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Effect of antimicrobial consumption on *Escherichia coli* resistance: assessment and forecasting using Dynamic Regression models in a French university hospital (2014-2019)

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Dynamic regression Antimicrobial resistance Antimicrobial consumption *Escherichia coli* Antimicrobial stewardship

Abbreviations:

AAPBI, anti-pseudomonal activity penicillin and beta-lactamase inhibitor; AMC, antimicrobial consumption; AMR, antimicrobial resistance; ARIMA, autoregressive integrated moving average; ASP, antimicrobial stewardship programs; AST, antimicrobial susceptibility testing; DDD, defined daily doses; DR, dynamic regression; DRPC, dynamic regression by principal components; EUCAST, European committee on antimicrobial susceptibility testing; LTF, linear transfer function; MAPE, mean absolute percentage error; PBI, penicillin and beta-lactamase inhibitor; WHO, World Health Organization.

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a b s t r a c t

Introduction:

The aim of this study was to determine the correlation between antimicrobial consumption (AMC) and antimicrobial resistance (AMR) in *Escherichia coli* at a hospital level, and assess the capacity of dynamic regression (DR) models to predict AMR for their use in deployment of antimicrobial stewardship programs (ASPs).

Methods:

A retrospective epidemiological study was conducted in a French tertiary hospital between 2014 and 2019. DR models were used to assess the correlation between AMC and AMR from 2014 to 2018. The predictive abilities of the models were estimated by comparing the predicted data with those observed in 2019.

Results:

Rates of fluoroquinolone and cephalosporin resistance decreased. AMC increased overall but decreased for fluoroquinolone. DR models highlighted that the decrease in use of fluoroquinolone and the increase in use of anti-pseudomonal activity penicillin with beta-lactamase inhibitor (AAPBI) explained 54% of the decrease in fluoroquinolone resistance and 15% of the decrease in cephalosporin resistance. In addition, penicillin/beta-lactamase inhibitor (PBI) consumption explained 53% of PBI resistance, and beta-lactam use explained 36% of penicillin resistance, with both remaining stable over time. DR models had predictive capabilities with margins of error from 8% to 34%.

Conclusion:

Over a six-year period in a French tertiary hospital, decreasing rates of resistance to fluoroquinolones and cephalosporins were correlated with decreasing use of fluoroquinolone and increasing use of AAPBI, whereas rates of resistance to penicillin remained high and stable. The results indicate that DR models should be used with caution for AMR forecasting and ASP implementation.

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1. Introduction

Antimicrobial resistance (AMR) is increasing worldwide [1]. AMR leads to increased complexity of care, mortality and hospital length of stay [2]. Human activity, particularly antimicrobial consumption (AMC), is one of the main factors responsible for AMR [3]. As a result, the World Health Organization (WHO) requested that countries monitor AMC and implement antimicrobial stewardship programs (ASPs) to reduce AMR [4]. In Europe, after several years of effort, AMR is reaching steady-state or is even starting to decline [5]. However, AMR remains a concern in hospital settings [6], prompting healthcare authorities to continue AMR surveillance and encourage novel ASPs.

Digital interventions are promising tools for surveillance and ASP development [7]. At hospital level, dynamic regression (DR) models have been used to assess the impact of AMC on AMR [8–11]. DR models are considered the most relevant methodology [12] and can be used to predict AMR using AMC data [13]. However, the predictive ability of these models remains questionable [14].

The aim of this study was to describe trends in AMC and AMR rates in *Escherichia coli*, the most frequently isolated nosocomial pathogen in France [6], using DR models in a French teaching hospital, and to investigate the correlation between AMC and AMR, and the burden of each antibiotic class on AMR acquisition in *E. coli* strains. Also assessed was the ability of DR models to predict AMR, with a view to using them in future ASP implementations.

2. Methods

2.1. Study design and settings

A retrospective ecological study in a French teaching hospital was conducted between January 2014 and December 2019, using the ConsoRes software (a tool for monitoring data on AMC and AMR provided by the French Public Health Agency).

The Nimes University Hospital has 1773 beds, including 46 for critical care, 24 for haematooncology, 235 for surgery and 190 for long-term. During the study period, between 41 300 and 50 100 inpatients per year were admitted and the average days of hospitalisation was 55 200 days/month and increased each year up to 57 500 days/month in 2019.

2.2. Bacterial samples

All microbiological samples that were positive for *E. coli* collected during the study period were analysed. Samples obtained from outpatients, or collected in the emergency department or within 48 h from hospital admission were excluded, unless the patient had been

hospitalized within the previous 30 days, according to the definition of nosocomial infection [15]. Paediatric and ambulatory ward samples were also excluded. All samples were de-duplicated based on patient identity and antimicrobial phenotype.

