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Original article

A time series analysis approach to quantify change in antibiotic resistance and antibiotic consumption during COVID-19 epidemics: a multicentre cross-national ecological study on behalf of QUantifying change in Antibiotic Resistance, ANTibiotic use, and INfection control during COVID-19 Epidemics study project

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ABSTRACT

Objectives: We aimed to assess the impact of COVID-19 on antibiotic consumption (AMC) and antimicrobial resistance (AMR) in the new epidemiological scenario from a cross-national perspective.
Methods: A quasi-experimental retrospective multicentre ecological study was conducted to explore the impact of COVID-19 on AMC and AMR using routinely generated retrospective time series data. This study included nine Healthcare University Hospitals from Europe and Israel on behalf QUantifying

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change in Antibiotic Resistance, ANTibiotic use, and INfection control during COVID-19 Epidemics project. Total effects were defined as the difference between the pre-COVID-19 period (ranging from January 2015 or January 2016 to February 2020) and during the COVID-19 pandemic period (March 2020 to July 2021 or December 2021). The outcomes were incidence density (ID) of carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Klebsiella pneumoniae*, extended-spectrum beta-lactamase-producing *Escherichia coli*, vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Pseudomonas aeruginosa* and *Clostridioides difficile*, as monthly isolates per 1000 patient days and the monthly AMC ranked according to the Access, Watch, and Reserve WHO classification system.

Results: We assessed 15.9 million total hospital bed days, 315 736 COVID-19 bed days, 52 557 monthly bacterial isolates, and 461 739 monthly antimicrobial defined daily doses. The COVID-19 pandemic had a significant impact on the consumption of overall hospital antibiotics combined in all centres except two. Prescriptions for piperacillin/tazobactam, glycopeptides, and ceftazidime/avibactam increased, whereas third-generation cephalosporins, macrolides, and fluoroquinolones returned to pre-pandemic levels after an initial surge, in all centres. A positive relationship between the pandemic intensity and VRE ID was observed in 6 of 9 (66%) centres followed by methicillin-resistant *S. aureus*-ID and carbapenem-resistant *P. aeruginosa*-ID 3 of 4 (44%) for both. A negative relationship was found for extended-spectrum beta-lactamase-producing *E. coli* ID.

Discussion: The COVID-19 pandemic was associated with higher usage of broad-spectrum antibiotics and higher incidence of multidrug-resistant bacteria, with great variability by countries. These results could support international action plans that embed AMR as a priority in the post-COVID-19 era.

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Introduction

The COVID-19 pandemic severely disrupted healthcare systems, exacerbating the global spread of antimicrobial resistance (AMR) [1]. Overcrowding and depleted resources compromised antimicrobial stewardship (AMS) and shifted infection prevention and control (IPC) efforts towards COVID-19 measures [2]. Despite a relatively low bacterial superinfection rate (5–27%) in COVID-19 hospitalized patients, broad-spectrum antibiotics were widely prescribed in the initial two pandemic waves, with 80–100% of patients receiving at least one course [2–4]. This was driven by exponential increases in intensive care unit (ICU) admissions, invasive procedures (mechanical ventilation, catheters), and prolonged hospital stays, leading to a higher prevalence of nosocomial infections [1].

Critically ill patients with COVID-19 faced elevated risks of healthcare-associated infections, particularly ventilator-associated pneumonia and bloodstream infections (BSIs), with nearly doubled mortality [5]. Studies show healthcare-associated infection rates surged with COVID-19 waves, and clusters of isolates accounted for significant increases in BSIs and multidrug-resistant organisms (MDROs) [6]. Healthcare personnel redirected IPC strategies to prevent COVID-19 transmission, often at the expense of preventing nosocomial bacterial cross-transmission. Reports indicate issues like double gloving, reduced assistance time, burnout, and decreased hand hygiene compliance [7,8]. A systematic review found that up to 60.8% of COVID-19-related superinfections were caused by antibiotic-resistant organisms, with prior antibiotic exposure being a key risk factor [6]. Common MDROs included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Klebsiella pneumoniae* (CRKP), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). However, reported AMR prevalence varied significantly by study, country, and clinical setting, with higher rates in Eastern Mediterranean, South-East Asia, and Western Pacific regions compared with the Americas, and in ICUs vs. non-ICU settings [6,9,10].

With the pandemic declared over, high-quality research is crucial to fully understand the impact of antibiotic consumption on AMR prevalence during and after COVID-19. Few studies have linked antibiotic resistance rates with AMS and IPC initiatives, potentially underestimating COVID-19's overall effect on AMR and antimicrobial consumption (AC) in hospitals, compounded by inconsistent AMR definitions and reporting. Our multi-country study aims to assess the direct impact of the COVID-19 pandemic, including two years of data, on AMC and AMR in this new epidemiological scenario, providing evidence to support national guidelines and international action plans prioritizing AMR in the post-COVID-19 era.

Methods

Study design and setting

A quasi-experimental retrospective multicentre ecological study (Supplementary Section) was conducted to explore the impact of COVID-19 on AMC and AMR using routinely generated retrospective time series data collected from January 2015 to December 2021. This multicentre study included nine University Hospitals: Modena University Hospital (Modena, Italy), Besançon University Hospital (Besançon, France), Craigavon Area Hospital (Craigavon, United Kingdom), Rambam Health Care Campus (Haifa, Israel), Clinical Hospital Centre Rijeka (Rijeka, Croatia), Rabin Medical Center (Tel Aviv, Israel), Mater Dei Hospital (Msida, Malta), Antrim Hospital (Antrim, United Kingdom) and Ljubljana University Medical Centre (Ljubljana, Slovenia).

The study was approved by the Modena University Hospital institutional review board (reference number 0007073/22 of 9 March 2022), which waived the need for the patients to sign the informed consent since the ecological nature of the project.

