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Antimicrobial use and antimicrobial resistance in Enterobacterales and *Enterococcus faecium*: a time series analysis

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SUMMARY

Background: Irish and European antimicrobial resistance (AMR) surveillance data have highlighted increasing AMR in Enterobacterales and vancomycin resistance in *Enterococcus faecium* (VRE). Antimicrobial consumption (AC) in Irish hospital settings is also increasing.
Methods: A retrospective time series analysis (TSA) was conducted to evaluate the trends and possible relationship between AC of selected antimicrobials and AMR in Enterobacterales and vancomycin resistance in *E. faecium*, from January 2017 to December 2020.
Results: Increased AC was seen with ceftriaxone ($P = 0.0006$), piperacillin/tazobactam ($P = 0.03$) and meropenem ($P = 0.054$), while ciprofloxacin and gentamicin use trended downwards. AMR rates in *Escherichia coli*, *Klebsiella pneumoniae* and other Enterobacterales were largely stable or decreasing, an increase in ertapenem resistance in the latter from 0.58% in 2017 to 5.19% in 2020 ($P = 0.003$) being the main concern. The proportion of *E. faecium* that was VRE did not changed significantly (64% in 2017; 53% in 2020, $P = 0.1$). TSA identified a correlation between piperacillin/tazobactam use and the decreasing rate of ceftriaxone resistance in *E. coli*.
Conclusion: Our data suggest that the hospital antimicrobial stewardship programme is largely containing, but not reducing AMR in key nosocomial pathogens. An increase in AC following the COVID-19 pandemic appears as yet to have had no impact on AMR rates.

Introduction

Antimicrobial resistance (AMR) is a significant threat to public health [1]. Increasing rates of AMR among Enterobacterales and of vancomycin-resistance in *Enterococcus faecium* (VRE) are causing concern across Europe [2] and in Ireland [3].

There is a well-established link between inappropriate and excessive antimicrobial use and selection of AMR [4]; AMR in Enterobacterales is of particular concern [5]. Antimicrobial stewardship (AMS) interventions are an important element in tackling AMR and are well established in Irish hospitals [6]. However, the median overall rate of antimicrobial consumption

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(AC) in Irish hospitals increased by 16% between 2009 and 2019 [7]. The COVID-19 pandemic has had a significant impact on healthcare systems and delivery worldwide [8]. Many routine AMS activities have been reduced and the impact of this on AMR is yet to be determined [9]. Furthermore, evidence suggests that there has been widespread and excessive prescription of antimicrobials in COVID-19 patients due to the difficulty in identifying which patients have bacterial pneumonia [10].

There is a lack of studies linking AC and AMR in the Irish hospital setting. Given the prevailing trends in AC and AMR in Ireland and the knowledge that AC is generally recognized as the primary driver of AMR, it is important to investigate how changes in AC influence bacterial susceptibilities. Such information could inform development of policies to manage AMR, particularly following the COVID-19 pandemic.

In this study we aim to investigate the trends and possible relationships between AC and AMR in Enterobacterales species, and the proportion of *E. faecium* that are VRE, between 2017 and 2020 in an Irish hospital. These AMR data were also compared with EU and other Irish hospital data.

Methods

Hospital setting

The study hospital is a 271-bed, inner-city, acute University Teaching Hospital, in the Republic of Ireland. The hospital is comprised of various medical and surgical specialities, a paediatric unit, and a general intensive care unit. The hospital established a formal AMS programme in 2007. Key AMS events and policies implemented prior to and during the study period are summarized in Supplementary Table S1.

Antimicrobial consumption

Quarterly aggregated hospital AC data (dispensed to inpatients on all hospital wards) for antimicrobial agents indicated for treatment of infections caused by Enterobacterales were collated. These antibiotics were ceftriaxone, ciprofloxacin, levofloxacin, ertapenem, meropenem, piperacillin/tazobactam, gentamicin, co-trimoxazole and aztreonam; vancomycin usage data were also collected. Antimicrobials dispensed to the outpatient setting were excluded.