Microbiological species and antimicrobial susceptibility testing (AST) results were obtained from the Department of Microbiology using chromogenic medium or mass spectrometry Vitek®MS (bioMérieux, Marcy-l'Étoile, France) and Vitek 2®(AST-372, bioMérieux) automated system and/or disk diffusion method on Mueller-Hinton agar (Bio-Rad, Hercules, CA, USA), according to the European committee on antimicrobial susceptibility testing (EUCAST) guidelines [16]. Microorganisms were classified as susceptible or resistant using the EUCAST breakpoints [16]. All isolates classified as intermediate were reclassified as resistant.

The resistance rate to a given class of antimicrobial was defined as the percentage of isolate that was non-susceptible to ≥ 1 antimicrobial of this class. The resistance rate to each class of antimicrobial was studied monthly.

2.3. Antimicrobial consumption

Data on AMC were extracted monthly from the pharmacy software. The AMC was determined by counting the number of antimicrobials delivered in care units and expressed in defined daily doses (DDD)/1000 inpatient-days according to the ATC/DDD classification [17].

The focus of the study was on the consumption of penicillin extended-spectrum (J01CA), penicillin and beta-lactamase inhibitor (PBI) (J01CR), anti-pseudomonal activity penicillin and beta-lactamase inhibitor (AAPBI) (J01CR05), cephalosporin (J01D), carbapenem (J01DH), monobactam (J01DF), fluoroquinolone (J01MA), aminoglycoside (J01GB) and sulfamethoxazole-trimethoprim (J01EE01). Consumption of fourth-generation cephalosporin (J01DE01) was not pooled with other cephalosporins because of its broader spectrum of activity and was studied separately. The AMC of the emergency department and paediatric wards was excluded. Antimicrobials dispensed to outpatients were also excluded.

2.4. Statistical analysis

All statistical analyses were performed with R software (version 4.2.0). *P*-values < 0.05 were considered statistically significant. Time series analyses were managed with the Forecast package [18]. AMC trends were evaluated by linear regression and Cochran–Armitage tests were used for AMR. Autoregressive integrated moving average (ARIMA) models were used to describe *E. coli* resistance to several antimicrobial classes. DR models were used to study the relationship between the use of several antimicrobial classes and resistance to a chosen antimicrobial class. The Linear Transfer Function (LTF) was used to link the output series (antimicrobial resistance) to the input series (the use of several antimicrobials) considering possible time lags (delay of antimicrobial effect on AMR acquisition). A dimensionality reduction strategy was used to avoid multicollinearity. More precisely, DR by principal components (DRPC) models were used as described by del Moral & Valderrama [19]. This model enables several antimicrobial classes at different time lags to be considered as input to predict the output (resistance to a given antimicrobial class). In general, one or two principal components were used to summarise the information of the use of different antimicrobial classes. Cross-correlations were used to describe the temporal relationship between AMC and

AMR. The data were split into a train set (2014-2018 period) and a test set (2019 period). The models were built in the train set and R^2 (determination coefficient) was reported to evaluate the percentage of the variance of the observed time-series explained by the model. Forecasts were made with the test set and the accuracy of predictions was evaluated using mean absolute percentage error (MAPE). For each monthly plotted time series, a moving average time series with a window of 7 months (the average of the value observed for one month, the three previous months and the three next months) was added to give a better visual representation.

2.5. Ethics approval

The Institutional Review Board of Nimes University Hospital approved the study protocol (No. 210307) and waived the need for patient signed consent. This study was conducted according to the guidelines of the Declaration of Helsinki.

3. Results

3.1. Trends in antimicrobial consumption

Trends in AMC are shown in Table 1. Extended-spectrum penicillins, PBIs and cephalosporins were the most commonly prescribed antimicrobials. The AMC of half the antimicrobial classes increased: extended-spectrum penicillins ($\beta = 2.35$, $P < 0.001$), AAPBI ($\beta = 1.43$, $P < 0.001$), fourth-generation cephalosporins ($\beta = 0.127$, $P < 0.001$), monobactams ($\beta = 0.03$, $P = 0.002$), and sulfonamides ($\beta = 0.25$, $P = 0.006$). Interestingly, a significant decrease was observed in fluoroquinolone consumption ($\beta = -2.6$, $P < 0.001$). The AMC of other antimicrobial classes was unchanged.

3.2. Trends in antimicrobial resistance

A total of 12 721 samples were screened, 7661 of which were included in the study. Among them, 1241 samples (16%) were collected within the first 48 hours of admission from patients discharged within the last 30 days. Included samples were provided mainly from rehabilitation units ($N = 1214$, 16%), long-term care beds ($N = 869$, 11%), the department of obstetrics and gynaecology ($N = 591$, 8%), intensive care units ($N = 552$, 7%) and the department of gerontology ($N = 541$, 7%).