Definitions and data collections

The pre-COVID-19 period was defined as January 2015 to February 2020, and the COVID-19 pandemic period was from March

2020 to July 2021 or December 2021, depending on the availability of data in each hospital (Supplementary Appendix).

Infection time series

Pathogens collected were *A. baumannii*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *Escherichia coli*, *Enterococcus faecium* and *Clostridioides difficile* (CD). The incidences of all MDRO isolates from blood/urine/respiratory hospital samples (clinical samples only) were expressed as incidence density (ID) rate, as monthly isolates/100 patient days (PDs), only non-duplicated isolates (one per person per month/admission, only isolated strains with an interval of 30 days between the previous strain and the next were considered non-duplicates, regardless of phenotype), were collected, without distinguishing between nosocomial and community samples. Samples from rectal or nasal screenings were considered colonization and excluded. The total number of positive CD samples/tests per laboratory was collected independently of the type of diagnostic test currently used (a positive laboratory assay for CD toxin A and/or B in stools or a toxin-producing CD organism detected in stool via culture or other means, e.g. a positive PCR).

Antibiotic consumption time series

The monthly data of AC were expressed as defined daily dose (DDD)/1000 PD, total consumption, and single-class consumptions, for the whole hospital. The antibiotic classes were ranked according to the Access, Watch, and Reserve classification system of antibiotics developed in 2017 by the WHO [11]. Single class of antibiotics considered were amoxicillin/clavulanate, piperacillin/tazobactam, anti-pseudomonal cephalosporins (ceftazidime, cefepime), third-generation cephalosporins (cefotaxime, ceftriaxone, cefixime), ceftazidime/avibactam, ceftolozane/tazobactam, carbapenems (meropenem, imipenem, ertapenem), fluoroquinolones (moxifloxacin, ciprofloxacin, levofloxacin, ofloxacin), macrolides (azithromycin, clarithromycin, erythromycin), oxazolidinones (linezolid, tedizolid), and anti-MRSA cephalosporins (ceftaroline, ceftobiprole).

Because increased relative rates of clusters and MDROs were associated with increasing monthly rates of COVID-19 discharges, to adjust for this confounder, monthly in-patient days, monthly COVID-19 bed days and epidemic period for each centre were also collected.

Outcomes

The primary outcome was quantifying the effect of the COVID-19 pandemic on the change in AC (total consumption or change in antibiotic classes) and in AMR incidence rates in-hospital settings. Secondary outcomes were changes in trends and levels of MDRO ID and AC between pre-pandemic COVID-19 and the pandemic periods.

Statistical analysis

To study change in antibiotic consumption and the ID rates of selected MDROs between the period before the pandemic (first period) and during the pandemic (second period), we used a strategy based on time series intervention analysis. The changes in the Level (CL) and the Trends (CT) before the Intervention (the pandemic) were compared with the evolution of the dependent series. The changes produced between the first and second periods on antibiotic consumption or the MDROs' incidence were evaluated by adjusting linear transfer functions (time series intervention analysis), following the Pankratz methodology [12]. Further details of statistical analysis are reported in the Supplementary Section. The output of the models was as follows:

- Tt: PRETREND (trend before the COVID-19 pandemic—January 2015 or January 2016—February 2020)
- TS: POSTREND (changes I PRETREND during and after the COVID-19 pandemic—March 2020—July 2021 or December 2021)
- LS: EPIDEMIC (change in level—January 2015 or January 2016—February 2020 vs. March 2020—July or December 2021)

X: COVID-BD (direct effect of the monthly absolute number of COVID-19 bed days) included as X term in both antibiotic use and ID resistance models. To measure the goodness of fit, the R-squared is used. The interpretation of this value would imply that the variations of the dependent variable are explained by the model in a percentage that is obtained by multiplying R2 by 100. Analyses were performed using the SCA Statistical System version 8.1 (scausa.com, Scientific Computing Associates Corp., IL).

