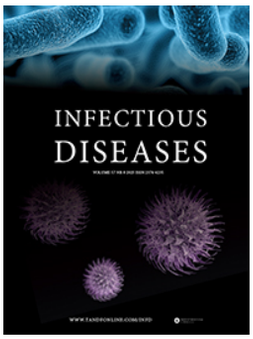

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RESEARCH ARTICLE

Comparison of antibiotic consumption and resistance in intensive care units in France before and during the COVID-19 pandemic

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ABSTRACT

The COVID pandemic significantly impacted intensive care unit (ICU) antibiotic consumption (AMC) and resistance (AMR). This study examines these effects over a 6-year period in 6 French ICUs.

Objectives: To evaluate the impact of the COVID pandemic on AMC and AMR in ICUs, focusing on changes in consumption patterns and bacterial resistance profiles.

Methods: Data were prospectively collected from 3 university hospitals, covering 6ICUs. The study compared two periods: before (2017–2019: befPAND period) and during (2020–2022: perPAND period) the pandemic. Antibiotic consumption was measured using Defined Daily Doses (DDD) globally per unit and per 1,000 patient-days in each unit. Antibiotic resistance was assessed from bacterial cultures from selected clinical cultures taken from ICU patients. Statistical analysis compared trends between the two periods.

Results: Total antibiotic consumption of all units increased by 28% during the pandemic period, but DDD/1000 patient-days of all units remained stable. There was an increase in the use of broad-spectrum antibiotics, particularly those classified as 'Reserve' by the WHO (5.6% to 9.6%, $p < 0.0001$).

Results: The number of positive cultures increased in the perPAND period for *Staphylococcus epidermidis*, *Enterobacter* sp., and *Pseudomonas aeruginosa*. Resistance levels showed an increase in *Enterococcus* species, *Pseudomonas aeruginosa,* and *Stenotrophomonas maltophilia*, while methicillin-resistant *Staphylococcus aureus* and 3rd generation cephalosporins enterobacterales resistance remained stable.

Conclusions: The COVID pandemic increased the overall antibiotic consumption, but not the 1000-patients-day consumption in ICUs. However, one of the main effects was to shift usage towards more broad-spectrum antibiotics, which may contribute to growing resistance.

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Introduction

Monitoring and describing antibiotic consumption (AMC) and antibiotic resistance (AMR) in healthcare facilities is an important part of assessing antibiotic stewardship programmes (ASPs) [1]. However, the complexity of the data, due to a significant number of antibiotic molecule categories and bacterial species, makes the message conveyed difficult for intensive care unit (ICU) practitioners to understand.

ICUs are an appropriate focus for ASP efforts because of the massive use of antibiotics in relation to several factors, including the frequency of previous antibiotic treatments and the severity of resistant bacterial infections [2]. Patients also present a high risk of acquiring healthcare-associated infections due to frequent invasive procedures. Since the beginning of the COVID-19 pandemic, despite this being related to a viral infection, there have been concerns about the concomitant increase in antibiotic resistance due to the extensive use of antibiotics associated with a feared or real bacterial co- or superinfection [3].

The aim of this multicenter study aimed to evaluate the effect of the COVID-19 pandemic on AMC and AMR in a network of ICUs in France.

Material and methods

Setting

This study used data collected prospectively over, 6 years (2017–2022) in three university hospitals, part of a hospital system serving a city of 1.4 million inhabitants in France. Before the pandemic period (2017–19:befPAND), these hospitals comprised six adult ICUs included in our study. During the pandemic period (2020–22: perPAND), several ICUs were created by repurposing clinical units into ICUs during the different waves (extra-ICUs), changing the recruitment and profile of patients admitted to ICUs. Five of the ICUs (two medical units, two surgical units, and one mixed unit) had to deal with COVID ICU patients in their regular units and in extra-ICU beds managed by their own medical team (COVID unit: COV units); one mixed ICU remained fully dedicated to the COVID-free patients during the 3-year pandemic (FreeCOV unit) and will serve as a reference unit.

Data source and indicators

Antibiotic consumption

The data on the consumption on antibiotics for systemic use for each ICU was collected from the hospital pharmacy over a period of six years (2017–2022). It was reported as an aggregated metric of Defined Daily Dose (DDD) per 1000 patient-days. The number of patient-days and the proportion of COVID patients were obtained from the hospital information system. The DDD values were calculated based on the number of antibiotic units delivered to each ICU, using the Anatomical Therapeutic Chemical (ATC) index with DDDs that are updated annually by the WHO Collaborating Centre, along with the ATC/DDD tool [4]. We described antibiotic consumption according to the 14 classes of antibiotics [5] belonging to the J01 group of the ATC classification (Table S1), the AWaRe classification developed by the WHO [6], and the ECDC classification of currently available antibiotics, including broad-spectrum antibiotics (Table S2) [5].