Annual rates of AMR are presented in Table 2. The highest average rates of AMR were observed for resistance to extended-spectrum penicillins and PBIs (56% and 37%, respectively). Resistance to other beta-lactams ranged from 16% for AAPBI to 11% for cephalosporins, whereas carbapenem resistance was rare, found in only 35 samples (0.4%). Average rates of resistance to sulfonamides, fluoroquinolones and aminoglycosides were 28%, 25% and 8%, respectively.

Rates of resistance to cephalosporins (from 13% to 9%), fluoroquinolones (from 30% to 19%), and aminoglycosides (from 9% to 6%) decreased, whereas the resistance rates to other classes remained stable. Interestingly, decreases in resistance to cephalosporins and fluoroquinolones were correlated ($R^2 = 63\%$).

Table 1
Annual consumption of antimicrobial class from 2014 to 2019.

| Antimicrobial class | Annual antibiotic consumption in DDD/1000 inpatient-days Mean monthly use (min – max) | Change trends | P-value |
|---|--|---------------|---------|
| Aminoglycosides ¹ | 12 (7 – 19) | No | 0.08 |
| Carbapenems ² | 9 (4 – 14) | No | 0.12 |
| Fourth-generation cephalosporin ³ | 0.6 (0 – 3) | Increase | <0.001* |
| Other cephalosporins ⁴ | 35 (25 – 48) | No | 0.11 |
| Monobactams ⁵ | 0.1 (0 – 0.4) | Increase | 0.002* |
| Extended-spectrum penicillins ⁶ | 51 (37 – 68) | Increase | <0.001* |
| Penicillins and beta-lactamase inhibitor ⁷ | 62 (46 – 80) | No | 0.74 |
| Penicillins anti-pseudomonal activity and beta-lactamase inhibitor ⁸ | 13 (7 – 18) | Increase | <0.001* |
| Fluoroquinolones ⁹ | 24 (14 – 41) | Decrease | <0.001* |
| Sulfonamides ¹⁰ | 4 (2 – 9) | Increase | 0.006* |

- ¹ amikacin, gentamicin, tobramycin;
² meropenem, imipenem, ertapenem;
³ ceftepime;
⁴ ceftriaxone, cefotaxime, ceftazidime;
⁵ aztreonam;
⁶ amoxicillin, piperacillin;
⁷ amoxicillin-clavulanic acid, ampicillin-sulbactam;
⁸ piperacillin-tazobactam, ticarcillin-clavulanic acid;
⁹ ofloxacin, norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin;
¹⁰ sulfamethoxazole-trimethoprim
 DDD - defined daily doses

Table 2
Annual resistance rates of antimicrobial class from 2014 to 2019.

| Antimicrobial class | Rate of resistance in <i>E. coli</i> strains (%) | | | | | | Trend | Cochran Armitage test P-value |
|--|--|------|------|------|------|------|----------|----------------------------------|
| | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | | |
| Aminoglycosides ¹ | 9 | 10 | 8 | 8 | 8 | 6 | Decrease | 0.012* |
| Carbapenems ² | 0.4 | 1.4 | 0.5 | 0.0 | 0.4 | 0.2 | No | 0.242 |
| Fourth-generation cephalosporin ³ | 15 | 14 | 14 | 13 | 18 | 14 | No | 0.084 |
| Other cephalosporins ⁴ | 12 | 13 | 11 | 11 | 10 | 9 | Decrease | <0.001* |
| Monobactams ⁵ | 18 | 17 | 17 | 13 | 24 | 21 | No | 0.585 |
| Extended-spectrum penicillins ⁶ | 58 | 56 | 57 | 54 | 56 | 55 | No | 0.21 |
| Penicillins and beta-lactamase inhibitor ⁷ | 45 | 40 | 33 | 28 | 42 | 42 | No | 0.155 |
| Anti-pseudomonal activity penicillins and beta-lactamase inhibitor ⁸ | 17 | 17 | 15 | 14 | 15 | 15 | No | 0.074 |
| Fluoroquinolones ⁹ | 30 | 32 | 24 | 22 | 22 | 19 | Decrease | <0.001* |
| Sulfonamides ¹⁰ | 28 | 26 | 26 | 26 | 28 | 25 | No | 0.778 |

- ¹ amikacin, gentamicin, tobramycin;
² meropenem, imipenem, ertapenem;
³ ceftepime;
⁴ ceftriaxone, cefotaxime, ceftazidime;
⁵ aztreonam;
⁶ amoxicillin, piperacillin;
⁷ amoxicillin-clavulanic acid, ampicillin-sulbactam;
⁸ piperacillin-tazobactam, ticarcillin-clavulanic acid;
⁹ ofloxacin, norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin;
¹⁰ sulfamethoxazole-trimethoprim

3.3. Correlation between antimicrobial consumption and resistance in *E. coli*

Cross-correlations are reported in Table 3.