AC data were obtained from the hospital pharmacy electronic dispensing records for the study period (1st January 2017 to 31st December 2020). These data were converted to the standardized WHO's Anatomical Therapeutic Chemical (ATC) Classification of defined daily dose (DDD) and antibiotic usage was expressed as quarterly aggregated DDDs according to the 2018 ATC classification and normalized per 100 hospital/bed days used (BDU) [11].

Microbiology and AMR data

Isolates of Enterobacterales from clinical microbiology specimens (blood, sterile fluid, sputum, urine and wound samples) from inpatients were included. Duplicate isolates from the same patient [12] were excluded. Bacterial identification and antibacterial susceptibility testing was performed in the hospital clinical microbiology laboratory using the Vitek®2 (bioMérieux) system according to the manufacturer's guidelines. Antimicrobial susceptibilities were assessed according to European Committee for Antimicrobial Susceptibility Testing (EUCAST) [13]. All non-susceptible isolates (i.e. resistant and intermediate) were considered resistant. AMR data were extracted from the hospital microbiology laboratory database. We also compared our data to European Antimicrobial Resistance Surveillance Network (EARS-Net) reports of population-weighted EU-/EEA-wide AMR rates [3]. These are based on data on *E. faecium*, *Escherichia coli*, and *Klebsiella pneumoniae* in invasive samples (blood or cerebrospinal fluid) and submitted by medical microbiology laboratories across Europe, including the study hospital. While there is some variability in reporting, data from Ireland is estimated to cover 96% of the population.

Statistical analysis

Initial analysis of the evolving trends in AC and AMR rates was conducted by linear regression analysis. Further analysis was conducted using time series analysis (TSA), which has been used previously to investigate possible correlations between AC and AMR where the data are measured repeatedly at equal intervals of time [14–16]. The Box–Jenkins method of TSA modelling was used to develop univariate autoregressive integrated moving average (ARIMA) models of the AC and AMR data [17]. Following the development of univariate ARIMA models, a linear transfer function modelling method [15,16] was used to investigate the dynamic relationship between antimicrobial use and the incidence of resistant isolates, considering possible time delays (lag times). These methods are described in detail in the Supplementary data. All statistical analyses were performed with R version 4.0.3.

The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidance for reporting observational studies [18] and the STROBE-AMS recommendations for reporting epidemiology studies of AMR and informing improvement in AMS [19].

Ethics

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (reference numbers ECM4(p) and ECM3(xx)).

Results

Hospital trends in AC

The trends in AC of the individual antimicrobials can be seen in Figure 1. Increasing trends were seen in ceftriaxone consumption ($P = 0.0006$), piperacillin/tazobactam consumption ($P = 0.03$) and meropenem consumption ($P = 0.054$). Decreasing trends were seen in ciprofloxacin consumption ($P = 0.0012$) and gentamicin consumption ($P = 0.057$). Further trend analysis of AC is contained in Supplementary Table S2.

Hospital trends in AMR

The annual rates of AMR for *E. coli and K. pneumoniae*, and of vancomycin resistance in enterococci and VRE incidence in our hospital, and compared with Irish and European resistance

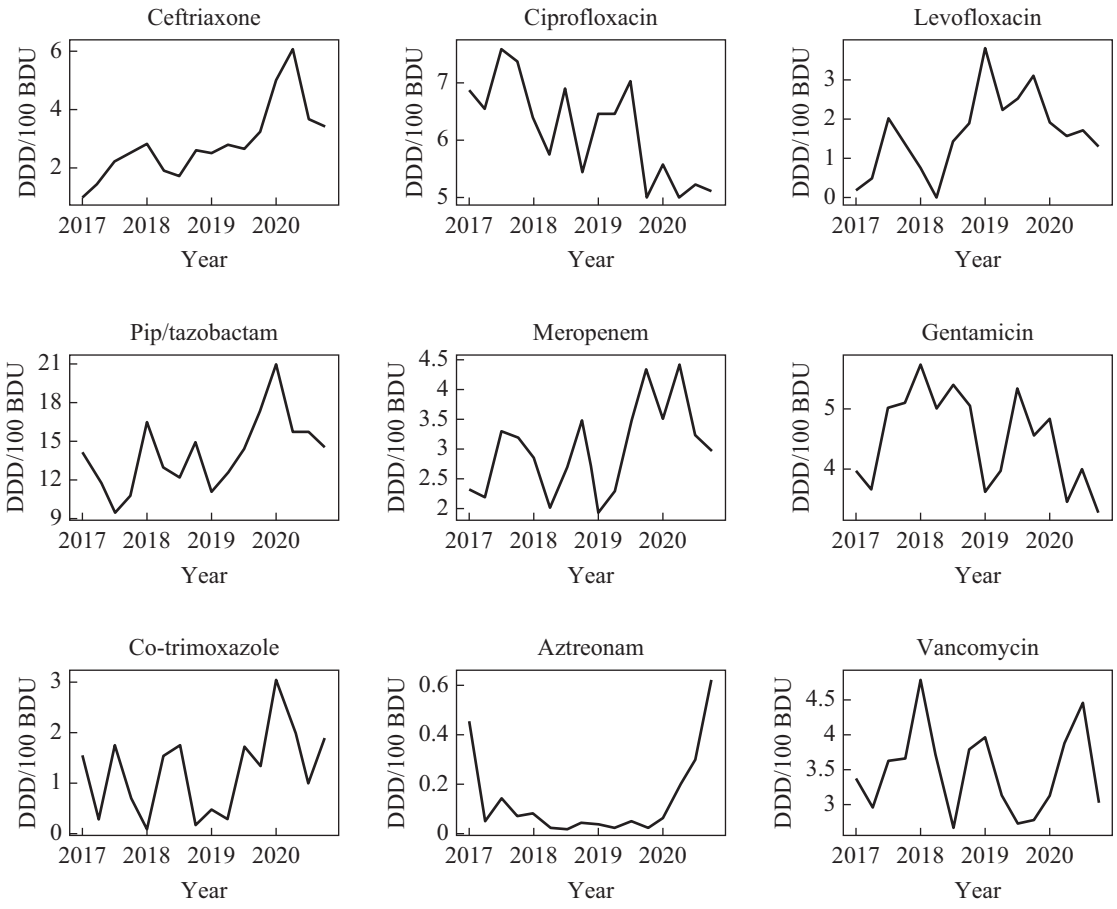

Figure 1. Quarterly antimicrobial consumption rates of selected antimicrobials from Q1 2017 to Q4 2020. BDU, bed days used; DDD, defined daily dose.

data are shown in Table I. Figures 2–4 show quarterly trends in AMR for *E. coli*, *K. pneumoniae* and other Enterobacterales, respectively.

For *E. coli*, although the graphs suggest that resistance rates were trending downwards for most antibiotics except co-trimoxazole, the differences did not reach statistical significance (e.g., ceftriaxone $P = 0.136$, ciprofloxacin $P = 0.138$, piperacillin/tazobactam $P = 0.143$). Notably, fluoroquinolone resistance rates were consistently higher than national and EU rates. The proportion of *E. coli* that were ESBL producers was

Table I
Percentage of clinical isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Enterococcus faecium* resistant to selected antimicrobials from the study hospital (Hosp), Ireland (Ire) and the European Union (EU) 2017–2019

Bacteria	Antimicrobial agent/group	2017			2018			2019			2020
		Hosp	Ire	EU	Hosp	Ire	EU	Hosp	Ire	EU	Hosp
E. coli	Third-generation cephalosporin*	21	12	14.9	15.8	12.9	15.1	13.2	12	15.1	14.2
	Carbapenems**	1.4	0	0.1	1.6	0	0.1	1.1	0	0.3	0
	Fluoroquinolones#	32.5	23.6	25.7	31.5	23.9	25.3	27.7	20.4	23.8	25.7
	Aminoglycosides	12.7	11.9	11.4	10.4	11.7	11.1	11.4	11.8	10.8	9.1
K. pneumoniae	Third-generation cephalosporin*	19.6	14.9	31.2	17.8	14.5	31.7	11.9	17.6	31.3	10.8
	Carbapenems**	0	0.2	7.1	1.4	0.6	7.5	0	0.9	7.9	1.92
	Fluoroquinolones#	22.4	5.9	30.5	23.3	8.1	19.5	8	5.3	19.3	12.5
	Aminoglycosides	17.8	11.9	24.1	14.6	13	22.7	10	11	22.3	3.85
E. faecium	Vancomycin resistance	64.1	38.2	14.9	56.3	40.2	17.3	48.6	38.4	18.3	53

Only study hospital data was available for 2020 at the time of writing.
* EU and Ire data relates to cefotaxime/ceftriaxone/ceftazidime, study hospital data relates to ceftriaxone resistance.
** EU and Ire data relates to imipenem/meropenem, study hospital data relates to ertapenem resistance.
\# EU and Ire data relates to ciprofloxacin/levofloxacin/ofloxacin, study hospital data relates to ciprofloxacin resistance.

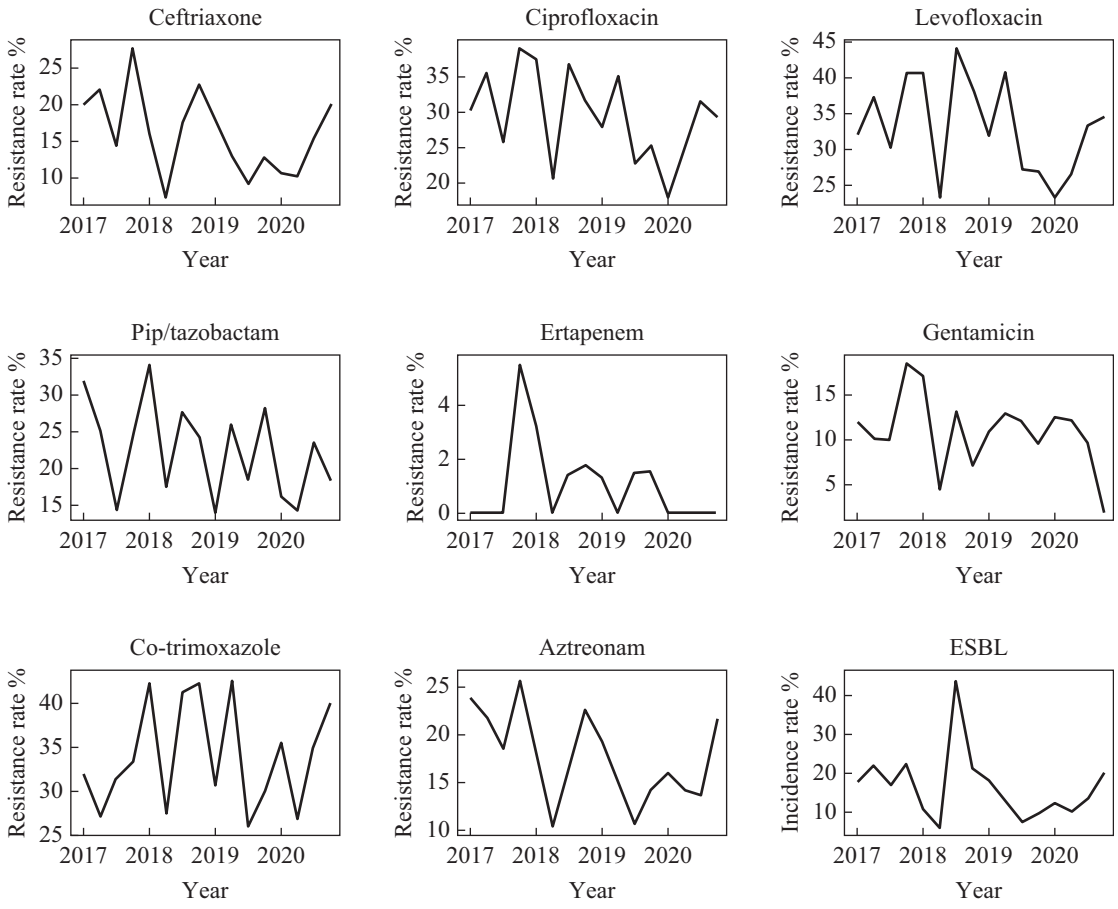

Figure 2. Quarterly *Escherichia coli* resistance rates to selected antimicrobials from Q1 2017 to Q4 2020. ESBL, extended-spectrum beta-lactamase.

19.8% in 2017, compared with 14.1% in 2020 ($P = 0.323$). Further details on the annual rates of resistance in *E. coli* are given in Supplementary Table S3.

Likewise, there were no statistically significant trends in resistance to antibiotics amongst *K. pneumoniae* (Figure 3). Third-generation cephalosporin resistance was considerably higher in the EU than in Ireland or the study hospital. Fluoroquinolone resistance rates fell faster, but later, than in either the EU or Ireland. Further details on the annual rates of resistance in *K. pneumoniae* are given in Supplementary Table S3. The proportion of *K. pneumoniae* isolates that were ESBL-producing fell from 19.8% in 2017 to 8.88% in 2020 ($P = 0.0254$). Further details on the annual rates of resistance in *K. pneumoniae* are contained in Supplementary Table S4.

Trends in antibiotic resistance amongst other Enterobacterales are shown in Figure 4. The most common genera in this category were *Citrobacter, Enterobacter, Proteus* and *Serratia*. The most important trend was the rise in ertapenem resistance from 0.58% in 2017 to 5.19% in 2020 ($P = 0.003$). Further details on the annual rates of resistance are contained in Supplementary Table S5.

There was no significant change in the rates of vancomycin resistance in *E. faecium* over the study period ($P = 0.1$). However, the rate in our hospital was considerably higher than the rates nationally, or in the EU.

Incidence and dynamic regression of E. coli resistance to ceftriaxone and the influence of piperacillin/tazobactam

For ceftriaxone resistance in *E. coli* we identified an ARIMA model [17] with one significant moving average term of order 2. The transfer function model was developed which explained 86% ($R^2 = 86$) of the variation in incidence with piperacillin/tazobactam consumption as a statistically significant explanatory variable for ceftriaxone resistance in *E. coli*. A 1% increase in piperacillin/tazobactam use would result in a 1.33% decrease in ceftriaxone resistance immediately and a further 0.488 % decrease in 3 months. The transfer function model also included the moving average term of the resistance rate itself with a lag of 6 months. Further details are given in Supplementary Table S5.

Discussion

This study contains an analysis of the rates of AC and AMR in an Irish teaching hospital using TSA. The findings show that while overall AC rates and broad-spectrum antimicrobial (ceftriaxone, piperacillin/tazobactam and meropenem) use increased over the study period there was not a corresponding

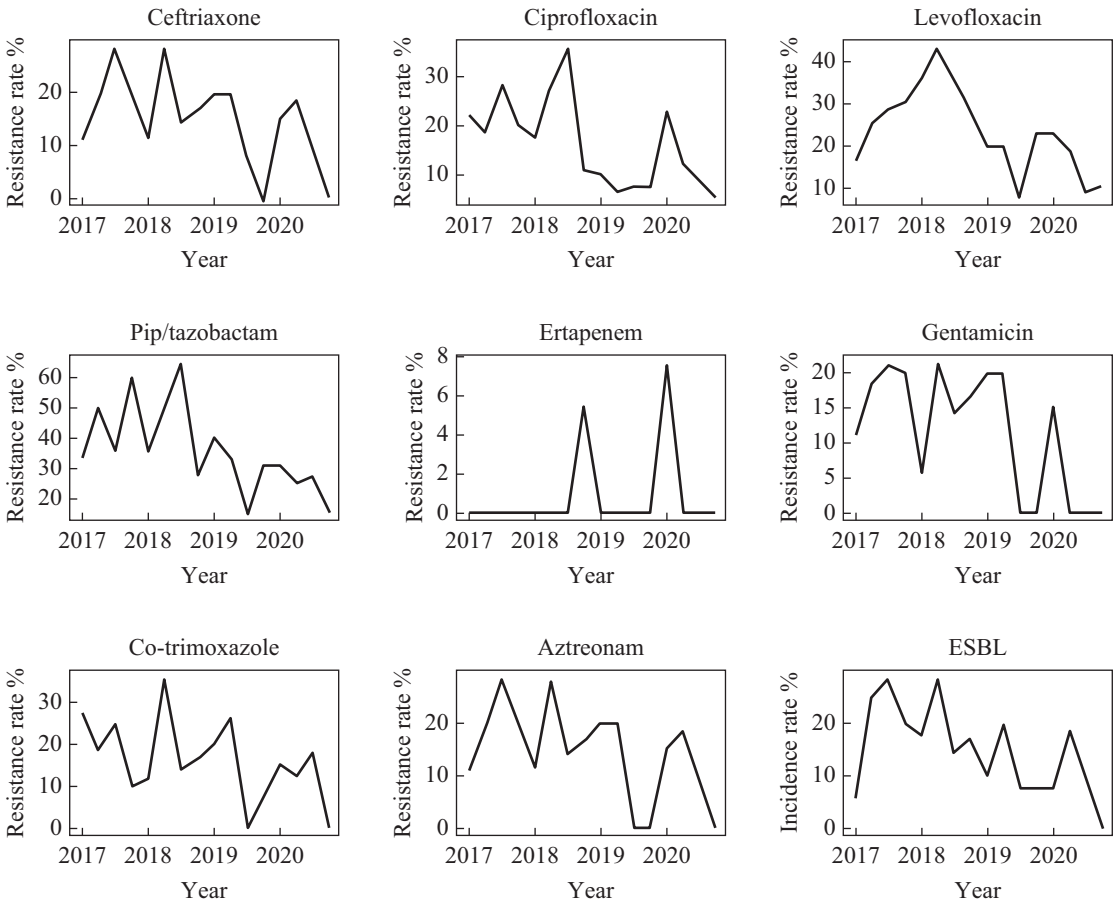

Figure 3. Quarterly *Klebsiella pneumoniae* resistance rates to selected antimicrobials from Q1 2017 to Q4 2020. ESBL, extended-spectrum beta-lactamase.

increase generally in rates of AMR. These findings suggest that hospital AC is just one of several factors that influence the rates of AMR seen in the hospital setting. The main trend of concern is rising rates of ertapenem resistance, especially in the group of 'other Enterobacterales', which follows a national trend [20].

Nevertheless, we feel that overall, our data do indicate that the hospital AMS programme is having a positive impact on Gram-negative AMR rates [21]. A recent analysis of AC and AMR data from the EU similarly identified stabilization of AMR rates in *E. coli* and *K. pneumoniae* attributed to the impact of AMS initiatives [22]. We note that others have reported that AMS programmes have been reported to be less effective in reducing VRE rates [21]. Further work is required to address the increasing frequency of carbapenemase-producing Enterobacterales (CPE). The most effective AMS interventions targeting CPE are those that address carbapenem use and incorporate education and restrictive measures [23,24]. The reduction in AMS activities [9] seen during the COVID-19 pandemic is likely to have contributed to the increased carbapenem use seen during this study.

When each of the AC-AMR combinations (e.g., AC and ertapenem resistance, AC and VRE rates) were cross-correlated using linear regression of the ARIMA model residuals, only one significant correlation between antimicrobial use and AMR was identified. This may have been because it is difficult to demonstrate a statistically significant correlation due to the complex and evolving nature of AMR despite the link between AMR and AC being well established [25]. A recent study from the Netherlands in the outpatient setting found that the association between antimicrobial use and resistance was weak [26]. Suggested factors for the lack of correlation included patient-related factors (e.g., age, sex), individual patient antimicrobial exposure, resistance mechanisms to antimicrobials between different bacteria [26] and the interaction with the use of other antimicrobials [15].

In this study a correlation between piperacillin/tazobactam use and the rate of resistance to ceftriaxone in *E. coli* was observed using TSA. Over the study period the rate of resistance to ceftriaxone in *E. coli* decreased while the use of ceftriaxone increased particularly in 2020. The increased consumption of ceftriaxone during 2020 did not appear to have an immediate impact on the rate of ceftriaxone resistance but this should be monitored due to a potential lag in the influence of the increased use on rates of resistance. The use of piperacillin/tazobactam also tended to increase during the study period but using TSA a correlation was identified with the decrease in ceftriaxone resistance in *E. coli*. This effect has also been seen in a study involving the substitution of piperacillin/tazobactam for a broad-spectrum cephalosporin (ceftazidime) which resulted in decreasing levels of ceftazidime resistance in other Enterobacterales [27]. Resistance strain

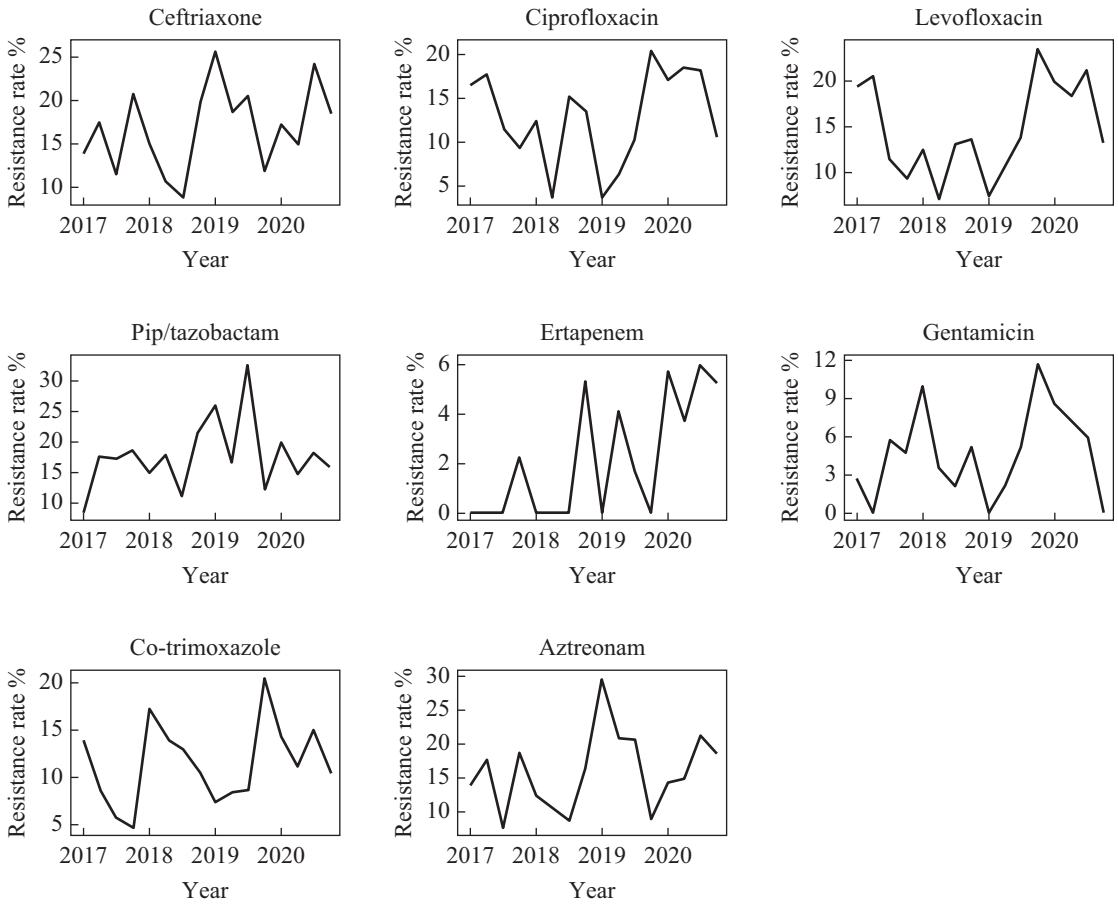

Figure 4. Quarterly resistance rates for other Enterobacterales species to selected antimicrobials from Q1 2017 to Q4 2020.

dynamics can play an important role in changes in AMR rates in *E. coli* species and are influenced by antimicrobial consumption changes [16]. In situations where there are high levels of resistance to third-generation cephalosporins such as ceftriaxone, as seen in the study hospital, efforts to substitute ceftriaxone with piperacillin/tazobactam should be considered.

Consumption of broad-spectrum antimicrobials, ceftriaxone, piperacillin/tazobactam and meropenem, increased over the course of the study, especially in 2020, during the COVID-19 pandemic. Much of this increase was associated with treatment of suspected pneumonia in patients with suspected or proven COVID-19 [28]. Studies have estimated that up to 72% of hospitalized COVID-19 patients received antimicrobials, while the rate of bacterial co-infection ranged from 6% to 11% [29,30]. Increased prescribing of broad-spectrum antimicrobials and decreased AMS activities has led to concerns that AMR may proliferate in hospitals because of COVID 19. However, thus far the COVID-19 pandemic appears to have had limited impact on AMR rates, either in our hospital or elsewhere [31]. One potential explanation for this is that the COVID-19 pandemic has improved infection prevention and control practices [32]; AMS programmes are more effective when implemented alongside infection prevention and control measures [21].

The focus of this study was on AC and AMR in the hospital setting but it is important to acknowledge the impact of community antimicrobial use has on AMR, as antimicrobial use in one setting can impact AMR in the other [33]. The COVID-19 pandemic is likely to have impacted on AC and AMR in the community, through factors such as decreased travel and socialising, as well as factors such as social distancing and hand hygiene. Other limitations of this study are that it was a single-centre retrospective study, meaning that the findings may not be generalizable. Also, the study only encompassed samples collected for routine clinical reasons. By not undertaking systematic screening of all hospitalized patients, there is a risk that the AMR data are not representative of the whole hospital population. Other studies have suggested more frequent observations should be used when conducting TSA [14] however this was not practical for our study. The use of a longer reporting period should be considered in future studies with the use of monthly data to increase sensitivity to identify possible correlations.

In conclusion, the decreasing or generally stable rates of AMR found in this study provide some assurance that the hospital AMS programme is assisting in controlling AMR, although a rise in ertapenem resistance in Enterobacterales is concerning. We also noted that broad-spectrum AC increased in association with the COVID-19 pandemic, and suggest that improved infection prevention and control practice may have been important in containing AMR during this period. Wider use of TSA to analyse routine AC and AMR data as part of AMS

programmes should be considered, as it allows investigation of correlations between antibiotic use and resistance to other antibiotics.

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Conflict of interest statement
None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.11.003.

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