Antibiotic resistance

The database used to analyse bacterial resistance was extracted from the bacteriology laboratory's electronic records, covering a six-year period from 25 January 2017, to 31 December 2022. We extracted data on each culture-positive bacterial isolate from clinical samples taken from ICU patients during their stay in the ICU, for which an antibiogram was performed. To ensure ease of interpretation, only bacterial species and samples listed in a restrictive list (Table S3) were analysed, closely resembling a list developed by the CDC [6]. The following samples were included because they were considered as invasive and carried a risk of resistance in ICU patients: blood cultures, respiratory tract samples of all types (including Broncho Alveolar Lavage [BAL], tracheal aspiration, and mini BAL), all catheter samples (including central venous, arterial, and peripherally inserted central catheters), and cerebrospinal fluid (CSF).

The following bacteria were selected to be included as they are the most prevalent in ICU patients. Among Gram-positive cocci: *Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium* and *Streptococcus pneumoniae*; among the Gram-negative bacteria: all Enterobacterales and specific non-fermenting bacteria such as *Pseudomonas aeruginosa, Acinetobacter species,* and *Stenotrophomonas maltophilia*. All bacteria and resistance indicators are described in Table S4. Duplicate strain elimination was performed in two stages: only one sample per type of sample and per patient was retained. Then, for the same antibiogram, only the oldest sample for each patient was retained, regardless of the sample type. The sample with the most complete antibiotic susceptibility testing was retained. The level of resistance was assessed based on the proportion of resistance for a limited number of key antibiotics to ensure the clarity of the results (Table S4).

Statistical analysis

Antibiotic consumption was expressed as DDDs/1000 patient-days, the data were compared between the two periods by the Chi-squared test. Linear regression was applied to analyse trends in consumption throughout the study period. Trends were described by the regression coefficient (average annual change) and significance (p value) from the regression formula. P value of < 0.05 was considered as significant.

The level of resistance of the two periods were computed in terms of percentage of resistance in the species for each bacteria and after duplicate strain elimination, and compared using the Chi-squared test.

Results

Patients

During the 6-year study period, 29566 patients were included (14765 patients in the befPAND period and 14801 patients in the perPAND period), corresponding to a total of 186847 patient-days (81832 befPAND *vs* 105015 perPAND). The number of patient-days increased due to longer stays and bed number extension in the ICUs in the perPAND period. Overall, 3000 COVID patients were included (Table 1).

Antibiotic consumption

Total DDD

Total antibiotic consumption increased from 122003 DDDs in the befPAND period to 156126 DDDs in the perPAND, a 28% rise. However, the number of DDDs/1000 patient-days remained stable both in COV-units (1495 befPAND *vs* 1496 perPAND; $p = 0.96$), and in the COVID-free unit (1521 befPAND *vs* 1576 perPAND, $p = 0.56$; Table 2). In both periods, all units had an antibiotic consumption exceeding 1000 DDDs/1000 patient-days.

Table 3 listed some targeted molecules cited as frequently prescribed in ICUs with their DDD: 3of which particularly prescribed in ICUs (third-generation cephalosporins: cefotaxime and ceftriaxone, and anti-*Pseudomonas* cephalosporin ceftazidime) or second-line antibiotics (piperacillin-tazobactam, cefepime, carbapenem, colimycin, linezolid, daptomycin, tigecycline, ceftazidime-avibactam, ceftolozane-tazobactam) [7]. Table 4 shows most prescribed molecules up to 75% of the total antibiotics DDDs

Table 1. Total number of patients and of patient-days during the befPAND and the perPAND period in the 6 studied ICUs.

Year	2017	2018	2019	befPAND period	2020	2021	2022	perPAND period
Number of admitted patients	5001	4842	4922	14765	5475	4738	4588	14801
In COV units	-	-	-	-	*4782*	*4032*	*4054*	*12868*
Of which N COVID-19 patients	-	-	-	-	*1216*	*1354*	*430*	*3000*
in FreeCOV unit	-	-	-	-	*693*	*706*	*534*	*1938*
Number of patient-days	26910	27469	27453	81832	36041	36867	32107	105015

COVID-19 units had patients with and without COVID-19 (COVunits), and one was free of COVID-19 patients (FreeCOV unit).

Table 2. Total defined daily doses (DDD)/1000 patient-days by unit and overall: the first unit in hospital A was an almost COVID-free unit (free COV unit).

Hospital	Unit	2017	2018	2019	befPAND	2020	2021	2022	perPAND
A	FreeCOV unit	1431	1416	1702	1521	1483 (2)	1561 (4)	1686 (4)	1576 (8)
A	Mixed ICU	1944	1615	1345	1644	1558 (350)	1470 (348)	1531 (96)	1518 (794)
B	Surgical ICU	1242	1357	1219	1275	1437 (266)	1466 (404)	1489 (111)	1463 (781)
B	Medical ICU	1687	1476	1270	1472	1500 (237)	2107 (235)	1841 (82)	1800 (554)
C	Surgical ICU	1339	1593	1310	1408	1344 (60)	1484 (81)	1304 (33)	1380 (174)
C	Medical ICU	1818	1683	1442	1649	1116 (301)	1241 (282)	1373 (104)	1236 (687)
	Mean COV units	1577	1524	1381	1495	1406	1555	1537	1496
	Mean, all units	1567	1537	1375	1491	1400	1559.	1502	1487

The second unit of hospital A, the third and fourth units in hospital B, the fifth and sixth units of hospital C were all units with COVID and non-COVID patients. During the perPAND period, the numbers of COVID 19 patients by units are associated between brackets.

Table 3. Defined daily doses (DDD)/1000 patient-days of targeted molecules in ICU.

Molecules	2017	2018	2019	befPAND	2020	2021	2022	perPAND	*p* value
Third generation cephalosporins: cefotaxime and ceftriaxone	170	188	199	185	196	189	166	184	0.92
Cefotaxime	*100*	*147*	*170*	*140*	*173*	*172*	*149*	*165*	0.44
Ceftriaxone	*70*	*40*	*29*	*46*	*23*	*16*	*18*	*19*	0.12
Ceftazidime	30	25	28	28	42	48	36	42	0.09
Piperilline-tazobactam	144	71	126	114	119	131	143	131	0.55
Cefepime	56	107	67	77	80	95	67	81	0.74
Carbapenems (imipenem, meropenem)	104	110	77	97	104	111	130	114	0.41
Colimycine	27	20	11	19	15	22	19	19	0.92
Linezolid	23	31	30	28	38	50	55	48	0.02
Daptomycine	14	34	29	26	48	54	70	57	0.04
Tigecyclin	1	2	1	1	1	2	1	1	–
Ceftazidime-avibactam + ceftolozane-tazobactam	3	4	6	4	5	10	18	11	0.15
Total DDDs	572	591	574	579	648	711	705	688	

The last line is the total of these targeted molecules. *P*-values compare the DDD/1000 patient-days between the 2 period befPAND and perPAND.

Table 4. Antibiotics agents in DDD accounting up to 75% of antibiotic use in ICUs.

	BefPAND period			PerPAND period	
Molecule	DDDs/1 000 patient-days (percentage)	Cumulated %	Molecule	DDDs/1 000 patient-days (percentage)	Cumulated %
Cefotaxime	140 (9.4)	9.4	Cefotaxime	165 (11.1)	11.1
Amoxicillin – clavulanic acid	136 (9.1)	18.5	Piperacillin - tazobactam	131 (8.8)	19.9
Piperacillin - tazobactam	114 (7.6)	26.1	Amoxicillin – clavulanic acid	111 (7.5)	27.4
Sulfamethoxazole - trimethoprim	108 (6.8)	32.9	Meropenem	86 (5.8)	33.2
Vancomycin	86 (5.8)	38.6	Cefepime	81 (5.4)	38.6
Metronidazole	86 (5.7)	44.4	Amikacin	71 (4.8)	43.4
Cefepime	77 (5.1)	49.5	Sulfamethoxazole - trimethoprim	70 (4.7)	48.1
Amikacin	72 (4.8)	54.3	Vancomycin	69 (4.7)	52.8
Amoxicillin	70 (4.7)	59.0	Amoxicillin	63 (4.2)	57.0
Spiramycin	55 (3.7)	62.6	Erythromycin	62 (4.1)	61.1
Erythromycin	48 (3.2)	65.9	Daptomycin	57 (3.8)	64.9
Imipenem	48 (3.2)	69.1	Cefazoline	50 (3.4)	68.3
Ceftriaxone	46 (3.1)	72.2	Linezolid	48 (3.2)	71.5
Meropenem	45 (3.0)	75.2	Metronidazole	45 (3.0)	74.5
Total top 15 DDD	1131		Total top 15 DDD	1109	

prescription in both period [8]. Cefotaxime, amoxicillin-clavulanic acid and piperacillin-tazobactam were the three most commonly consumed antibiotics.

Both the AWaRe and ECDC classifications found a decrease in the consumption of access group (AWaRe) and Standard group (ECDC) during the befPAND period. The Access-to-Watch ratio of the AWaRe classification decreased during the befPAND period from 0.72 to 0.60 in the perPAND period, $p = 0.0172$. It should also be noted that the antibiotic consumption of the Reserve group of the AWaRe classification nearly doubled, increasing from 5.6% to 9.6%, $p < 0.0001$ (Table 5).

Table 5. Classification of antibiotics according to the WHO (AWaRe) and ECDC classifications based on their impact on bacterial resistance.

	Year	2017	2018	2019	befPAND	2020	2021	2022	perPAND
AWARE	Access	623 (39.8)	609 (39.7)	534 (38.8)	588 (39.4)	471 (33.6)	508 (32.6)	523 (34.8)	500 (33.6)
	Watch	868 (55.4)	831 (54.1)	762 (55.4)	820(55.0)	813 (58.1)	902 (57.9)	800 (53.3)	840 (56.7)
	Access-Watch ratio	0.72	0.73	0.70	0.72	0.58	0.56	0.65	0.60
	Reserve	75 (4.8)	96 (6.3)	79 (5.7)	83 (5.6)	114 (8.1)	144 (9.2)	172 (11.4)	142 (9.6)
ECDC	Standard	897 (57.3)	844 (54.9)	730 (53.1)	822 (55.2)	678 (48.4)	752 (48.3)	712 (47.4)	714 (48.0)
	Broad spectrum	670 (42.7)	693 (45.1)	645 (46.9)	669 (44.8)	722 (51.6)	807 (51.7)	790 (52.6)	773 (52.0)
	Total	1567	1537	1375	1491	1400	1560	1502	1487

Antibiotic resistance

The number of positive cultures increased from 4702 positive samples in the befPAND period to 9305 in the perPAND period (Respiratory samples: 3091 *vs* 5474; blood samples: 1611 *vs* 3831). The relative frequency of each bacterial species was also different between the two periods; there was a higher proportion of *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, and a lower proportion of *Staphylococcus aureus* and *Escherichia coli* (Table 6) in the perPAND period compared to the befPAND period. Table 7 reports the resistance levels to key antibiotics for the principal bacteria isolated in ICU patients: Gram-positive cocci, different enterobacterales and non-fermenting Gram-negative bacteria.

Among Gram-positive bacteria, methicillin resistance for *Staphylococcus aureus* remained stable. Amoxicillin-resistant *Enterococcus* species (*faecalis* and *faecium*) increased ($p = 0.006$) only for Enterococcus faecium. Among Gram-negative bacteria, Enterobacterales were the most common family, rising from 1482 *vs* 2548 strains. Resistance to third-generation cephalosporins was stable for *Escherichia coli* (NS) and *Enterobacter* spp. (the most increased Enterobacterales), and decreased for *Klebsiella* spp. ($p < 0.005$). *Klebsiella pneumoniae* (prePAND: 249 strains; perPAND: 510 strains, with 37.3% and 30.2% 3GC resistance, respectively) is more prevalent than *Klebsiella oxytoca* (prePAND: 77 strains; perPAND: 137 strains, with 19.5% and 10.9% 3GC resistance, respectively). Resistance to 3rd generation cephalosporins (3GC) was reduced in both *Klebsiella* species ($p < 0.001$). Among *Enterobacter* species, the most prevalent was *Enterobacter cloacae* (49% and 58% in the pre- and per-PAND periods, respectively), which comparable resistance to 3rd generation cephalosporins. Among non-fermenting Gram-negative bacteria, the combined resistance of *Pseudomonas aeruginosa* to ceftazidime and carbapenems increased significantly from 10%to 13% ($p = 0.04$). The frequence of *Acinetobacter* sp. was limited (less than 100 positive cultures) as well as *Acinetobacter baumanii* also (less than 50 positive cultures in the pandemia period. Resistance to carbapenems (meropenem, imipenem) of *Acinetobacter* spp. did not decrease significantly on a limited number of strains. The level of resistance of *Stenotrophomonas maltophilia* to Sulfamethoxazole/Trimethoprim was increased ($p < 0.0001$) (Table 7).

Discussion

The aim of this study was double: to summarise the use of antibiotics and describe the relationship between antibiotics use and resistance, in data easy to read for clinicians involved in ICUs

Despite some limitations, the use of WHO AWaRe seems to be a recognised metrics to described antibiotics use [9]. The main result of the present study is the stability of antibiotic consumption in terms of DDD/1000 patient-days over the two periods, despite an increase in total DDD. The latter is related to longer lengths of stay, accompanied by an increase in bed capacity, but without a notable change in the total number of patients despite a decrease in the number of surgical patients (due to surgery cancellation) and trauma patients (resulting from changes in traffic patterns during lockdown) during the COVID-19 pandemic. The increase of length of stay is explained by several factors. On the one hand, due to overwork, and, possibly a lack of experience among staff assigned to the additional ICU beds, adherence to infection prevention and control measures was likely reduced [10]. On the other hand, pulmonary secondary superinfections increased severity and excess mortality [11]. During the initial phase of the pandemic, the tendency was to overprescribe prophylactic treatments despite the viral nature of the infection, due to the fear of initial bacterial co-infections [3,12]. Subsequent published study have

Table 6. Bacteria isolated in respiratory, catheter-related, CNS infections and all type of bloodstream infections up to 75%. NfreeCOV unit: number of strains in the COVID-free unit.

befPAND ($N = 4556$)	N (%)	Cumulated percentage	NCOV unit ($N = 604$)	Per PAND ($N = 9024$)	N (%)	Cumulated percentage	NCovid free ($N = 1692$)
Staphylococcus aureus	754 (16.5)	16.5	91	*Pseudomonas aeruginosa*	1440 (16.0)	16.0	228
Pseudomonas aeruginosa	659 (14.5)	31.0	93	*Staphylococcus epidermidis*	1346 (14.9)	30.9	362
Escherichia coli	499 (11.0)	42.0	79	*Staphylococcus aureus*	999 (11.1)	41.9	148
Staphylococcus epidermidis	363 (8.0)	49.9	59	*Escherichia coli*	713 (7.9)	49.8	108
Klebsiella pneumonia	280 (6.1)	56.1	35	*Klebsiella pneumoniae*	579 (6.4)	56.3	91
Enterobacter cloacae	182 (4.0)	60.1	22	*Enterobacter cloacae*	341 (3.8)	60.0	53
Streptococcus pneumoniae	180 (4.0)	64.0	0	*Enterobacter aerogenes*	300 (3.3)	63.4	36
Stenotrophomonas maltophilia	159 (3.5)	67.5	16	*Staphylococcus hominis*	294 (3.3)	66.6	11
Enterococcus faecalis	117 (2.6)	70.1	18	*Stenotrophomonas maltophilia*	276 (3.1)	69.7	40
Enterobacter aerogenes	114 (2.5)	72.6	17	*Enterococcus faecalis*	226 (2.5)	72.2	54

Table 7. Antibiotic resistance of bacterial strains isolated in ICUs classified according to the type of bacteria.

		Meticillin-resistant *S. aureus* % (*n*/*N*)		Amoxicillin-resistant *Enterococcus* sp % (*n*/*N*)	
Hospital	Type of unit	befPAND	perPAND	befPAND	perPAND
A	freeCOV- unit	14.7 (11/75)	2.4 (3/127)	44.1 (15/34)	25.6 (20/78)
A	Mixed ICU	8.0 (7/87)	6.5 (6/92)	28.0 (7/25)	35.6 (21/59)
B	Surgical ICU	4.8 (2/42)	4.5 (3/66)	56.1 (23/41)	50.0 (24/48)
B	Medical ICU	11.4 (17/149)	6.2 (13/209)	45.1 (23/51)	30.8 (28/91)
C	Surgical ICU	10.2 (17/167)	9.9 (17/171)	46.4 (13/28)	30.0 (6/20)
C	Medical ICU	2.7 (4/148)	6.9 (14/204)	38.7 (12/31)	17.0 (9/53)
Total COVID-19 units		7.9 (47/593)	7.1 (53/742)	44.3 (93/210)	32.5 (88/275)
Total all units		8.7 (58/668)	6.4 (56/689)	44.3 (108/244)	25.6 (108/353)

		E. coli 3rdGC resistant		Klebsiella 3rdGC resistant		Enterobacter sp. 3rdGC resistant		Other Enterobacterales 3rdGC RESISTANT	
Hospital	Type of unit	befPAND	perPAND	befPAND	PerPAND	BefPAND	PerPAND	befPAND	PerPAND
A	FreeCOV-unit	16.4 (11/67)	10.8 (9/83)	33.3 (13/39)	18.1 (17/94)	32.6 (14/43)	30.7 (23/75)	0 (0/29)	13.9 (11/79)
A	Mixed ICU	13.8 (8/58)	12.3 (9/73)	41.5 (17/41)	13.9 (10/72)	29.3 (12/41)	45.0 (18/40)	9.3 (4/43)	12.5 (4/32)
B	Surgical ICU	4.4 (2/45)	8.6 (5/58)	37.5 (18/48)	29.2 (14/48)	56.821/37	52.0 (26/50)	21.7 (5/23)	17.6 (6/34)
B	Medical ICU	7.9 (7/89)	9.3 (15/161)	26.9 (18/67)	23.1 (36/156)	44.1 (26/59)	58.7 (98/167)	7.6 (5/66)	11.9 (18/151)
C	Surgical ICU	15.4 (14/91)	9.5 (9/95)	35.9 (23/64)	41.8 (38/91)	53.7 (36/67)	47.3 (44/93)	13.2 (7/53)	15.2 (14/92)
C	Medical ICU	6.7 (6/89)	15.7 (18/115)	17.5 (10/57)	21.0 (22/105)	37.0 (27/73)	42.3 (52/123)	9.8 (5/51)	7.8 (10/128)
Total COVID-19 units		10.9 (48/439)	11.1 (65/585)	31.3 (99/316)	24.2 (137/566)	42.5 (136/320)	47.6 (261/548)	11.4 (26/229)	11.8 (61/518)
Total all units		11.7 (59/506)	11.1 (74/668)	31.5 (112/355)	23.3 (154/660)	41.3 (150/363)	45.6 (284/623)	10.1 (26/258)	12.1 (72/597)

		P aeruginosa R cefta R imipenem/meropenem		*Acinetobacter* spp R imipenem/meropenem		*S maltophilia* R TMP/SMX	
Hospital	Type of unit	befPAND	perPAND	befPAND	perPAND	befPAND	perPAND
A	FreeCov-unit	13.8 (8/58)	10.7 (16/149)	0 (0/6)	0 (0/13)	7.7 (1/13)	21.4 (6/28)
A	Mixed ICU	10.2 (9/88)	15.4 (12/78)	0 (0/3)	0 (0/11)	0 (0/18)	18.2 (2/11)
B	Surgical ICU	9.9 (11/111)	16.0 (39/244)	50.0 (1/2)	0 (0/9)	10 (2/20)	27.8 (10/36)
B	Medical ICU	10.5 (11/105)	12.7 (16/126)	38.5 (5/13)	0 (0/15)	3 (1/33)	19.1 (9/47)
C	Surgical ICU	10.5 (11/105)	12.7 (16/126)	14.3 (2/14)	0 (0/15)	3.1 (1/32)	33.3 (10/30)
C	Medical ICU	7.0 (5/71)	14.7 (22/150)	0 (0/12)	27 (5/18)	5 (1/20)	25.6 (10/39)
Total COVID-19 units		9.6 (46/480)	14.1 (118/834)	16.0 (8/50)	6.2 (5/81)	4.4 (6/136)	24.6 (47/191)
Total all units		10.0 (54/538)	13.6 (134/983)	14.3 (8/56)	5.4 (5/93)	4.7 (7/149)	24.2 (53/219)

First table: Gram-positive resistant bacteria. Second table: Gram-negative Enterobacterales resistant to 3rd generation cephalosporins. Third table: Non-fermenting Gram-negative bacteria.

shown above all the presence of secondary superinfections while initial bacterial co-infection remained rare [13].

It is of note that DDDs always exceeded 1000 DDDs/1000 patient-days, as commonly described in ICUs [14]. Before the pandemic, despite a heterogeneity of ICUs antibiotics policy and casemix, a gradual decrease in the consumption among the ICU units as a whole was probably related to the introduction of antibiotic stewardship programs [2]. With the onset of the pandemic, the was reversed, with an increase observed in several studies [15]. To assess the impact of the pandemic on the antibiotic prescription patterns, we used the AWaRe classification of the WHO, dividing the antibiotics into three groups (Access, Watch, Reserve). There was a more frequent use of antibiotics in the Watch category and a doubling of the antibiotics to be used with caution (Reserve group). The impact of these antibiotics on bacterial resistance could be a target for future studies of antibiotic consumption in ICUs [16]. Using the ECDC classification also found an increase in the consumption of broad-spectrum antibiotics, which, during the befPAND, accounted for more than half of all antibiotics. These two indices have not been used in the context of an ICU specifically [8]. Herein use of these classifications suggest that these are useful tools to improve the antibiotic use and assess elements to analyse an antibiotic treatment policy; in our opinion, ICUs being specially exposed to multi-drug resistant bacteria, the WHO AWaRe classification appears to be a more suitable option to monitor the antibiotics policy of an ICU, since it describes and summarises also the consumption of most recent antibiotics [16]. The variations of some antibiotics deservesspecific attention: there was an increase in cefotaxime at the expense of ceftriaxone over the study period, the former being considered less harmful to the intestinal microbiota [17]. It must be noted that, before the pandemic, the limited decreaseof piperacillin/tazobactam was due to a shortage of this antibiotic and waspartially replaced by cefepime [18]; carbapenems (meropenem and imipenem) were not routinely used in the treatment of community-acquired or early nosocomial pneumonia [19]. We were therefore faced with antibiotic therapy tailored to the most common pathology, namely ventilator-associated pneumonia. We noticed also that imipenem was progressively replaced by meropenem during the perPAND period, probably in relation with concerns about stability and toxicity in ICU patients [20]. Overall, there is no striking difference between the COVID-19-free unit and the other units.

The bacterial ecology showed some limited changes between the study periods. Many of these change may be related to the antibiotics policy [21]. The level of resistance is considered from a therapeutic point of view. This study is based on data from a group of ICUs and a common bacteriological unit within the same university hospitals, where there have been many discussions within the institution, resulting in some degree of harmonisation between the units. For instance, this is particularly important for certain bacterial categories, such as Enterobacteriaceae, where resistance to treatment with third-generation cephalosporins is an important marker. Although the incidence of *Staphylococcus aureus* was increasing, methicillin-resistant *Staphylococcus aureus* (MRSA) continued to decrease, which was not surprising as COVID patients came from the community with low MRSA rates in France (MRSA between 5 and 10%)as in the rest of Europe [22]. In our cohort, there is no significant difference in amoxicillin resistance in Enterococcus faecium. It should be noted that the increased use of cephalosporins is not statistically significant in our pandemic cohort compared to other European units [23]. The proportion of vancomycin-resistant Enterococcus, already low, did not increase significantly. Among Enterobacterales, antibiotic resistance in *E. coli* was stable during the total study period. The decrease in 3rd generation cephalosporin (3GC) resistance among *Klebsiella* was unexpected. Reasons for this modification include fewer chronic patients being hospitalised (often carriers of multi-resistant bacteria) and the reinforcement of hygiene and infection prevention measures [23]. It is noteworthy that the increase in samples testing positive for *Enterobacter* spp. occurred during both phases, before and during the pandemic. It was probably related to a major use of third-generation cephalosporins, despite the gradual replacement of ceftriaxone by cefotaxime, with a less marked effect on the gut microbiome [17]. One of the main changes was the marked increase in *Pseudomonas aeruginosa* in most units, including the COVID-19-free unit. Resistance to ceftazidime was considered the main marker of antibiotic resistance for this species, but we specifically studied combined resistance to ceftazidime and carbapenems, which partly defines 'difficult-to-treat' *Pseudomonas*, which is increasing [24]. Bongiovanni reviewed the literature on Pseudomonas aeruginosa infections. He concluded that factors such as the use of immunosuppressive

medications, such as corticosteroids or tocilizumab, as well as the duration of hospitalisation and mechanical ventilation, may explain the frequency of difficult-to-treat Pseudomonas infections [25]. Another characteristic of ICUs in France, already present in the units of the present study before pandemia, is the almost complete absence of *Acinetobacter* sp., a phenomenon also observed in other European countries such as Northern Europe countries, and the presence of a large contingent of *Stenotrophomonas maltophilia* [26], which is much more common in France than *Acinetobacter* [27]. Globally, these bacterial epidemiological characteristics can be compared with the literature on the subject, in particular with the study reported by Langford et al. [28], which showed virtually no effect on Gram-positive bacteria, particularly *Staphylococcus aureus*, a non-significant increase in *Enterobacterales* and an increase in non-fermenting Gram-negative bacteria.

The main limitation of the present study is the use of DDDs, which tends to overestimate antibiotic consumption compared to Days of Therapy (DOT) [29]. DDD needs to be treated as a counting unit and did not provide information on the doses administered or truly prescribed to the patient. However, it makes it possible to compare ICUs, since these units received comparable patients and probably used antibiotics on a common basis. The data were not collected at individual level and therefore did not allow analysis of individual treatments.

Another limitation is the difficulty of generalising our results, since they are clearly related to an antibiotic stewardship programme related itself to a local bacterial epidemiology, which may not be applicable for instance in southern or northern Europe [3].

A major aspect of our work is the long-standing healthcare-associated infections in ICUs monitoring since many years by the REA-REZO network. Using the same methodology, the evolution of antibiotic consumption and resistance have been monitored in six ICUs over a six-year period.

In conclusion, antibiotic consumption and resistance in ICUs have evolved due to the pandemic. It was marked by increased use of Watch and Reserve antibiotics according to WHO, stable consumption per 1000 patient-days, and changes in bacterial resistance, including an increase in VAP and specific pathogens such as *Pseudomonas* spp. and *Stenotrophomonas maltophilia,* not fully explained by the resistance modifications. The findings highlight the need for continued antibiotic stewardship and surveillance in ICU settings to mitigate the impacts of the pandemic on AMR.

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Ethical approval

Ethical approval was not needed for this study due to the aggregated nature of data.

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References

[1] Murphy CV, Reed EE, Herman DD, et al. Antimicrobial stewardship in the ICU. Semin Respir Crit Care Med. 2022;43(1):131–140. doi: 10.1055/s-0041–1740977.

[2] Timsit J-F, Bassetti M, Cremer O, et al. Rationalizing antimicrobial therapy in the ICU: a narrative review. Intensive Care Med. 2019;45(2):172–189. doi: 10.1007/s00134-019-05520-5.

[3] De Waele JJ, Derde L, Bassetti M. Antimicrobial stewardship in ICUs during the COVID-19 pandemic: back to the 90s? Intensive Care Med. 2021;47(1):104–106. doi: 10.1007/s00134-020-06278-x.

[4] ATCDDD. ATCDDD - ATC/DDD Index [Internet]. 2024. https://atcddd.fhi.no/atc_ddd_index/

[5] European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA). Antimicrobial consumption and resistance in bacteria from humans and food-producing animals: fourth joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA JIACRA IV - 2019-2021. EFSA J Eur Food Saf Auth. 2024;22:e8589.

[6] CDC. Antibiotic Use in the United States, 2023 Update: Progress and Opportunities [Internet]. Antibiot. Prescr. Use; 2024. https://www.cdc.gov/antibiotic-use/hcp/data-research/stewardship-report.html.

[7] Abu-Rub LI, Abdelrahman HA, Johar A-RA, et al. Antibiotics prescribing in intensive care settings during the COVID-19 era: a systematic review. Antibiot Basel Switz. 2021;10(8):935. doi: 10.3390/antibiotics10080935.

[8] Plachouras D, Kärki T, Hansen S, et al. Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use, 2016 to 2017. Euro Surveill Bull Eur Sur Mal TransmEur Commun Dis Bull. 2018;23:1800393.

[9] Young D, McKenzie CA, Gupta S, et al. Exploring antibacterial usage and pathogen surveillance over five years in a tertiary referral teaching hospital adult general Intensive Care Unit (ICU). Pathog Basel Switz. 2024;13(11): 961. doi: 10.3390/pathogens13110961.

[10] Aziz S, Arabi YM, Alhazzani W, et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines. Intensive Care Med. 2020;46(7):1303–1325. doi: 10.1007/s00134-020-06092-5.

[11] Vacheron C-H, Lepape A, Savey A, et al. Attributable mortality of ventilator-associated pneumonia among patients with COVID-19. Am J Respir Crit Care Med. 2022;206(2):161–169. doi: 10.1164/rccm.202202-0357OC.

[12] Schouten J, De Waele J, Lanckohr C, et al. Antimicrobial stewardship in the ICU in COVID-19 times: the known unknowns. Int J Antimicrob Agents. 2021;58(4):106409. doi: 10.1016/j.ijantimicag.2021.106409.

[13] Grasselli G, Scaravilli V, Mangioni D, et al. Hospital-acquired infections in critically ill patients with COVID-19. Chest. 2021;160(2):454–465. doi: 10.1016/j.chest.2021.04.002.

[14] Ismail D. Cost of antibiotics in medical intensive care. J Hosp Infect. 2022;124:47–55. doi: 10.1016/j.jhin.2022.03.003.

[15] Langford BJ, So M, Raybardhan S, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect. 2021;27(4):520–531. doi: 10.1016/j.cmi.2020.12.018.

[16] Benkő R, Matuz M, Pető Z, et al. Trends in the hospital-sector consumption of the WHO AWaRe Reserve group antibiotics in EU/EEA countries and the United Kingdom, 2010 to 2018. Eurosurveillance. 2022;27(41): 2101058. doi: 10.2807/1560-7917.ES.2022.27.41.2101058.

[17] Grohs P, Kernéis S, Sabatier B, et al. Fighting the spread of AmpC-hyperproducing Enterobacteriaceae: beneficial effect of replacing ceftriaxone with cefotaxime. J Antimicrob Chemother. 2014;69(3):786–789. doi: 10.1093/jac/dkt403.

[18] King ST, Barber KE, Parham JJ, et al. Shifts in antimicrobial consumption and infection rates before and during a piperacillin/tazobactam shortage. J Glob Antimicrob Resist. 2017;11:111–113. doi: 10.1016/j.jgar.2017.07.015.

[19] Kalil AC, Metersky ML, Klompas M, et al. Executive Summary: management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):575–582. doi: 10.1093/cid/ciw504.

[20] Salmon-Rousseau A, Martins C, Blot M, et al. Comparative review of imipenem/cilastatin versus meropenem. Med Mal Infect. 2020;50(4):316–322. doi: 10.1016/j.medmal.2020.01.001.

[21] Lanckohr C, Bracht H. Antimicrobial stewardship. Curr Opin Crit Care. 2022;28(5):551–556. doi: 10.1097/MCC.0000000000000967.

[22] Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual epidemiological report for 2022 [Internet]. 2023. https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2022

[23] Falcone M, Tiseo G, Giordano C, et al. Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. J Antimicrob Chemother. 2021;76(4):1078–1084. doi: 10.1093/jac/dkaa530.

[24] Tamma PD, Aitken SL, Bonomo RA, et al. Infectious diseases society of America 2022 guidance on the treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant

Enterobacterales (CRE), and pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2022;75(2):187–212. doi: 10.1093/cid/ciac268.

[25] Bongiovanni M, Barda B. Pseudomonas aeruginosa bloodstream infections in SARS-CoV-2 infected patients: a systematic review. J Clin Med. 2023;12(6):2252. doi: 10.3390/jcm12062252.

[26] Carbonell N, Oltra MR, Clari MÁ. Stenotrophomonas maltophilia: the Landscape in Critically Ill Patients and Optimising Management Approaches. Antibiotics. 2024;13(7):577. doi: 10.3390/antibiotics13070577.

[27] Kinross P, Gagliotti C, Merk H, et al. Large increase in bloodstream infections with carbapenem-resistant Acinetobacter species during the first 2 years of the COVID-19 pandemic, EU/EEA, 2020 and 2021. Euro Surveill Bull Eur Sur Mal TransmEur Commun Dis Bull. 2022;27:2200845.

[28] Langford BJ, Soucy J-PR, Leung V, et al. Antibiotic resistance associated with the COVID-19 pandemic: a systematic review and meta-analysis. Clin Microbiol Infect. 2023;29(3):302–309. doi: 10.1016/j.cmi.2022.12.006.

[29] Ronda M, Padullés A, Grau I, et al. Impact of a prospective audit and feedback antimicrobial stewardship programme on carbapenem consumption: a quasi-experimental study (IPANEMA study). J Antimicrob Chemother. 2023;78(7):1705–1710. doi: 10.1093/jac/dkad160.