Fluoroquinolone resistance was significantly correlated with the use of fourth-generation cephalosporins (lag 0; $r = -0.26$), AAPBIs (lag 0 to 3; $r = -0.52$ to -0.39), PBIs (lag 1; $r = 0.24$) and fluoroquinolones (lag 0 to 5; $r = 0.58$ to 0.50). The best multivariate DR model included fluoroquinolone and AAPBI consumption and explained around 54% of the variability in resistance using principal component analysis (Figure 1 and Table 4).

Similarly, cephalosporin resistance was significantly correlated with the consumption of fourth-generation cephalosporins (lag 0; $r = -0.26$), AAPBIs (lag 0 to 2; $r = -0.35$ to -0.29) and fluoroquinolones (lag 0 to 4; $r = 0.34$ to 0.29). DR model analysis included these three antimicrobial classes and explained 15% of variability in resistance (Figure 1 and Table 4).

PBI resistance was correlated with the use of AAPBIs (lag 4 to 10; $R^2 = 21\%$ to 28%), fluoroquinolones (lag 0, 1; $r = 0.25$ and 0.26) and carbapenems (lag 6; $r = -0.25$). However, the best DR model integrated only PBI consumption and explained 53% of PBI resistance (Figure 1 and Table 4).

Extended-spectrum penicillin resistance was correlated with the consumption of cephalosporins (lag 5, 8; $r = -0.26$ and -0.27), PBIs (lag 0, 5; $r = 0.26$ and -0.24) and carbapenems (lag 0; $r = 0.25$).

Multivariate DR model explained 36% of resistance to this class of antimicrobial (Figure 1 and Table 4).

No correlation was found between AMC of other class and AMR acquisition.

3.4. Assessment of DR models as AMR forecasting tools

The comparison of resistance rates predicted for 2019 using the DR models to those observed in 2019 highlighted an error associated with the forecasted value of 12% for fluoroquinolone resistance, 34% for cephalosporin resistance, 20% for PBI resistance and 8% for extended-spectrum penicillin resistance. Curves of observed versus predicted resistance rates are depicted in Figure 1.

4. Discussion

This study investigated the correlation between AMC and acquisition of AMR in *E. coli* strains in a teaching hospital and reported coefficients of correlation $r < 0.6$. Over a six-year period, AMC increased overall and AMR decreased. The DR models highlighted that the decrease in fluoroquinolone use and the increase in AAPBI consumption explained 54% of the decrease in fluoroquinolone resistance and 15% of the decrease in cephalosporin resistance. In addition, 53% of PBI resistance was explained by PBI consumption and 36% of extended-spectrum penicillin resistance by the use of PBIs, cephalosporins and carbapenems, whereas AMR and AMC remained stable for these classes. Moreover, DR models have also demonstrated variable forecasting capacity that could limit their use for ASP conception.

Certain phenomena may have influenced the variation in AMC during the study period. First, local and national ASPs encouraged physicians to increase the use of extended-spectrum penicillins and sulfonamides and to decrease fluoroquinolone consumption [20]. Second, 20 additional intensive care beds and 7 additional haematology beds were opened in the hospital in 2016. This may explain, at least in part, the increased consumption of PBIs, AAPBIs and fourth-generation cephalosporins, as these care units are among the highest consumers of beta-lactams. Also, some prescriptions for fluoroquinolone may have been replaced by prescriptions for AAPBI and fourth-generation cephalosporin. These changes in AMC have

induced changes in the AMR of several bacteria, particularly *E. coli*, also reported nationally [20].

Table 3
Cross-correlation analysis with lag times.

| Resistance | Significant antimicrobial use correlation ($P < 0.05$) | Lag (month) | r^1 |
|---|---|-------------|-----------------|
| Fluoroquinolones ² | Fluoroquinolones ² | 0 to 5 | [0.50 - 0.57] |
| | Fourth-generation cephalosporin ³ | 0 | -0.26 |
| Other cephalosporins ⁶ | Penicillins anti-pseudomonal activity and beta-lactamase inhibitor ⁴ | 0 to 3 | [-0.39 - -0.53] |
| | Penicillins and beta-lactamase inhibitor ⁵ | 1 | 0.24 |
| | Fourth-generation cephalosporin ³ | 0 | -0.26 |
| Penicillins and beta-lactamase inhibitor ⁶ | Penicillins anti pseudomonal activity and beta-lactamase inhibitor ⁴ | 0 to 2 | [-0.24 - -0.35] |
| | Fluoroquinolones ² | 0 to 4 | [0.24 - 0.34] |
| Extended-spectrum penicillin ⁸ | Penicillins anti-pseudomonal activity and beta-lactamase inhibitor ