption of 155.68 ml/1000BD (95% CI: 71.02 to 240.33; p = 0.00). On the other hand, we found many more significant correlations in the medical department, where every unit increase in COVID patient incidence led to an increase of +0.85 DDD/1000BD (95% CI: 0.42 to 1.28; p = 0.00) of total antibiotic consumption, +0.11 DDD/1000BD (95% CI: 0.01 to 0.21; p = 0.03) of C3G consumption, +0.12 DDD/1000BD (95% CI: 0.04 to 0.21; p = 0.00) of cefotaxime consumption, 0.49 DDD/1000BD (95% CI: 0.34 to 0.65; p = 0.00) of Penicilin A - clavulinic acid consumption, +0.04 DDD/1000BD (95% CI: 0.02 to 0.05; p = 0.00) of Vancomycin consumption, and + 492.66 ml/1000BD (95% CI: 209.01 to 776.31; p = 0.00) of hydroalcoholic solution usage.

Subsequent to this step, we performed 2280 combinations of univariate regression for each ward, with 20 antibiotics as the output and all antibiotic, microbiologic, and organizational variables as the outcome variables. Setting the significance threshold at 20% probability value, 208 outcome variables are usable after removing multicollinear variables, variables with incomplete observations over the period, and instances where the outcome variable is the same as the main predictor. Afterwards we fitted 33 multivariate linear regression models (20

from the medical department and 13 from the ICU), utilizing the stepwise selection process based on AIC criteria to obtain our final models (see Table 4).

Table 3. *Final Model Formula for Research Question 3*

outcome	formula
	ICU
atb	atb ~ time.id + covidtot + diab + cancer + sej + deces + inv + dms + cen
azithromycin	azithromycin ~ time.id + covidtot + cancer
c3g	c3g ~ time.id + covidtot + urg + diab + sej + dms
carbapenem	carbapenem ~ time.id + covidtot + cancer
cefepime	cefepime ~ time.id + covidtot + sej + invdur + dms
cefotaxime	cefotaxime ~ time.id + covidtot + urg + diab + sej + deces + inv + dms
cephalosporin	cephalosporin ~ time.id + covidtot + urg + diab + sej + dms
ciprofloxacin	ciprofloxacin ~ time.id + covidtot + diab + invdur + cen
fluoroquinolone	fluoroquinolone ~ time.id + covidtot + diab + sej + invdur + cen
macrolide	macrolide ~ time.id + covidtot + cancer + sej + dms
pena	pena ~ time.id + covidtot + diab + invdur
vancomycin	vancomycin ~ time.id + covidtot + cancer
	Medicine
amikacin	amikacin ~ time.id + covidtot + cancer + inv
atb	atb ~ time.id + covidtot + urg
azithromycin	azithromycin ~ time.id + covidtot + cen
c3g	c3g ~ time.id + covidtot + urg + diab + sej + vvc + invdur
carbapenem	carbapenem ~ time.id + covidtot + dial + cancer + sej + age80 + vvc
cefepime	cefepime ~ time.id + covidtot + chimio + pat
cefotaxime	cefotaxime ~ time.id + covidtot + dial + urg + diab + vvc + invdur
ceftazidime	ceftazidime ~ time.id + covidtot + chimio
ceftriaxone	ceftriaxone ~ time.id + covidtot + age75
cephalosporin	cephalosporin ~ time.id + covidtot + sej + vvc
fluoroquinolone	fluoroquinolone ~ time.id + covidtot + dial + urg
gentamicin	gentamicin ~ time.id + covidtot + age75 + inv
macrolide	macrolide ~ time.id + covidtot + chimio + pat
metronidazole	metronidazole ~ time.id + covidtot + dial + urg + vvc
pena	pena ~ time.id + covidtot + diab
pip_taz	pip_taz ~ time.id + covidtot + dial + urg + vvc + invdur
sha	sha ~ time.id + covidtot + urg
vancomycin	vancomycin ~ time.id + covidtot + age80 + vvc

Through the interpretation of our final multivariate models, after controlling for the respective explanatory variables listed in the table above, we found several antibiotic variables that are correlated significantly with the COVID 19 pandemic, which is represented by the total

incidence of COVID 19 patients / 1000BD in each concerned department. In the ICU, only Cefepime and Hydroalcoholic Solution use were significantly associated with the pandemic, with every unit increase in COVID 19 patient incidence yielding a 0.56 DDD/1000BD (95% CI: 0.15 to 0.98; p = 0.01) and 141.53 ml/1000BD (95% CI: 50.57 to 232.49; p = 0.00) increase respectively. Many more antibiotic variables were found to be significantly associated with COVID 19 in the medical department. Our final models showed that for every unit increase in COVID 19 patient incidence, there was an increase of +0.65 DDD/1000BD (95% CI: 0.25 to 1.06; p = 0.00) in total antibiotic use, +0.44 DDD/1000BD (95% CI: 0.27 to 0.60; p = 0.00) of penicillin-clavulinic acid use, and +0.03 DDD/1000BD (95% CI: 0.02 to 0.05; p = 0.00) of vancomycin use, as well as a decrease of −0.01 DDD/1000BD (95% CI: −0.02 to 0.00; p = 0.04) in gentamicin use. The performance of these final models are also generally acceptable, with all of the interpreted models' parsimony improved through the stepwise regression and their adjusted R^2 values ranging from 0.20 - 0.44, which is classified as moderate for aggregated data types.

Research Question 4

COVID 19 Effect on the Profile of Microbiological Infection in the Hospital

We approached the fourth research question slightly differently than the others, as the outcome variable for this question are count data-types. A poisson regression approach with an offset of log(1000BD) was adopted to estimate COVID 19's effect on each recorded microbiological variable included in the study. We began by running all possible combinations of outcome and predictor variable in a univariate poisson regression, while keeping the core variables of time.id and covid patient incidence in the base equation. We tested a total of 3456 combinations, running 673 models in the end after removing those with no empirical basis, incomplete data for the whole study period, or insufficient variance. This was followed up by removing predictor variables with known multicollinearity, which resulted in 216 valid predictors with a p value of less than 0.20. After aggregating the valid predictors, 26 multivariate models were fitted and put through the stepwise regression process, 14 for the ICU and 12 for the medical department (see Table 5).

Table 5*. Final Model Formula for Research Question 3*

(models where covid is significantly associated with the outcome are marked in **bold**)

outcome	formula
	ICU
ab_all	ab_all ~ time.id + covidtot + macrolide

ab_blood	ab_blood ~ time.id + covidtot
c3gr_all	c3gr_all ~ time.id + covidtot + carbapenem + deces
c3gs_all	c3gs_all ~ time.id + covidtot + amikacin + macrolide + metronidazole + pena + sha + urg + vvc + dms
candida_blood	candida_blood ~ time.id + covidtot + azithromycin + vancomycin + deces + vvc
crpa_all	crpa_all ~ time.id + covidtot + dial + dms
eblse_all	eblse_all ~ time.id + covidtot + azithromycin + carbapenem + dial + deces + vvc
entero_all	**entero_all ~ time.id + covidtot + ceftazidime + fluoroquinolone + macrolide + metronidazole + pena + urg + sej + age80 + vvc**
entero_blood	**entero_blood ~ time.id + covidtot + azithromycin + carbapenem + fluoroquinolone + metronidazole + vvc**
hypercase_all	**hypercase_all ~ time.id + covidtot + carbapenem + penaac**
hypercase_blood	**hypercase_blood ~ time.id + covidtot + azithromycin + fluoroquinolone**
mssa_all	**mssa_all ~ time.id + covidtot + cephalosporin + metronidazole + deces**
pa_all	**pa_all ~ time.id + covidtot + cephalosporin + macrolide + metronidazole + dial + cancer**
pa_blood	**pa_blood ~ time.id + covidtot + amikacin + cefotaxime**
sm_all	sm_all ~ time.id + covidtot + cephalosporin + penaac
	Medicine
ab_all	**ab_all ~ time.id + covidtot + azithromycin + sha + chimio + vvc + invdur**
c3gr_all	c3gr_all ~ time.id + covidtot + amikacin + cefotaxime + fluoroquinolone + vancomycin + age80 + deces
c3gs_all	**c3gs_all ~ time.id + covidtot + ciprofloxacin + pena + deces + invdur**

crpa_all	crpa_all ~ time.id + covidtot + fluoroquinolone + cancer + deces + vvc + inv
entero_all	entero_all ~ time.id + covidtot + ciprofloxacin + metronidazole + pena + sej + invdur
entero_blood	entero_blood ~ time.id + covidtot + azithromycin + c3g + sha + dial + invdur
hypercase_all	**hypercase_all ~ time.id + covidtot + sha + chimio + age80 + cen**
hypercase_blood	hypercase_blood ~ time.id + covidtot + azithromycin + ceftazidime + chimio + diab
mssa_all	mssa_all ~ time.id + covidtot + fluoroquinolone + macrolide + invdur
pa_all	**pa_all ~ time.id + covidtot + cephalosporin + penaac + chimio + deces**
pa_blood	pa_blood ~ time.id + covidtot + cephalosporin + vancomycin + chimio + deces
mrsa_all	mrsa_all ~ time.id + covidtot + ceftriaxone + penaac

Recalling that the models are poisson regression models using the GEE approach, based on the interpretation of these final models, which accounted for all relevant covariates listed in the accompanying table, several microbiologic indicators were found to be significantly associated with the COVID-19 period, represented in this study through the proxy variable of COVID-19 incidence per 1000 bed-days in each department. In the ICU department for every unit increase of COVID 19 patient incidence, we were able to see a relative increase in the incidence of enterobacteriaceae infections, both total (IRR = 1.0015, 95% CI: 1.0009 to 1.0021; $p < 0.001$) and in blood cultures (IRR = 1.0020, 95% CI: 1.0006 to 1.0033; $p = 0.005$). This increase was also observed in hypercase producing infection, both in total detected infections (IRR = 1.0023, 95% CI: 1.0010 to 1.0037; $p < 0.001$) and in hemoculture confirmed samples (IRR = 1.0041, 95% CI: 1.0013 to 1.0070; $p = 0.004$). A significant positive association was also observed for MSSA infections (IRR = 1.0012, 95% CI: 1.0001 to 1.0023; $p = 0.03$), and for Pseudomonas aeruginosa, both overall (IRR = 1.0022, 95% CI: 1.0012 to 1.0033; $p < 0.001$) and in blood cultures (IRR = 1.0040, 95% CI: 1.0016 to 1.0065; $p = 0.001$). In the medicine department, the changes were somewhat more apparent, where each increase in the incidence of enterobacteriaceae infections was associated with a 11.5% increase in total acinetobacter baumannii incidence (IRR = 1.1150, 95% CI: 1.0207 to 1.2181; p=0.016), and a 3.2% increase in the incidence of total infection by hypercase-producing infections (IRR = 1.0322, 95% CI: 1.0124 to 1.0524; $p = 0.001$). On the other hand, the pandemic was associated

with a reduction in incidence of total C3Gs infections (IRR = 0.9936, 95% CI: 0.9877 to 0.9995; p = 0.033) and total pseudomonas aeruginosa infections (IRR = 0.9764, 95% CI: 0.9552 to 0.9980; p = 0.033) which may be indicative of a shift in infection patterns, and consequently certain resistance selection due to the COVID 19 pandemic. Please keep in mind that these IRRs are produced with a continuous variable and therefore appear very small due to the incremental nature of the predictive variables. Performance analysis of these models reflected that overdispersion may be present and therefore a repeat analysis with a negative binomial approach will be planned in further studies.

Discussion

Research Question 1

The first research question of this study aimed to explore the effect of the policy change in Saint-Joseph Saint-Luc Hospital in Lyon on the prescription pattern of the consumption of antibiotics targeted by the intervention (i.e., cefotaxime and ceftriaxone) for two departments: the intensive care unit (ICU) and the medical department. As our findings indicated, the intervention was successful in increasing the use of cefotaxime by +442.04 DDD/1000BD (95%CI 246.37 to 637.71; p = 0.00) and 8.14 DDD/1000BD (95% CI: 5.54 to 10.74; p < 0.001), as well as reducing the use of ceftriaxone by −297.38 DDD/1000BD (95% CI: −394.92 to −199.83; p = 0.00) and −6.39 DDD/1000BD (95% CI: −7.97 to −4.81; p = 0.00) in the ICU and Medical department respectively, within one month of the intervention. This success and the fact that almost no significant post-intervention changes in trend were detected through our models indicated the persistence of the effect until the end of the study period. This finding mirrors the findings of a previous study done in the same hospital with a shorter time period and a different regression method, where it was found that ceftriaxone consumption decreased significantly and cefotaxime usage increased after the intervention point (Tan *et al.*, 2018), indicating both the replicability of the study and supporting our interpretation of the intervention's persistence over the years.

We also found that there was a correlation between the duration of hospital stay with increasing cefotaxime use in the ICU department where consumption increased by 4.28 DDD/1000BD (95% CI: 2.48 to 6.08; p < 0.001) for every unit increase of mean duration of stay. This finding could be due to the fact that patients that stay longer in the ICU are often more severely ill than those who stay in other departments, as was reported in a past national study in Ethiopia which showed that prolonged stays in ICUs were significantly associated with readmission and complication (Bekele *et al.*, 2024). Through the descriptive analysis we have performed, we found that antibiotic usage, mostly from groups of fluoroquinolones, cephalosporines, macrolides, penicillin, and vancomycin are generally on a downward trend between the pre and post intervention period. At the moment, there is no evidence that this

trend is directly related to the intervention itself, but may rather be due to the general campaign in the french setting promoting more responsible antibiotic use, both in the community and in the hospital setting, which was reported to have found moderate success, seeing antibiotic consumption plateauing over the past decade, albeit being reported as having had less success in maintaining this reduction recently (Carlet *et al.*, 2020).

Research Question 2

In terms of the intervention's effect towards microbiologic infection and resistance pattern, we found a general decrease in ESBLE infection −3.81 (95% CI: −6.75 to −0.88; p = 0.01) and C3G-Res infections -4.57 (95% CI: -9.21 to 0.07, p = 0.05) which is consistent with the findings of two previous studies done on the subject (Tan *et al.*, 2018; Bouiller *et al.*, 2024). Some other findings were also noted for this particular research question, such as the decrease in MSSA incidence of −1.42 DDD/1000BD (95% CI: −2.57 to −0.27; p = 0.02) and increase in MRSA 0.04 (95% CI: 0.01 to 0.07; p = 0.01) over time which, while correlated, is unlikely to be causal as they are not usually treated by the intervention antibiotics (Sevin *et al.*, 2021).

Research Question 3

We were able to observe the significant increase in hydroalcoholic solution use in both departments, which was most likely due to the early scramble towards hygiene and protective measures in the early stages of the pandemic (Huang *et al.*, 2021; Si Ali *et al.*, 2023). A study in a tertiary hospital in Spain also reflected this finding, showing that hand hygiene practice adherence increased during COVID 19, reflecting a positive change that may also aid in the reduction of hospital acquired infections, both in the practitioner's side and patient's side (Guerrero-Soler *et al.*, 2024). Our models also reflected that multiple antibiotics in both ICU and the medical department had higher usage during the pandemic including cefepime in the ICU department and total antibiotic, penicillin-clavulanic acid, and vancomycin which is most likely due to the early use of broad-spectrum antibiotics during the COVID pandemic as a prophylactic and/or curative measure against a suspected bacterial co-infection (Barišić *et al.*, 2025). Additionally, some of these increases were also observed in a very recent, national level French study, reflecting what is likely to be a general trend in the french healthcare system (Layan *et al.*, 2024) The association that the duration of invasive ventilation with the incidence of ESBLE found in this study is also likely due to the fact that it is one of the main ports of entry for this infection, especially during COVID where individuals ventilated with severe COVID often receive a battery of antibiotics. (Livermore, 2021)

Organisation Variable

While not part of the study in general, our findings demonstrated that the ICU and medical department of our target hospital saw an increase in mean age, which is most likely due to the aging population of France (Beland and Viriot Durandal, 2013). The higher number of stays and invasive ventilation is most likely related to hospital-level policy and/or treatment decision changes. While this is not related to the intervention, this is still interesting to note. In the medical department, we conversely found a reduction in average duration of stay, which may be a reflection of the hospital's policy to reduce care length in order to minimize the occurrence of hospital acquired infection.

Strengths and Limitations

This study had several strengths and limitations. In terms of strength, we utilized the interrupted time series method to evaluate the impact of the intervention on antibiotic prescription and microbiological infection patterns, allowing us to infer causality better than other similar methodologies, especially in combination with the longitudinal nature of our data. On one of the questions, our utilisation of the generalized estimated equation based poisson regression allows finer control for autocorrelation and assessment of overdispersion. The choice to use total COVID patient load at the department level, each with each own care profile, meant that we utilized a continuous and robust variable for the COVID pandemic, reflecting the real burden of the disease against the outcome variables we are regressing them against, which is a superior approach compared to generalized periods which may not reflect the reality in the center our study is based in.

On the other hand, some limitations also exist in the study. During the course of our data collection activity, we encountered difficulties related to changes in data collection policies, variables collected in different ways, and changes in personnel between data collection periods. This led to our inability to collect reliable data on some variables, which may compromise the quality of our estimates. Additionally, the aggregate nature of individual data and the fact that there are no qualitative elements regarding practitioner preference for certain antibiotics makes it difficult to connect our findings with factors such as cross department referrals and cross-specialty habits. One last limitation of our study is that it is a single center study, observational in nature without any real control for population where the intervention was not applied, possibly leading to some covariates being unmeasured.

Conclusion and Recommendation

Aligned with the research question we can say the following conclusions:

- The intervention has had the desired effect on cefotaxime and ceftriaxone prescription pattern and habits in both the ICU and Medical departments. This effect was shown to be sustained over time, until the end of 2019.
- The intervention has also had an impact in reducing the selection of resistant microbes, particularly extended spectrum beta lactamase producing enterobacteriaceae and third generation cephalosporin resistant antibiotics
- COVID 19 has had a definite impact on the prescription pattern of antibiotics, with increases in antibiotic types consistent with the rush to prescribe observed globally in the beginning, often as a way to “prevent” suspected bacterial coinfection. This change is also reflected in its impact on resistant bacterial selection and antibiotics.

Recommendations include:

- Better data collection policies at the hospital level
- Continuing the implementation of antibiotic stewardship in hospitals across the country.

This is particularly important as studies have shown that appropriate antibiotic treatment is associated with a better survival and shortened duration of hospital stay in medical patients with bacterial infections (Fraser *et al.*, 2006) and that it is important to reduce other, even non hospital related infection like CAP (Ryu *et al.*, 2024)

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Appendix 1 - Period 2 ATB Descriptive Table

	Medicine			ICU		
Characteristic	**No COVID N = 46[1]**	**COVID N = 38[1]**	**p-value[2]**	**No COVID N = 46[1]**	**COVID N = 38[1]**	**p-value[2]**
Data Collection Date	2017-01-01 - 2023-12-01	2020-04-01 - 2023-05-01	**<0.001**	2017-01-01 - 2023-12-01	2020-04-01 - 2023-05-01	**<0.001**
Cefepim (DDD/1000BD)	0.94 (0.93)	1.87 (1.55)	**0.005**	191.81 (271.95)	234.31 (216.78)	0.10
Cefotaxime (DDD/1000BD)	11.35 (3.57)	12.73 (4.12)	0.3	701.15 (664.91)	800.10 (533.91)	0.3
Ceftazidime (DDD/1000BD)	0.61 (0.61)	0.78 (0.66)	0.12	219.12 (537.25)	156.00 (168.04)	0.3
Ceftriaxone (DDD/1000BD)	2.26 (1.11)	1.76 (1.03)	**0.027**	18.74 (36.62)	11.04 (19.02)	0.3
Cephalosporine (DDD/1000BD)	22.52 (6.97)	26.86 (7.31)	**0.018**	2,111.29 (2,785.50)	2,128.21 (1,619.63)	0.5
Ciprofloxacine (DDD/1000BD)	0.92 (0.75)	1.07 (0.82)	0.3	102.69 (141.38)	45.03 (86.50)	**0.012**
Floroquinolone (DDD/1000BD)	5.26 (2.26)	5.96 (2.57)	0.3	170.56 (152.73)	126.22 (119.97)	0.14
Gentamicine (DDD/1000BD)	0.47 (0.41)	0.31 (0.28)	0.065	100.76 (135.38)	53.66 (55.81)	0.2
Total Macrolide (DDD/1000BD)	2.31 (1.51)	2.12 (1.20)	0.5	226.17 (226.26)	190.58 (152.95)	0.5
Metronidazole (DDD/1000BD)	6.42 (2.60)	7.03 (2.42)	0.2	264.81 (225.74)	276.18 (198.01)	0.6
Penicilin A (DDD/1000BD)	11.09 (3.97)	11.70 (4.53)	0.9	201.14 (313.14)	129.47 (169.82)	**0.043**
Penicilin A - Clavulanic Acid (DDD/1000BD)	25.62 (8.49)	27.80 (8.40)	0.4	508.71 (674.85)	416.15 (374.28)	0.2

Piperacilin/Tazobactam (DDD/1000BD)	2.31 (1.00)	2.97 (1.18)	**0.004**	587.03 (562.70)	529.49 (388.53)	0.5
Vancomycin (DDD/1000BD)	0.87 (0.64)	1.15 (0.90)	0.2	179.92 (157.50)	125.55 (146.62)	**0.047**
Hydroalcoholic Solution (ml/1000BD)	25,115.99 (12,863.41)	32,801.01 (12,995.66)	**0.004**	76,975.71 (44,553.92)	129,456.64 (56,262.47)	**<0.001**

[1] Min - Max; n (%); Mean (sd)

[2] Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test

Appendix 2 - RQ1 Full Regression Table

term	estimate	std.error	statistic	p.value	conf.low	conf.high
cefotaxime-ICU						
(Intercept)	−421.43	152.29	−2.77	**0.01**	−723.53	−119.32
time.id	−5.60	3.86	−1.45	0.15	−13.25	2.05
intervention1	442.04	98.64	4.48	**0.00**	246.37	637.71
time.post.int	6.73	4.07	1.65	0.10	−1.35	14.80
dial	0.87	0.51	1.72	0.09	−0.14	1.88
sej	4.28	0.91	4.71	**0.00**	2.48	6.08
dms	28.72	13.69	2.10	**0.04**	1.56	55.89
cefotaxime-Medicine						
(Intercept)	1.99	1.10	1.81	0.07	−0.19	4.17
time.id	−0.02	0.05	−0.49	0.63	−0.13	0.08
intervention1	8.14	1.31	6.20	**0.00**	5.54	10.74
time.post.int	0.07	0.05	1.28	0.20	−0.04	0.18
sej	−0.03	0.01	−3.00	**0.00**	−0.05	−0.01
ceftriaxone-ICU						
(Intercept)	342.73	65.29	5.25	**0.00**	213.22	472.24
time.id	2.14	1.97	1.08	0.28	−1.78	6.05
intervention1	−297.38	49.17	−6.05	**0.00**	−394.92	−199.83

time.post.int	−3.92	2.11	−1.86	0.07	−8.10	0.27
age80	1.81	1.06	1.71	0.09	−0.29	3.91
invdur	−0.15	0.08	−1.78	0.08	−0.31	0.02
sha.norm	1.71	1.15	1.48	0.14	−0.58	4.00
ceftriaxone-Medicine						
(Intercept)	10.74	0.65	16.61	**0.00**	9.46	12.03
time.id	−0.01	0.03	−0.17	0.86	−0.06	0.05
intervention1	−6.39	0.80	−8.03	**0.00**	−7.97	−4.81
time.post.int	−0.03	0.03	−0.97	0.33	−0.09	0.03
dms	1.62	0.72	2.24	**0.03**	0.19	3.05

Appendix 3 - RQ 2 Full Regression Table

term	estimate	std.error	statistic	p.value	conf.low	conf.high
c3gr_all-ICU						
(Intercept)	−0.87	3.23	−0.27	0.79	−7.28	5.55
time.id	−0.01	0.10	−0.10	0.92	−0.20	0.18
intervention1	−4.57	2.34	−1.96	0.05	−9.21	0.07
time.post.int	0.11	0.10	1.07	0.29	−0.09	0.31
eblse screening	0.14	0.07	1.94	0.06	0.00	0.29
carbapenem	0.01	0.00	1.77	0.08	0.00	0.01
ciprofloxacin	0.01	0.00	1.55	0.12	0.00	0.01

pena	0.00	0.00	1.73	0.09	0.00	0.00
invdur	0.01	0.00	1.80	0.08	0.00	0.02
c3gs_all-Medicine						
(Intercept)	7.72	0.71	10.86	**0.00**	6.31	9.14
time.id	−0.02	0.02	−1.00	0.32	−0.07	0.02
intervention1	−0.41	0.56	−0.74	0.46	−1.52	0.69
time.post.int	−0.04	0.02	−1.88	0.06	−0.09	0.00
fluoroquinolone	0.09	0.05	1.83	0.07	−0.01	0.19
eblse_all-ICU						
(Intercept)	−1.64	2.04	−0.81	0.42	−5.70	2.41
time.id	0.00	0.06	0.02	0.98	−0.12	0.12
intervention1	−3.81	1.48	−2.58	**0.01**	−6.75	−0.88
time.post.int	0.04	0.06	0.61	0.54	−0.09	0.17
eblse screening	0.12	0.05	2.46	**0.02**	0.02	0.21
carbapenem	0.00	0.00	1.56	0.12	0.00	0.01
ciprofloxacin	0.01	0.00	2.00	**0.05**	0.00	0.01
pena	0.00	0.00	2.37	**0.02**	0.00	0.00
invdur	0.01	0.00	2.51	**0.01**	0.00	0.01
eblse_all-Medicine						

(Intercept)	0.40	0.18	2.16	**0.03**	0.03	0.76
time.id	0.00	0.01	0.40	0.69	−0.01	0.02
intervention1	0.19	0.17	1.10	0.27	−0.15	0.53
time.post.int	−0.01	0.01	−1.62	0.11	−0.03	0.00
amikacin	0.41	0.15	2.69	**0.01**	0.11	0.71
carbapenem	0.14	0.07	2.01	**0.05**	0.00	0.27
gentamicin	0.08	0.04	1.82	0.07	−0.01	0.16
hypercase_all-ICU						
(Intercept)	0.66	1.43	0.46	0.65	−2.18	3.50
time.id	0.00	0.06	0.01	0.99	−0.12	0.12
intervention1	−0.66	1.49	−0.45	0.66	−3.62	2.29
time.post.int	0.05	0.06	0.74	0.46	−0.08	0.17
carbapenem	0.00	0.00	1.51	0.13	0.00	0.01
dial	0.01	0.01	1.60	0.11	0.00	0.03
hypercase_all-Medicine						
(Intercept)	0.28	0.10	2.78	**0.01**	0.08	0.47
time.id	−0.01	0.00	−1.79	0.08	−0.02	0.00
intervention1	0.24	0.10	2.38	**0.02**	0.04	0.45
time.post.int	0.00	0.00	0.99	0.32	0.00	0.01

carbapenem	0.06	0.04	1.41	0.16	−0.02	0.14
pip_taz	0.04	0.03	1.44	0.15	−0.02	0.10
hypercase_blood-ICU						
(Intercept)	−0.35	0.55	−0.63	0.53	−1.44	0.75
time.id	0.00	0.02	−0.03	0.98	−0.05	0.05
intervention1	0.11	0.61	0.18	0.86	−1.10	1.32
time.post.int	0.00	0.03	0.17	0.87	−0.05	0.06
cephalosporin	0.00	0.00	2.46	**0.02**	0.00	0.00
sha.norm	0.02	0.01	1.46	0.15	−0.01	0.05
hypercase_blood-Medicine						
(Intercept)	0.03	0.04	0.74	0.46	−0.05	0.11
time.id	0.00	0.00	−0.91	0.36	−0.01	0.00
intervention1	0.03	0.05	0.68	0.50	−0.06	0.13
time.post.int	0.00	0.00	0.95	0.34	0.00	0.01
amikacin	0.15	0.04	3.42	**0.00**	0.06	0.24
mrsa_all-ICU						
(Intercept)	0.12	0.60	0.20	0.84	−1.08	1.32
time.id	0.04	0.03	1.60	0.11	−0.01	0.09
intervention1	−0.76	0.67	−1.13	0.26	−2.09	0.58

time.post.int	−0.05	0.03	−1.89	0.06	−0.11	0.00
amikacin	0.00	0.00	−1.45	0.15	0.00	0.00
vancomycin	0.00	0.00	2.33	**0.02**	0.00	0.01
mrsa_all-Medicine						
(Intercept)	0.11	0.08	1.45	0.15	−0.04	0.27
time.id	0.00	0.00	0.21	0.83	−0.01	0.01
intervention1	−0.08	0.07	−1.04	0.30	−0.22	0.07
time.post.int	0.00	0.00	−0.53	0.59	−0.01	0.00
carbapenem	0.08	0.03	2.74	**0.01**	0.02	0.13
cefepime	−0.05	0.03	−1.71	0.09	−0.10	0.01
gentamicin	−0.04	0.02	−2.11	**0.04**	−0.08	0.00
pena	0.00	0.00	2.42	**0.02**	0.00	0.01
mrsa_blood-ICU						
(Intercept)	−0.07	0.30	−0.25	0.81	−0.67	0.52
time.id	0.04	0.01	2.82	**0.01**	0.01	0.07
intervention1	−0.65	0.34	−1.90	0.06	−1.33	0.03
time.post.int	−0.05	0.02	−2.96	**0.00**	−0.08	−0.02
mrsa_screening	−0.06	0.03	−2.14	**0.04**	−0.12	0.00
carbapenem	0.00	0.00	−1.96	0.05	0.00	0.00

mrsa_blood-Medicine						
(Intercept)	0.01	0.02	0.38	0.71	−0.04	0.05
time.id	0.00	0.00	−0.68	0.50	0.00	0.00
intervention1	0.03	0.02	1.18	0.24	−0.02	0.07
time.post.int	0.00	0.00	0.23	0.82	0.00	0.00
carbapenem	0.03	0.01	2.71	**0.01**	0.01	0.04
mssa_blood-ICU						
(Intercept)	−0.10	0.56	−0.18	0.85	−1.22	1.01
time.id	0.01	0.02	0.62	0.53	−0.03	0.06
intervention1	−1.42	0.58	−2.46	**0.02**	−2.57	−0.27
time.post.int	0.00	0.02	−0.07	0.95	−0.05	0.05
eblse screening	0.04	0.02	2.02	**0.05**	0.00	0.07
metronidazole	0.00	0.00	2.19	**0.03**	0.00	0.00

Appendix 4 - RQ3 Full Regression Table

Term	estimate	std.error	statistic	p.value	conf.low	conf.high
amikacin-Medicine						
(Intercept)	−1.05	0.41	−2.55	**0.01**	−1.88	−0.23
time.id	0.00	0.00	1.46	0.15	0.00	0.01
covidtot	0.00	0.00	0.78	0.43	0.00	0.01
cancer	0.02	0.01	1.44	0.15	−0.01	0.04
age80	0.01	0.00	1.96	0.05	0.00	0.01
inv	0.35	0.23	1.56	0.12	−0.10	0.81
atb-ICU						
(Intercept)	−46935.25	11844.15	−3.96	**0.00**	−70551.82	−23318.68
time.id	14.46	19.96	0.72	0.47	−25.34	54.27
covidtot	2.57	3.26	0.79	0.43	−3.93	9.07
diab	91.25	50.83	1.80	0.08	−10.11	192.61
cancer	121.21	43.85	2.76	**0.01**	33.76	208.65
sej	109.11	35.50	3.07	**0.00**	38.32	179.90
deces	−70.61	35.87	−1.97	0.05	−142.14	0.92
inv	64.98	32.70	1.99	0.05	−0.22	130.18
dms	1923.62	616.77	3.12	**0.00**	693.81	3153.44
cen	191.51	140.09	1.37	0.18	−87.81	470.84

atb-Medicine						
(Intercept)	−34.23	28.65	−1.19	0.24	−91.25	22.79
time.id	0.17	0.12	1.38	0.17	−0.07	0.41
covidtot	0.65	0.20	3.24	**0.00**	0.25	1.06
urg	0.92	0.22	4.27	**0.00**	0.49	1.35
azithromycin-ICU						
(Intercept)	−7.37	7.63	−0.97	0.34	−22.56	7.82
time.id	0.05	0.13	0.38	0.70	−0.21	0.31
covidtot	0.02	0.02	0.91	0.37	−0.02	0.06
cancer	0.44	0.24	1.79	0.08	−0.05	0.92
azithromycin-Medicine						
(Intercept)	5.38	2.18	2.47	**0.02**	1.05	9.71
time.id	0.00	0.00	1.20	0.23	0.00	0.01
covidtot	0.00	0.00	0.17	0.87	−0.01	0.01
cen	−0.08	0.03	−2.36	**0.02**	−0.14	−0.01
c3g-Medicine						
(Intercept)	−8.49	7.42	−1.14	0.26	−23.26	6.27
time.id	−0.04	0.04	−0.93	0.36	−0.11	0.04
covidtot	0.01	0.04	0.20	0.84	−0.08	0.10

dial	0.05	0.02	3.26	**0.00**	0.02	0.09
urg	0.17	0.05	3.43	**0.00**	0.07	0.27
diab	−0.19	0.10	−1.90	0.06	−0.38	0.01
carbapenem-ICU						
(Intercept)	−275.67	116.88	−2.36	**0.02**	−508.31	−43.03
time.id	2.05	1.00	2.05	**0.04**	0.06	4.05
covidtot	0.05	0.17	0.30	0.76	−0.29	0.39
cancer	9.98	1.90	5.26	**0.00**	6.20	13.75
invdur	0.28	0.17	1.64	0.11	−0.06	0.63
carbapenem-Medicine						
(Intercept)	−2.06	0.52	−3.93	**0.00**	−3.10	−1.02
time.id	0.00	0.00	−0.61	0.55	−0.01	0.01
covidtot	−0.01	0.01	−1.30	0.20	−0.03	0.01
dial	0.01	0.00	4.39	**0.00**	0.01	0.02
deces	0.07	0.05	1.42	0.16	−0.03	0.16
cefepime-ICU						
(Intercept)	−1308.32	556.53	−2.35	**0.02**	−2416.28	−200.35
time.id	0.71	1.20	0.59	0.56	−1.69	3.10
covidtot	0.56	0.21	2.72	**0.01**	0.15	0.98

urg	−3.67	2.11	−1.74	0.09	−7.87	0.53
sej	7.03	2.12	3.32	**0.00**	2.81	11.25
dms	85.42	38.81	2.20	**0.03**	8.15	162.68
cefepime-Medicine						
(Intercept)	7.20	2.31	3.11	**0.00**	2.60	11.80
time.id	0.03	0.01	3.32	**0.00**	0.01	0.05
covidtot	0.02	0.01	1.52	0.13	−0.01	0.05
chimio	−0.15	0.06	−2.69	**0.01**	−0.26	−0.04
dms	−1.07	0.48	−2.25	**0.03**	−2.03	−0.12
cefotaxime-ICU						
(Intercept)	−4437.32	1142.42	−3.88	**0.00**	−6713.14	−2161.50
time.id	−2.28	2.45	−0.93	0.35	−7.15	2.60
covidtot	0.76	0.40	1.92	0.06	−0.03	1.55
diab	9.84	6.51	1.51	0.13	−3.13	22.81
sej	19.73	4.24	4.65	**0.00**	11.29	28.18
dms	266.57	78.98	3.38	**0.00**	109.23	423.91
cefotaxime-Medicine						
(Intercept)	−6.34	5.97	−1.06	0.29	−18.21	5.54
time.id	−0.03	0.03	−0.97	0.34	−0.09	0.03

covidtot	0.04	0.04	1.02	0.31	−0.03	0.11
dial	0.05	0.01	3.50	**0.00**	0.02	0.07
urg	0.14	0.04	3.53	**0.00**	0.06	0.22
diab	−0.19	0.08	−2.42	**0.02**	−0.35	−0.03
ceftazidime-Medicine						
(Intercept)	−0.46	0.47	−0.98	0.33	−1.40	0.47
time.id	0.00	0.00	0.46	0.64	0.00	0.01
covidtot	0.01	0.01	0.86	0.39	−0.01	0.02
chimio	0.07	0.03	2.49	**0.01**	0.01	0.13
ceftriaxone-ICU						
(Intercept)	14.36	9.08	1.58	0.12	−3.72	32.44
time.id	−0.23	0.16	−1.46	0.15	−0.54	0.08
covidtot	0.00	0.03	−0.11	0.92	−0.06	0.05
cancer	0.45	0.29	1.56	0.12	−0.12	1.03
ceftriaxone-Medicine						
(Intercept)	−1.43	1.63	−0.88	0.38	−4.68	1.81
time.id	−0.01	0.01	−1.33	0.19	−0.02	0.00
covidtot	−0.02	0.01	−1.57	0.12	−0.04	0.00
age75	0.02	0.01	2.43	**0.02**	0.00	0.03

cephalosporin-ICU						
(Intercept)	−17500.07	4593.55	−3.81	**0.00**	−26652.92	−8347.22
time.id	6.98	9.84	0.71	0.48	−12.62	26.58
covidtot	2.09	1.66	1.26	0.21	−1.22	5.39
urg	−36.99	17.20	−2.15	**0.03**	−71.26	−2.72
diab	38.52	26.18	1.47	0.15	−13.65	90.69
sej	87.24	18.66	4.68	**0.00**	50.07	124.42
dms	1032.63	317.56	3.25	**0.00**	399.88	1665.37
cephalosporin-Medicine						
(Intercept)	−37.70	12.63	−2.99	**0.00**	−62.84	−12.56
time.id	0.07	0.06	1.30	0.20	−0.04	0.18
covidtot	0.05	0.07	0.73	0.47	−0.09	0.20
urg	0.25	0.09	2.84	**0.01**	0.07	0.42
sej	0.05	0.02	2.13	**0.04**	0.00	0.09
vvc	1.85	0.84	2.20	**0.03**	0.18	3.52
ciprofloxacin-ICU						
(Intercept)	−972.81	281.83	−3.45	**0.00**	−1534.24	−411.38
time.id	−0.24	0.57	−0.42	0.67	−1.39	0.90
covidtot	−0.11	0.10	−1.11	0.27	−0.32	0.09

diab	5.86	1.15	5.10	**0.00**	3.57	8.14
invdur	0.20	0.10	2.05	**0.04**	0.01	0.39
cen	12.32	4.05	3.04	**0.00**	4.25	20.39
ciprofloxacin-Medicine						
(Intercept)	−2.54	1.25	−2.02	**0.05**	−5.03	−0.04
time.id	0.01	0.01	2.35	**0.02**	0.00	0.02
covidtot	0.00	0.01	−0.47	0.64	−0.02	0.01
urg	0.03	0.01	2.75	**0.01**	0.01	0.04
fluoroquinolone-ICU						
(Intercept)	−713.22	326.19	−2.19	**0.03**	−1363.17	−63.27
time.id	−0.31	0.66	−0.47	0.64	−1.64	1.01
covidtot	−0.16	0.12	−1.38	0.17	−0.40	0.07
diab	5.74	1.77	3.24	**0.00**	2.21	9.27
sej	0.72	0.51	1.40	0.16	−0.30	1.73
invdur	0.23	0.13	1.85	0.07	−0.02	0.49
cen	7.77	4.65	1.67	0.10	−1.49	17.04
fluoroquinolone-Medicine						
(Intercept)	−9.17	3.23	−2.84	**0.01**	−15.60	−2.73
time.id	−0.05	0.02	−2.21	**0.03**	−0.09	0.00

covidtot	−0.02	0.02	−0.98	0.33	−0.07	0.02
dial	0.04	0.01	4.52	**0.00**	0.02	0.06
urg	0.06	0.03	2.36	**0.02**	0.01	0.12
gentamicin-Medicine						
(Intercept)	−0.05	0.25	−0.21	0.83	−0.55	0.45
time.id	−0.01	0.00	−4.31	**0.00**	−0.01	−0.01
covidtot	−0.01	0.00	−2.06	**0.04**	−0.02	0.00
dial	0.00	0.00	2.86	**0.01**	0.00	0.01
inv	0.43	0.26	1.62	0.11	−0.10	0.96
macrolide-ICU						
(Intercept)	−1781.15	570.50	−3.12	**0.00**	−2917.64	−644.66
time.id	−0.12	0.96	−0.12	0.90	−2.03	1.80
covidtot	0.19	0.16	1.20	0.23	−0.13	0.51
cancer	3.56	2.11	1.68	0.10	−0.65	7.77
sej	4.23	1.51	2.79	**0.01**	1.21	7.24
deces	−2.60	1.72	−1.52	0.13	−6.02	0.81
inv	2.87	1.54	1.86	0.07	−0.20	5.93
dms	62.96	29.12	2.16	**0.03**	4.94	120.98
cen	9.91	6.53	1.52	0.13	−3.11	22.93

macrolide-Medicine						
(Intercept)	−11.73	11.76	−1.00	0.32	−35.15	11.69
time.id	0.00	0.01	−0.21	0.84	−0.02	0.01
covidtot	0.02	0.02	1.00	0.32	−0.01	0.04
chimio	0.16	0.06	2.79	**0.01**	0.05	0.28
pat	−0.01	0.01	−1.65	0.10	−0.03	0.00
cen	0.23	0.15	1.52	0.13	−0.07	0.53
metronidazole-Medicine						
(Intercept)	−1.52	4.43	−0.34	0.73	−10.34	7.29
time.id	−0.02	0.02	−0.69	0.49	−0.06	0.03
covidtot	0.00	0.03	−0.08	0.94	−0.05	0.05
dial	0.02	0.01	2.08	**0.04**	0.00	0.04
urg	0.08	0.03	2.76	**0.01**	0.02	0.14
diab	−0.13	0.06	−2.20	**0.03**	−0.25	−0.01
pena-ICU						
(Intercept)	238.04	149.05	1.60	0.11	−58.81	534.90
time.id	−0.35	1.33	−0.27	0.79	−3.00	2.29
covidtot	−0.27	0.22	−1.20	0.23	−0.71	0.18
diab	7.74	2.64	2.93	**0.00**	2.48	13.01

invdur	−0.42	0.22	−1.89	0.06	−0.87	0.02
pena-Medicine						
(Intercept)	22.83	4.36	5.23	**0.00**	14.15	31.51
time.id	0.03	0.02	1.55	0.12	−0.01	0.07
covidtot	0.02	0.05	0.41	0.68	−0.07	0.11
diab	−0.31	0.11	−2.88	**0.01**	−0.53	−0.10
penaac-Medicine						
(Intercept)	21.32	5.01	4.25	**0.00**	11.34	31.30
time.id	−0.24	0.05	−5.13	**0.00**	−0.34	−0.15
covidtot	0.44	0.08	5.34	**0.00**	0.27	0.60
dial	0.05	0.03	1.90	0.06	0.00	0.11
pip_taz-Medicine						
(Intercept)	−4.14	1.55	−2.67	**0.01**	−7.22	−1.05
time.id	0.00	0.01	0.31	0.76	−0.02	0.02
covidtot	0.01	0.01	0.52	0.60	−0.02	0.03
dial	0.01	0.00	3.17	**0.00**	0.01	0.02
urg	0.03	0.01	2.62	**0.01**	0.01	0.06
vvc	−0.27	0.13	−2.13	**0.04**	−0.52	−0.02
invdur	−0.31	0.22	−1.37	0.17	−0.75	0.14

sha-ICU						
(Intercept)	−408899.16	147433.15	−2.77	**0.01**	−702801.78	−114996.54
time.id	370.04	241.38	1.53	0.13	−111.15	851.23
covidtot	141.53	45.63	3.10	**0.00**	50.57	232.49
chimio	23890.21	13551.42	1.76	0.08	−3124.05	50904.47
diab	856.87	633.66	1.35	0.18	−406.31	2120.06
cancer	−786.89	549.44	−1.43	0.16	−1882.19	308.41
sej	978.25	418.35	2.34	**0.02**	144.29	1812.21
dms	10540.33	7657.75	1.38	0.17	−4725.13	25805.79
cen	3695.62	1688.75	2.19	**0.03**	329.15	7062.09
sha-Medicine						
(Intercept)	−54807.84	20774.69	−2.64	**0.01**	−96167.08	−13448.61
time.id	6.56	151.61	0.04	0.97	−295.28	308.39
covidtot	247.18	136.05	1.82	0.07	−23.68	518.03
dial	99.72	71.28	1.40	0.17	−42.19	241.64
urg	235.18	153.89	1.53	0.13	−71.18	541.55
age80	212.12	145.22	1.46	0.15	−76.99	501.24
vancomycin-ICU						
(Intercept)	−42.79	64.44	−0.66	0.51	−171.05	85.47

time.id	−0.12	0.76	−0.16	0.88	−1.63	1.39
covidtot	−0.06	0.13	−0.49	0.63	−0.32	0.19
cancer	3.50	1.72	2.04	**0.04**	0.09	6.91
sej	0.81	0.47	1.72	0.09	−0.13	1.76
vancomycin-Medicine						
(Intercept)	−1.55	0.76	−2.02	**0.05**	−3.06	−0.03
time.id	−0.01	0.00	−2.52	**0.01**	−0.01	0.00
covidtot	0.03	0.01	4.76	**0.00**	0.02	0.05
age80	0.02	0.01	3.10	**0.00**	0.01	0.03
vvc	0.21	0.08	2.69	**0.01**	0.05	0.36
invdur	−0.23	0.14	−1.62	0.11	−0.50	0.05

Appendix 5 - RQ4 Full Regression Table

term	estimate	std.error	statistic	p.value	conf.low	conf.high
ab_all-ICU						
(Intercept)	0.00	0.50	263.93	**0.00**	0.00	0.00
time.id	0.99	0.01	0.24	0.62	0.97	1.02
covidtot	1.00	0.00	0.19	0.66	1.00	1.00
macrolide	1.00	0.00	17.18	**0.00**	1.00	1.00
ab_all-Medicine						
(Intercept)	0.00	2.56	55.49	**0.00**	0.00	0.00
time.id	1.01	0.02	0.21	0.65	0.97	1.04
covidtot	1.12	0.05	5.82	**0.02**	1.02	1.22
azithromycin	71.62	1.11	14.78	**0.00**	8.11	632.12
sha	1.00	0.00	11.02	**0.00**	1.00	1.00
chimio	1.84	0.14	18.91	**0.00**	1.40	2.43
vvc	0.46	0.32	5.72	**0.02**	0.25	0.87
invdur	5.07	0.29	32.11	**0.00**	2.89	8.89
ab_blood-ICU						
(Intercept)	0.00	0.22	68920.63	**0.00**	0.00	0.00
time.id	1.00	0.01	0.10	0.75	0.99	1.01

covidtot	1.00	0.00	0.04	0.85	1.00	1.00
c3gr_all-ICU						
(Intercept)	0.00	0.30	345.69	**0.00**	0.00	0.01
time.id	0.99	0.01	1.82	0.18	0.98	1.00
covidtot	1.00	0.00	3.18	0.07	1.00	1.00
carbapenem	1.00	0.00	19.57	**0.00**	1.00	1.00
deces	1.01	0.01	1.78	0.18	1.00	1.02
c3gr_all-Medicine						
(Intercept)	0.00	1.01	30.60	**0.00**	0.00	0.03
time.id	1.00	0.00	0.92	0.34	1.00	1.01
covidtot	1.01	0.01	0.75	0.39	0.99	1.02
amikacin	1.42	0.20	3.01	0.08	0.96	2.11
cefotaxime	1.08	0.02	10.74	**0.00**	1.03	1.13
fluoroquinolone	0.92	0.03	9.61	**0.00**	0.87	0.97
vancomycin	0.84	0.11	2.28	0.13	0.67	1.05
age80	0.99	0.01	3.90	**0.05**	0.97	1.00
deces	0.92	0.04	5.33	**0.02**	0.85	0.99
c3gs_all-ICU						
(Intercept)	0.00	0.97	86.99	**0.00**	0.00	0.00

time.id	1.01	0.00	8.52	**0.00**	1.00	1.01
covidtot	1.00	0.00	0.67	0.41	1.00	1.00
amikacin	1.00	0.00	9.91	**0.00**	1.00	1.00
macrolide	1.00	0.00	3.07	0.08	1.00	1.00
metronidazole	1.00	0.00	10.39	**0.00**	1.00	1.00
pena	1.00	0.00	10.57	**0.00**	1.00	1.00
sha	1.00	0.00	2.66	0.10	1.00	1.00
urg	1.02	0.00	14.99	**0.00**	1.01	1.03
vvc	1.01	0.00	9.84	**0.00**	1.01	1.02
dms	1.25	0.06	14.39	**0.00**	1.11	1.41
c3gs_all-Medicine						
(Intercept)	0.00	0.12	2344.56	**0.00**	0.00	0.00
time.id	1.01	0.00	25.49	**0.00**	1.00	1.01
covidtot	0.99	0.00	4.55	**0.03**	0.99	1.00
ciprofloxacin	0.93	0.04	3.61	0.06	0.86	1.00
pena	0.98	0.01	13.45	**0.00**	0.97	0.99
deces	1.04	0.02	4.26	**0.04**	1.00	1.07
invdur	1.09	0.03	10.07	**0.00**	1.04	1.16
candida_blood-ICU						

(Intercept)	0.00	1.05	76.32	**0.00**	0.00	0.00
time.id	1.02	0.01	1.87	0.17	0.99	1.04
covidtot	1.00	0.00	0.93	0.34	1.00	1.00
azithromycin	1.01	0.00	14.70	**0.00**	1.01	1.02
vancomycin	1.00	0.00	15.60	**0.00**	1.00	1.01
deces	0.94	0.02	6.78	**0.01**	0.91	0.99
vvc	1.03	0.01	3.44	0.06	1.00	1.06
crpa_all-ICU						
(Intercept)	0.00	1.13	36.18	**0.00**	0.00	0.01
time.id	1.02	0.01	4.54	**0.03**	1.00	1.03
covidtot	1.00	0.00	1.38	0.24	1.00	1.00
dial	1.00	0.00	2.10	0.15	1.00	1.01
dms	0.88	0.11	1.24	0.27	0.71	1.10
crpa_all-Medicine						
(Intercept)	0.00	3.28	38.34	**0.00**	0.00	0.00
time.id	1.03	0.02	4.44	**0.04**	1.00	1.06
covidtot	0.96	0.05	0.77	0.38	0.88	1.05
fluoroquinolone	0.81	0.10	4.04	**0.04**	0.66	0.99
cancer	1.21	0.09	4.86	**0.03**	1.02	1.43

deces	1.63	0.21	5.52	**0.02**	1.08	2.44
vvc	1.80	0.27	4.56	**0.03**	1.05	3.08
inv	0.00	5.02	1.48	0.22	0.00	42.09
eblse_all-ICU						
(Intercept)	0.00	0.56	147.80	**0.00**	0.00	0.00
time.id	1.00	0.01	0.07	0.80	0.98	1.02
covidtot	1.00	0.00	0.00	1.00	1.00	1.00
azithromycin	0.97	0.03	1.92	0.17	0.92	1.01
carbapenem	1.00	0.00	4.40	**0.04**	1.00	1.00
dial	0.99	0.00	5.34	**0.02**	0.99	1.00
deces	1.02	0.01	3.89	**0.05**	1.00	1.03
vvc	1.01	0.01	2.71	0.10	1.00	1.02
entero_all-ICU						
(Intercept)	0.01	0.31	271.00	**0.00**	0.00	0.01
time.id	1.01	0.00	7.40	**0.01**	1.00	1.01
covidtot	1.00	0.00	22.41	**0.00**	1.00	1.00
ceftazidime	1.00	0.00	12.47	**0.00**	1.00	1.00
fluoroquinolone	1.00	0.00	4.11	**0.04**	1.00	1.00
macrolide	1.00	0.00	3.52	0.06	1.00	1.00

metronidazole	1.00	0.00	5.55	**0.02**	1.00	1.00
pena	1.00	0.00	5.05	**0.02**	1.00	1.00
urg	1.01	0.01	5.89	**0.02**	1.00	1.02
sej	0.99	0.00	11.17	**0.00**	0.98	0.99
age80	1.02	0.01	9.53	**0.00**	1.01	1.03
vvc	1.01	0.00	12.47	**0.00**	1.01	1.02
entero_all-Medicine						
(Intercept)	0.01	0.40	159.70	**0.00**	0.00	0.01
time.id	1.01	0.00	36.93	**0.00**	1.01	1.01
covidtot	1.00	0.00	2.10	0.15	0.99	1.00
ciprofloxacin	0.93	0.04	3.22	0.07	0.86	1.01
metronidazole	1.03	0.01	5.25	**0.02**	1.00	1.05
pena	0.98	0.01	11.06	**0.00**	0.97	0.99
sej	1.00	0.00	2.58	0.11	1.00	1.00
invdur	1.08	0.03	6.65	**0.01**	1.02	1.15
entero_blood-ICU						
(Intercept)	0.00	0.44	244.36	**0.00**	0.00	0.00
time.id	1.00	0.00	1.04	0.31	1.00	1.01
covidtot	1.00	0.00	8.01	**0.00**	1.00	1.00

azithromycin	0.99	0.00	9.47	**0.00**	0.98	1.00
carbapenem	1.00	0.00	10.74	**0.00**	1.00	1.00
fluoroquinolone	1.00	0.00	3.64	0.06	1.00	1.00
metronidazole	1.00	0.00	10.52	**0.00**	1.00	1.00
vvc	1.01	0.01	3.66	0.06	1.00	1.02
entero_blood-Medicine						
(Intercept)	0.00	0.63	122.45	**0.00**	0.00	0.00
time.id	1.02	0.01	12.50	**0.00**	1.01	1.03
covidtot	0.99	0.01	1.78	0.18	0.97	1.01
azithromycin	0.58	0.24	5.21	**0.02**	0.36	0.93
c3g	1.07	0.02	13.77	**0.00**	1.03	1.11
sha	1.00	0.00	6.24	**0.01**	1.00	1.00
dial	0.99	0.00	3.46	0.06	0.99	1.00
invdur	1.39	0.08	17.62	**0.00**	1.19	1.61
hypercase_all-ICU						
(Intercept)	0.00	0.23	605.89	**0.00**	0.00	0.01
time.id	0.99	0.01	3.67	0.06	0.98	1.00
covidtot	1.00	0.00	11.35	**0.00**	1.00	1.00
carbapenem	1.00	0.00	13.27	**0.00**	1.00	1.00

penaac	1.00	0.00	4.95	**0.03**	1.00	1.00
hypercase_all-Medicine						
(Intercept)	0.00	7.22	14.36	**0.00**	0.00	0.00
time.id	1.01	0.01	3.53	0.06	1.00	1.02
covidtot	1.03	0.01	10.31	**0.00**	1.01	1.05
sha	1.00	0.00	8.36	**0.00**	1.00	1.00
chimio	1.17	0.05	10.35	**0.00**	1.06	1.29
age80	0.98	0.01	3.61	0.06	0.96	1.00
cen	1.33	0.10	8.15	**0.00**	1.09	1.62
hypercase_blood-ICU						
(Intercept)	0.00	0.47	238.36	**0.00**	0.00	0.00
time.id	0.99	0.01	1.53	0.22	0.96	1.01
covidtot	1.00	0.00	8.28	**0.00**	1.00	1.01
azithromycin	0.96	0.02	5.20	**0.02**	0.94	0.99
fluoroquinolone	1.00	0.00	2.29	0.13	1.00	1.01
hypercase_blood-Medicine						
(Intercept)	0.00	3.59	8.35	**0.00**	0.00	0.04
time.id	1.03	0.01	4.95	**0.03**	1.00	1.05
covidtot	1.01	0.01	0.40	0.52	0.98	1.04

azithromycin	0.10	0.71	10.05	**0.00**	0.03	0.42
ceftazidime	1.43	0.20	3.10	0.08	0.96	2.14
chimio	1.22	0.13	2.48	0.12	0.95	1.57
diab	0.93	0.06	1.61	0.20	0.82	1.04
mssa_all-ICU						
(Intercept)	0.00	0.31	441.37	**0.00**	0.00	0.00
time.id	1.00	0.01	0.01	0.92	0.99	1.01
covidtot	1.00	0.00	4.77	**0.03**	1.00	1.00
cephalosporin	1.00	0.00	28.23	**0.00**	1.00	1.00
metronidazole	1.00	0.00	7.63	**0.01**	1.00	1.00
deces	1.02	0.01	11.27	**0.00**	1.01	1.04
mssa_all-Medicine						
(Intercept)	0.00	0.28	840.05	**0.00**	0.00	0.00
time.id	1.01	0.00	3.00	0.08	1.00	1.01
covidtot	1.00	0.01	0.00	0.96	0.98	1.02
fluoroquinolone	1.11	0.03	11.42	**0.00**	1.04	1.18
macrolide	0.86	0.06	6.43	**0.01**	0.77	0.97
invdur	1.27	0.09	6.78	**0.01**	1.06	1.53
pa_all-ICU						

(Intercept)	0.01	0.26	376.18	**0.00**	0.00	0.01
time.id	1.00	0.00	0.13	0.71	0.99	1.01
covidtot	1.00	0.00	17.77	**0.00**	1.00	1.00
cephalosporin	1.00	0.00	5.29	**0.02**	1.00	1.00
macrolide	1.00	0.00	1.65	0.20	1.00	1.00
metronidazole	1.00	0.00	8.67	**0.00**	1.00	1.00
dial	1.00	0.00	4.08	**0.04**	1.00	1.00
cancer	0.98	0.01	5.71	**0.02**	0.97	1.00
pa_all-Medicine						
(Intercept)	0.00	0.85	207.31	**0.00**	0.00	0.00
time.id	1.01	0.00	10.38	**0.00**	1.01	1.02
covidtot	0.98	0.01	4.56	**0.03**	0.96	1.00
cephalosporin	1.02	0.01	3.49	0.06	1.00	1.05
penaac	1.03	0.02	2.56	0.11	0.99	1.07
chimio	1.09	0.03	7.58	**0.01**	1.03	1.17
deces	1.20	0.06	9.10	**0.00**	1.07	1.35
pa_blood-ICU						
(Intercept)	0.00	0.38	315.44	**0.00**	0.00	0.00
time.id	0.99	0.01	0.68	0.41	0.98	1.01

covidtot	1.00	0.00	10.68	**0.00**	1.00	1.01
amikacin	1.00	0.00	10.82	**0.00**	1.00	1.01
cefotaxime	1.00	0.00	5.70	**0.02**	1.00	1.00
pa_blood-Medicine						
(Intercept)	0.00	2.61	40.20	**0.00**	0.00	0.00
time.id	0.99	0.01	1.52	0.22	0.97	1.01
covidtot	1.01	0.02	0.38	0.54	0.97	1.05
cephalosporin	1.12	0.03	14.20	**0.00**	1.06	1.19
vancomycin	0.24	0.41	12.25	**0.00**	0.11	0.54
chimio	1.19	0.11	2.82	0.09	0.97	1.47
deces	1.46	0.13	8.49	**0.00**	1.13	1.89
sm_all-ICU						
(Intercept)	0.00	0.46	214.27	**0.00**	0.00	0.00
time.id	1.00	0.01	0.21	0.64	0.99	1.02
covidtot	1.00	0.00	1.29	0.26	1.00	1.00
cephalosporin	1.00	0.00	24.29	**0.00**	1.00	1.00
penaac	1.00	0.00	10.93	**0.00**	1.00	1.00
mrsa_all-Medicine						
(Intercept)	0.00	1.96	38.36	**0.00**	0.00	0.00

time.id	1.01	0.02	0.35	0.56	0.97	1.05
covidtot	0.93	0.04	2.92	0.09	0.86	1.01
ceftriaxone	0.56	0.33	3.04	0.08	0.29	1.07
penaac	1.10	0.05	3.67	0.06	1.00	1.22

Abstract *en Français*