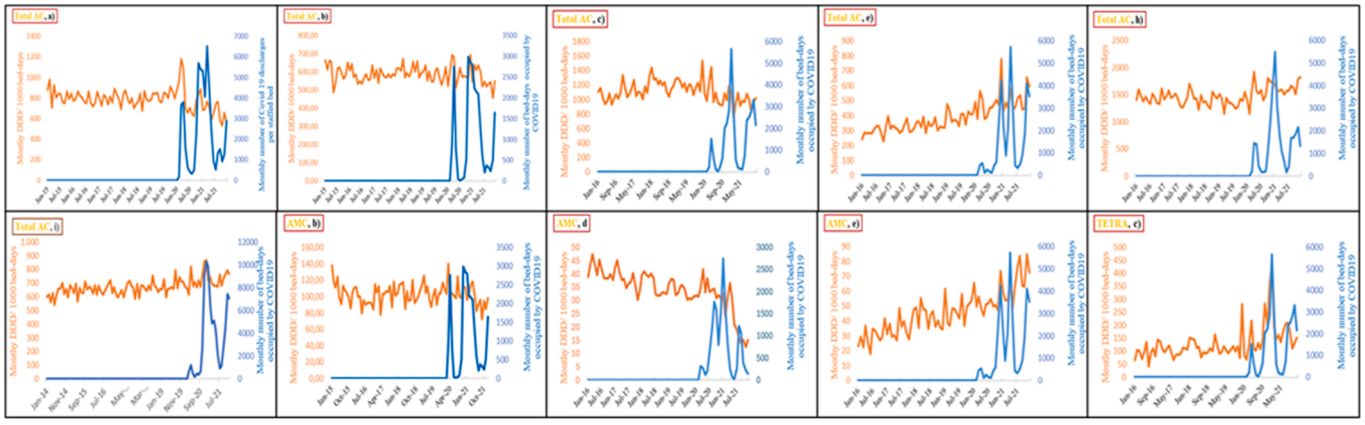

Fig. 1. On the *y*-axis: in orange, changes in trends and levels of antibiotic consumption in general and antibiotics from the Access group included in the study (expressed as defined monthly daily dose [DDD] per 1000 bed days [BD]) in relation to COVID-19 bed days (in blue). The *x*-axis represents time. The variability explained by the final models is indicated with the *R*-squared value (only statistically significant correlations were included in the figure, such as total antibiotic consumption in centre a) (Modena). AC, antibiotic consumption; AMC, amoxicillin-clavulanate; TETRA, tetracyclines. (a) Azienda Ospedaliero-Universitaria Policlinico, Modena (Italy). (b) Centre Hospitalier Universitaire Jean Minjoz, Besançon(France). (c) Craigavon Area Hospital in the Southern Health and Social Care Trust, Craigavon (North Ireland, United Kingdom). (d) Rambam Health Care Campus, Haifa (Israel). (e) Clinical Hospital Center of Rijeka, Rijeka (Croatia). (f) Rabin Medical Center, Petah Tikva (Israel). (g) Mater Dei Hospital, Msida (Malta). (h) Antrim Area Hospital, Antrim (Northern Ireland, United Kingdom). (i) Ljubljana University Medical Centre (Ljubljana, Slovenia).

Table 1
Effect of COVID-19 pandemic on antibiotic consumption (DDD per 1000 patient-days), by antibacterial group or agent, ordered by AWaRe Antibiotic classification [13], in nine hospitals, January 2015–December 2021

		N° hospitals with				
Antibacterial group or agent (ATC code)		**Consumption positively associated with the COVID-19 pandemic**	**Consumption initially positively, then negatively affected by the COVID-19 pandemic**	**Consumption negatively affected by the COVID-19 pandemic**	**Consumption not affected by the COVID-19 pandemic**	***R-square***
Antibacterial for systemic use, Total (J01)		IT-MOD, FR-BES, UK-CRA, HR-RIJ, UK-ANT, SI-LJU		IS-RBM	IS-RAB	0.563 (IT-MOD); 0.285 (FR-BES); 0.473 (UK-CRA); 0.263 (IS-RBM); 0.736 (HR-RIJ); - (IS-RAB); 0.781 (MT-MDH); 0.536 (UK-ANT); 0.504 (SI-LJU)
Access group						
-	Amoxicillin/clavulanic acid (J01CR02)	FR-BES, IS-RBM, HR-RIJ		IT-MOD, UK-CRA, SI-LJU	IS-RAB, MT-MDH, UK-ANT	0.582 (IT-MOD); 0.112 (FR-BES); 0.427 (UK-CRA); 0.602 (IS-RBM); 0.712 (HR-RIJ); 0.651 (IS-RAB); 0.725 (MT-MDH); 0.503 (UK-ANT); 0.530 (SI-LJU)
-	Tetracyclines	UK-CRA			UK-ANT	0.601 (UK-CRA); 0.384 (UK-ANT)
Watch group						
-	Cefotaxime (J01DD01), ceftriaxone (J01DD04) and cefixime (J01DD08)	FR-BES, UK-CRA, HR-RIJ	IT-MOD	IS-RAB, MT-MDH, UK-ANT	IS-RBM, SI-LJU	0.616 (IT-MOD); 0.381 (FR-BES); 0.248 (UK-CRA); 0.833 (IS-RBM); 0.787 (HR-RIJ); 0.604 (IS-RAB); 0.777 (MT-MDH); 0.168 (UK-ANT), - (SI-LJU)
-	Ceftazidime (J01DD02) and cefepime (J01DE01)	FR-BES, UK-CRA, SI-LJU		HR-RIJ, IS-RAB	IT-MOD, IS-RBM, MT-MDH, UK-ANT,	0.441 (IT-MOD); 0.286 (FR-BES); 0.206 (UK-CRA); 0.228 (IS-RBM); 0.834 (HR-RIJ); 0.498 (IS-RAB); - (MT-MDH); - (UK-ANT); 0.557 (SI-LJU)
-	Piperacillin/tazobactam (J01CR05)	IT-MOD, FR-BES, IS-RBM, IS-RAB, MT-MDH, UK-ANT, UK-ANT		HR-RIJ	UK-CRA	0.516 (IT-MOD); 0.250 (FR-BES); 0.387 (UK-CRA); 0.348 (IS-RBM); 0.610 (HR-RIJ); 0.643 (IS-RAB), 0.905 (MT-MDH); 0.650 (UK-ANT); 0.802 (SI-LJU)
-	Carbapenems (J01DH)	IS-RBM, HR-RIJ, MT-MDH, UK-ANT		UK-CRA	IT-MOD, FR-BES, IS-RAB, UK-ANT	0.220 (IT-MOD); 0.361 (FR-BES); 0.366 (UK-CRA); 0.352 (IS-RBM); 0.658 (HR-RIJ); 0.207 (IS-RAB); 0.801 (MT-MDH); 0.269 (UK-ANT); 0.358 (SI-LJU)
-	Glycopeptides (J01XA)	IT-MOD, HR-RIJ, IS-RAB, MT-MDH, UK-ANT		UK-CRA	FR-BES, IS-RBM, UK-ANT	0.483 (IT-MOD); 0.729 (FR-BES); 0.283 (UK-CRA); 0.503 (IS-RBM); 0.687 (HR-RIJ); 0.182 (IS-RAB); 0.869 (MT-MDH); - (UK-ANT), 0.410 (SI-LJU)
-	Macrolides (J01FA)	HR-RIJ, UK-ANT, UK-ANT	IT-MOD, FR-BES	UK-CRA, IS-RAB, MT-MDH	IS-RBM	0.579 (IT-MOD); 0.624 (FR-BES); 0.193 (UK-CRA); 0.751 (IS-RBM); 0.567 (HR-RIJ); 0.646 (IS-RAB); 0.643 (MT-MDH); 0.267 (UK-ANT); 0.311 (SI-LJU)
-	Fluoroquinolones (J01MA)	FR-BES, UK-CRA, HR-RIJ, SI-LJU		MT-MDH	IT-MOD, IS-RBM, IS-RAB, UK-ANT	0.654 (IT-MOD); 0.310 (FR-BES); 0.289 (UK-CRA); 0.136 (IS-RBM); 0.652 (HR-RIJ); 0.404 (IS-RAB); 0.638 (MT-MDH); 0.396 (UK-ANT); 0.646 (SI-LJU)
Reserve group						
-	Ceftolozane/tazobactam (J01DI54)		IT-MOD		IS-RAB	0.602 (IT-MOD); - (IS-RAB);
-	Ceftazidime/avibactam (J01DD52)	IT-MOD, HR-RIJ, IS-RAB, MT-MDH, UK-ANT, SI-LJU				0.523 (IT-MOD); 0.834 (HR-RIJ); 0.498 (IS-RAB); 0.535 (MT-MDH), 0.307 (UK-ANT), 0.843 (SI-LJU)
-	Ceftaroline (J01DI02)	IT-MOD, SI-LJU				0.721 (IT-MOD); 0.627 (UK-ANT)
-	Daptomycin (J01XX09)	IT-MOD, MT-MDH, SI-LJU		FR-BES, UK-CRA	IS-RBM, IS-RAB, UK-ANT	0.497 (IT-MOD); 0.580 (FR-BES); 0.267 (UK-CRA); 0.330 (IS-RBM); 0.155 (IS-RAB); 0.495 (MT-MDH); - (UK-ANT) ; 0.266 (SI-LJU)
-	Oxazolidinones (linezolid, J01XX08; tedizolid, J01XX11)	IT-MOD, FR-BES		UK-CRA	IS-RBM, HR-RIJ, UK-ANT	0.396 (IT-MOD); 0.631 (FR-BES); 0.247 (UK-CRA); 0.068 (IS-RBM); 0.468 (HR-RIJ); 0.199 (UK-ANT)
-	Fosfomycin, parenteral (J01XX01)	IT-MOD, UK-CRA, HR-RIJ			FR-BES, IS-RAB, MT-MDH, UK-ANT	0.435 (IT-MOD); - (FR-BES); 0.297 (UK-CRA); 0.790 (HR-RIJ); - (IS-RAB); - (MT-MDH); - (UK-ANT)

AWaRe, Access, Watch, and Reserve; DDD, defined daily dose; FR-BES, Centre Hospitalier Universitaire Jean Minjoz, Besançon(France); HR-RIJ, Clinical Hospital Center of Rijeka, Rijeka (Croatia); IS-RAB, Rabin Medical Center, Petah Tikva (Israel); IS-RBM, Rambam Health Care Campus, Haifa (Israel); IT-MOD, Azienda Ospedaliero-Universitaria Policlinico, Modena (Italy); MT-MDH, Mater Dei Hospital, Msida (Malta); SI-LJU, Ljubljana University Medical Centre (Ljubljana, Slovenia); UK-ANT, Antrim Area Hospital, Antrim (Northern Ireland, UK); UK-CRA, Craigavon Area Hospital in the Southern Health and Social Care Trust, Craigavon (North Ireland, UK).

Table 2
The association between the COVID-19 pandemic on antimicrobial resistance (AMR), expressed as pathogen incidence density (in-hospital incidence density [ID] per 1000 COVID-19 patient days) of pathogens included in the high critical category of multidrug-resistant bacteria according to the 2017 WHO priority list [14], in nine hospitals, January 2015–December 2021

	Nº hospitals with				
Resistant pathogens (AMR ID)	**Incidence positively affected by the COVID-19 pandemic**	**Incidence initially positively, then negatively affected by the COVID-19 pandemic**	**Incidence negatively affected by the COVID-19 pandemic**	**Incidence not affected by the COVID-19 pandemic**	***R-square***
Gram negative					
- extended-spectrum beta-lactamases (ESBL) *E. coli*	HR-RIJ		IT-MOD, UK-CRA, IS-RBM, IS-RAB	FR-BES, MT-MDH, UK-ANT, SI-LJU	0.142 (IT-MC (FR-BES); 0.(CRA); 0.200 (0.439 (HR-RI RAB); - (MT- (UK-ANT); 0 LJU)
- carbapenem-resistant *Klebsiella pneumoniae* (CRKP)	HR-RIJ			IT-MOD, FR-BES, UK-CRA, IS-RBM, IS-RAB, UK-ANT, SI-LJU	0.261 (IT-MC BES); - (UK-(RBM); 0.706 (IS-RAB); - (I (UK-ANT); 0 LJU)
- carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)	IT-MOD, FR-BES, MT-MDH, SI-LJU		HR-RIJ	UK-CRA, IS-RBM, IS-RAB, UK-ANT	0.063 (IT-MC (FR-BES); - (0.178 (IS-RB (HR-RIJ); 0.3 0.367 (MT-M ANT); 0.319 (
- carbapenem-resistant *Acinetobacter baumannii* (CRAB)	HR-RIJ, SI-LJU			IT-MOD, FR-BES, UK-CRA, IS-RBM, IS-RAB, MT-MDH, UK-ANT	0.378 (IT-MC BES); - (UK-((IS-RBM); 0.1 RIJ); - (IS-RA MDH); - (UK (SI-LJU)
Gram positive					
- methicillin-resistant *Staphylococcus aureus* (MRSA)	IT-MOD, UK-CRA, HR-RIJ, MT-MDH	FR-BES		IS-RBM, IS-RAB, UK-ANT, SI-LJU	0.229 (IT-MC (FR-BES); 0.1 CRA); 0.455 (0.265 (HR-RI RAB); 0.210 ((UK-ANT); 0 LJU)
- vancomycin-resistant Enterococcus faecium (VRE)	IT-MOD, IS-RBM, HR-RIJ, IS-RAB, MT-MDH, UK-ANT			FR-BES, UK-CRA, SI-LJU	0.588 (IT-MC BES); 0.221 (0.239 (IS-RB (HR-RIJ); 0.6 0.771 (MT-M (UK-ANT); 0 LJU)
- *Clostridium difficile* (CD)	HR-RIJ, MT-MDH, SI-LJU		FR-BES	IT-MOD, UK-CRA, IS-RBM, IS-RAB, UK-ANT	- (IT-MOD); (BES); 0.150 ((IS-RBM); 0.1 RIJ); - (IS-RA (MT-MDH); (ANT); 0.181 (

FR-BES, Centre Hospitalier Universitaire Jean Minjoz, Besançon (France); HR-RIJ, Clinical Hospital Center of Rijeka, (Croatia); IS-RAB, Rabin Medical Center, Petah Tikva (Israel); IS-RBM, Rambam Health Care Campus, Haifa (Israel); IT-MOD, Azienda Ospedaliero-Universitaria Policlinico, Modena (Italy); MT-MDH, Mater Dei Hospital, Msida (Malta); SI-LJU, Ljubljana University Medical Centre (Ljubljana, Slovenia); UK-ANT, Antrim Area Hospital, Antrim (Northern Ireland, United Kingdom); UK-CRA, Craigavon Area Hospital in the Southern Health and Social Care Trust, Craigavon (North Ireland, United Kingdom).

Results

In this study, 15 890 992 total hospital bed days and 315 736 COVID-19 bed days, respectively, were assessed with a total of 52 557 monthly bacterial isolates and a total of 461 739 monthly antimicrobial DDDs.(see Fig. 1)

A detailed overview of hospital characteristics including AMS and IPC policies implemented during the study period is described in Supplementary Appendix.

Antibiotic consumption

The COVID-19 pandemic significantly affected the consumption trends of several antibiotics in the Watch group. Notably, third-generation cephalosporins and fluoroquinolones exhibited a significant increase in consumption trends in three out of nine centres, with *R*-squared values ranging from 0.168 (Antrim) to 0.833 (Rambam). Macrolides showed a significant increase in consumption during the initial pandemic waves, followed by a marked decline that ultimately nullified the overall pandemic effect (Table 1 and Fig. 2). For instance, in the Italian centre, third-generation cephalosporins and macrolides showed an initial increase in level (change in level [CL] of 5.510 and 9.825, respectively), followed by a negative effect on the trend (effect on change [EC] −0.001, $R^2 = 0.616$; EC −0.0007, $R^2 = 0.579$). A similar pattern was observed in Besançon, where macrolides had an initial change in level of 55.990, but a negative EC of −1.994 ($R^2 = 0.193$) (Supplementary Appendix). A positive association with the pandemic was also observed for piperacillin/tazobactam in seven of nine centres (78%), with R^2 values ranging from 0.250 in France to 0.905 in Malta. Glycopeptides showed a similar trend in five of nine centres, with R^2 ranging from 0.182 to 0.869. Conversely, consumption patterns for anti-Pseudomonas cephalosporins, carbapenems, and fluoroquinolones varied markedly across centres, with roughly half reporting a positive association with the pandemic and the other half showing no significant impact (R^2 range: 0.207 in Israel to 0.801 in Malta). Carbapenem consumption varied widely, ranging from 12 to 65 DDD/1000 PDs across sites. Regarding Reserve group antibiotics, ceftazidime/avibactam demonstrated a positive pandemic-related trend in six of nine centres (R^2 range: 0.307 in Antrim to 0.843 in Ljubljana). In contrast, fewer than half of the centres (4/9) reported a similar pattern for parenteral fosfomycin, daptomycin, and linezolid (Table 1 and Fig. 2).

AMR incidence

In Table 2, we reported the total effect of COVID-19 pandemic on AMR, in the nine centres included, during the study period. Fig. 3 shows trends of the most representative MDROs in relation with study time (pre- and during COVID-19 pandemic). As above, the results of the univariate analysis by individual centre are reported in the Supplementary Section. We observed a positive correlation of the pandemic intensity in 44% of the centres for MRSA (four out of nine centres) and in 66% for VRE (six out of nine centres). In Modena centre, the relationship between MRSA incidence and COVID-19 pandemic was initially positive, then negative (PT -0.0035, CL 0.1927, effect -0.00006, CT not measurable, R-squared 0.277). For most of the centres enrolled, the pandemic did not affect the CD incidence. The only pathogens that were inversely associated with the pandemic with a marked reduction were ESBL-producing *E. coli*. An increasing trend observed in some centres before the pandemic was completely reversed during the pandemic in 43% of the centres (pre-trend CT 0.0055, post-trend CT -0.0539, R-square 0.200). In most of the centres, we could not find any effect of the COVID-19 pandemic on incidence densities of Gram-negative MDROs: CRKP (seven centres out of nine), CRPA (four centres out of nine), CRAB (seven centres out of nine) (R-squared ranging from a minimum of 0.029 to a maximum of 0.749). However, in four out of nine centres, we observed a significant positive relationship with CRPA and the intensity of the pandemic (R-squared ranging from a minimum of 0.063 to a maximum of 0.385). The Croatian hospital accounted for the highest direct correlation between MDROs incidence and the COVID-19 pandemic (6 out of 7, 85.7%): all except CRPA registered a significant positive impact, including ESBL (effect 0.0001) confirming a positive pre-trend (PT 0.0070, R-square 0.439) and CD (effect 0.00007; CL of -0.3266). Finally, Table 3 summarizes the main findings together.

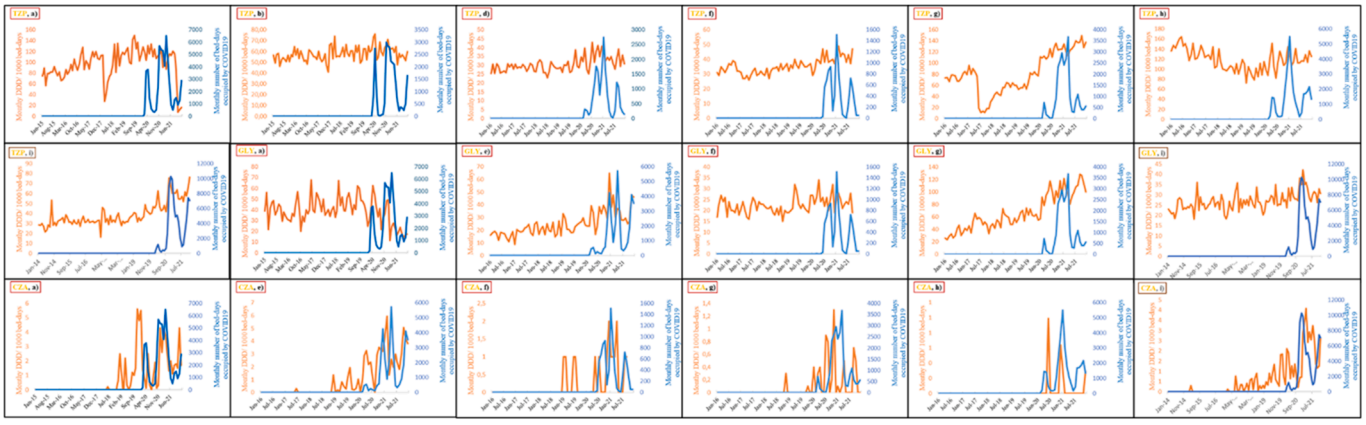

Fig. 2. On the *y*-axis: in orange, changes in trends and levels of antibiotic consumption from the Watch and Reserve groups included in the study (expressed as defined monthly daily dose [DDD] per 1000 bed days [BD]) in relation to COVID-19 bed days (in blue). The *x*-axis represents time. The variability explained by the R-squared value was determined by the final models. Only statistically significant correlations and a selection of the most representative antibiotic classes in terms of frequency were included in the figure, such as VRE incidence rate in centre a (Modena). TZP, piperacillin-tazobactam; GLY, glycopeptides; CZA, ceftazidime-avibactam. (a) Azienda Ospedaliero-Universitaria Policlinico, Modena (Italy). (b) Centre Hospitalier Universitaire Jean Minjoz, Besançon (France). (c) Craigavon Area Hospital in the Southern Health and Social Care Trust, Craigavon (North Ireland, United Kingdom). (d) Rambam Health Care Campus, Haifa (Israel). (e) Clinical Hospital Center of Rijeka, Rijeka (Croatia). (f) Rabin Medical Center, Petah Tikva (Israel). (g) Mater Dei Hospital, Msida (Malta). (h) Antrim Area Hospital, Antrim (Northern Ireland, United Kingdom). (i) Ljubljana University Medical Centre (Ljubljana, Slovenia).

Table 3
Correlation between antibiotic consumption and incidence density of MDROs per centre divided in positively and negatively affected by COVID-19 pandemic.

Antibiotic consumption **positively** affected by the COVID-19 pandemic								
Hospital	**IT-MOD**	**FR-BES**	**UK-CRA**	**IS-RBM**	**HR-RIJ**	**IS-RAB**	**MT-MDH**	**UK-ANT**
Total	■	■	■		■			■
Amoxiclav		■		■	■			
Cefotaxime		■	■		■			
Piperacillin-Tazobactam	■	■		■		■	■	■
Carbapenems				■	■		■	
Glycopeptides	■				■	■	■	
Macrolides					■			■
Fluoroquinolones		■	■		■			
Ceftazidime-avibactam	■				■	■	■	■
Fosfomycin IV	■		■		■			
MDROs incidence density **positively** affected by the COVID-19 pandemic								
Hospital	**IT-MOD**	**FR-BES**	**UK-CRA**	**IS-RBM**	**HR-RIJ**	**IS-RAB**	**MT-MDH**	**UK-ANT**
ESBL					■			
CRKP					■			
CRPA	■	■					■	
CRAB					■			
MRSA	■		■		■		■	
VRE	■			■	■	■	■	■
CDI					■		■	
Antibiotic consumption **negatively** affected by the COVID-19 pandemic								
Hospital	**IT-MOD**	**FR-BES**	**UK-CRA**	**IS-RBM**	**HR-RIJ**	**IS-RAB**	**MT-MDH**	**UK-ANT**
Total				■				
Amoxicillin-clavulanic	■		■					
Cefotaxime						■	■	■
Piperacillin-Tazobactam					■			
Carbapenems			■					
Glycopeptydes			■					
Macrolides			■				■	
Fluoroquinolones							■	
Ceftazidime-avibactam								
Fosfomycin IV								
MDROs incidence density **negatively** affected by the COVID-19 pandemic								
Hospital	**IT-MOD**	**FR-BES**	**UK-CRA**	**IS-RBM**	**HR-RIJ**	**IS-RAB**	**MT-MDH**	**UK-ANT**
ESBL	■		■			■		
CRKP								
CRPA								
CRAB								
MRSA								
VRE								
CDI								
AMS and IC policy during the COVID-19 pandemic								
Hospital	**IT-MOD**	**FR-BES**	**UK-CRA**	**IS-RBM**	**HR-RIJ**	**IS-RAB**	**MT-MDH**	**UK-ANT**
Stringency index	43.90	25.60	13.99	36.90	27.38	36.90	27.38	13.99

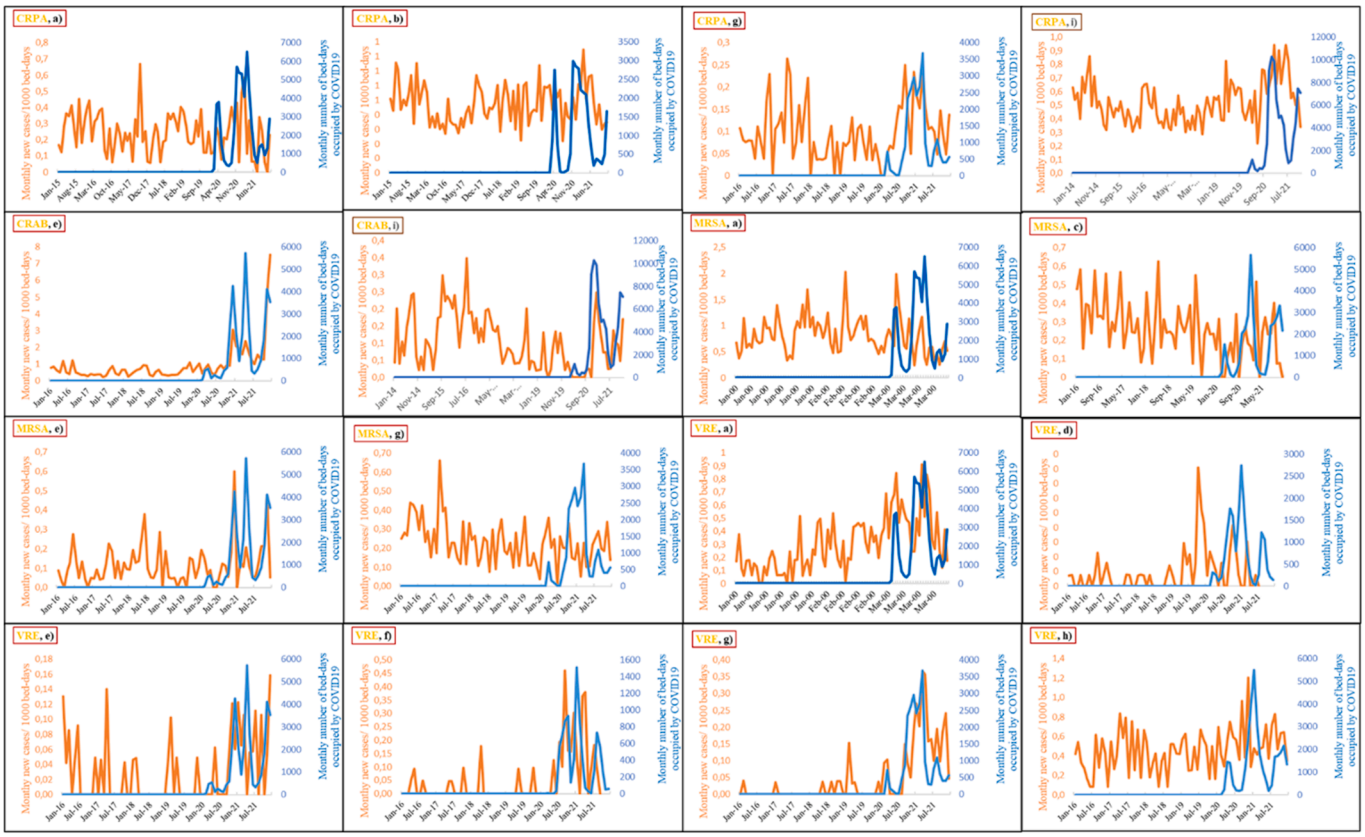

Fig. 3. On the *y*-axis: in orange, changes in trends and levels of incidence density of major MDRO infections (expressed as monthly new cases per 1000 bed days) in relation to COVID-19 bed days (in blue). The *x*-axis represents time (study period). The variability explained by the R-squared value was determined by the final models (only statistically significant variables and a selection of the most representative MDROs in terms of frequency were included in the figure). CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRAB, carbapenem resistant *Acinetobacter baumannii*; MDROs, multidrug-resistant organisms; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococci. (a) Azienda Ospedaliero-Universitaria Policlinico, Modena (Italy). (b) Centre Hospitalier Universitaire Jean Minjoz, Besançon (France). (c) Craigavon Area Hospital in the Southern Health and Social Care Trust, Craigavon (North Ireland, United Kingdom). (d) Rambam Health Care Campus, Haifa (Israel). (e) Clinical Hospital Center of Rijeka, Rijeka (Croatia). (f) Rabin Medical Center, Petah Tikva (Israel). (g) Mater Dei Hospital, Msida (Malta). (h) Antrim Area Hospital, Antrim (Northern Ireland, United Kingdom). (i) Ljubljana University Medical Centre (Ljubljana, Slovenia).

Discussion

This is, to our knowledge, the first intervention time series analysis aimed to investigate the direct role of the pandemic on AMC and AMR in a multicentre international study, in nine acute care hospitals across Europe and Israel. Although the pandemic affected both AMC and AMR in all centres, we observed substantial variations. These differences likely stem from heterogeneous implementation of IPC and AMS measures, as well as pre-existing AMR trends and local endemicity.

We found that total AC significantly increased with epidemic intensity, consistent with previous reports [13–18], in all centres except Israel. Notably, there was a shift towards broad-spectrum antimicrobials, particularly Watch and Reserve categories. Piperacillin/tazobactam and glycopeptides consistently increased across all centres during the pandemic, whereas carbapenems and intravenous fosfomycin increased in only four and three centres, respectively. Conversely, the consumption of penicillins, cephalosporins, and macrolides gradually decreased during and after pandemic waves, suggesting prescribers incorporated evolving evidence (e.g. discontinuation of azithromycin for COVID-19 [19]). Initial empirical therapies often combined ceftriaxone with azithromycin, later replaced by biomarker-guided decisions: low procalcitonin supported decision making in cessation of antibacterials, minimizing the public health impact of antibiotic overuse [20]. The increase in ceftazidime-avibactam was likely driven by a rise in carbapenem-resistant organisms and ceftolozane/tazobactam shortages [21]. Anti-Gram-positive antibiotic use also rose, particularly where MRSA and VRE incidences significantly increased.

Our findings confirm the strong correlation between MDROs and the COVID-19 pandemic, as noted in prior research [5,10,22–25]. Factors promoting this increase include prolonged hospital stays, invasive devices, antibiotic overuse, cross-transmission, and inadequate IPC measures. Immunosuppression, whether iatrogenic or virus-induced, likely contributed to bacterial superinfections, especially by *P. aeruginosa* and *S. aureus* [8,26–28].

VRE incidence showed a strong relationship with epidemic intensity in six centres, building on pre-pandemic increases likely amplified by COVID-19. Similarly, MRSA was positively affected in half of the centres. Although both were partly driven by AMS breakdown, MRSA appears to be returning to pre-pandemic levels, whereas VRE continues an upward trend, aligning with European Centre for Disease Prevention and Control reports and suggesting persistent hospital sources due to its higher propensity for horizontal spread and environmental persistence in overcrowded wards [29].

In contrast, most centres saw a significant reduction in ESBL-producing *E. coli* incidence during the pandemic. This decline is likely attributable to community factors: reduced antibiotic use outside hospitals due to social restrictions, decreased international

travel (a major risk factor for ESBL transmission), and fewer elective surgeries or hospitalizations for chronic diseases [30].

Unlike some systematic reviews, CRPA incidence positively correlated with pandemic intensity in four centres, whereas CRAB and CRKP spreading seemed unaffected. This difference might be due to CRPA being more sensitive to antibiotic overexposure among Gram-negative pathogens [31,32]. Notably, only one out of the four forementioned centres failed to show a decline in CRPA incidence after the first year of the epidemic, peaking at 10.2 DDD/1000 PD of carbapenems by the end of 2020. In stark contrast, the other three centres maintained carbapenem consumption below the critical threshold (2.5, 2.39, and 1.62 DDD/1000 PD, respectively [33]. Starting from this real-world observation, to predict the thresholds beyond which consumption of a given antibiotic leads to the development of resistance will be addressed in the second study, on behalf of the Quarantine project [34].

Interestingly, one centre demonstrated a sustained downward trend in CRAB incidence even pre-pandemic, highlighting the long-term effectiveness of specific IPC bundles [35]. Finally, only two centres showed a significant link between pandemic intensity and CDI, likely driven by increased overall AC and environmental persistence of *C. difficile* spores exacerbated by poor IPC adherence. However, CDI rates during the pandemic might be unreliable due to reduced diagnostic testing capacity and misattribution of diarrhoea to SARS-CoV-2 [36].

Our study has several limitations. The inherent focus of included centres on AMS and AMR may underestimate the actual burden of AC and AMR during COVID-19. Furthermore, the predominance of European centres (seven of nine) limits the generalizability of our findings. Although previous meta-analyses were more geographically diverse, they often included only ICU data, lacked pre-pandemic comparisons, and had shorter follow-up periods. Additional limitations include the absence of post-pandemic data, precluding assessment of long-term sustainability. Our statistical model's low explanatory power (low R-squared values) suggests that other factors significantly impact MDRO incidence. We also acknowledge unaddressed risk factors and the potential for underestimation of AMR rates due to reporting issues or reduced active surveillance.

Despite these limitations, our use of intervention time series methods provided a more robust estimation of total COVID-19 effects than less comprehensive study designs. Although centres could not provide monthly quantifiable data for all risk factors (e.g. IPC strategies, occupancy rates), we indirectly accounted for these through COVID-19 bed days, assuming pandemic intensity influenced these factors. Crucially, our study benefited from gathering generic information on IPC measures, collecting non-duplicate isolates from all clinical specimens (not just respiratory or BSI), including all antibiotic classes (including new reserve classes), and encompassing an extensive 7-year period with five pre-pandemic years, providing a broad and valuable dataset.

Conclusions

The COVID-19 pandemic had a significant impact on the consumption of overall hospital antibiotics combined in all centres except two. Nevertheless, although the increase in AMC was faster restored, this did not occur for MDROs nosocomial incidence, suggesting possible irreversible consequences on AMR rates. These data emphasize that AMS practices and infection control measures severely compromised during the COVID-19 pandemic, must be quickly recovered. The deep variability highlighted by our study strengthens the need of evidence-based recommendations tailored on local epidemiology, not only for AMS but also for diagnostics and infection control practices. Finally, as our study is unable to demonstrate the direct impact of AMC on AMR, we are working in a second study calculating thresholds on the antibiotic use to support international action plans that embed AMR as a priority in the post–COVID-19 era.

Author contributions

MM conceived, designed, and coordinated the study, wrote the study protocol, assisted with the literature search, assessed eligibility of manuscripts, collected additional published data, performed data extraction, designed the analysis, figures and tables, interpreted the data, and wrote the manuscript together with FM and EB. JMLL and CM were responsible for methodology and supervision. MP, MS, LC, GCB, CMcK, CW, YD-B, MA, IR, DP, AB, MSau, NS, VV-P, DY, VD, MAB, PZ, MS, DF, FM, MSc, SG, BB, and CM were responsible for writing—review and editing. MM, JMLL, and FM screened electronic literature search results for relevant manuscripts, assessed their eligibility, extracted data, and collected additional published data. FM and MM analysed and interpreted data, made figures and tables, and wrote the first draft of the manuscript. FM and MM designed and performed the electronic literature search. JMLL conceived, designed, and coordinated the study, wrote the study protocol, assisted with the literature search, assessed eligibility of manuscripts, collected additional published data, performed data extraction, designed the analysis, figures and tables, interpreted the data, and wrote the manuscript. MN and JH verified the data underlying the study. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication. All authors extracted and collected data for their single centre, read and agreed to the published version of the manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Transparency declaration

Conflict of interest

The authors declare that they have no conflicts of interest.

Financial report

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Data availability

The anonymized data file can be shared upon request to the corresponding author (filippomedioli@gmail.com), via a link allowing the file to be downloaded through an institutional secure server. Single-centre results can be found in Supplementary Section.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.06.009.

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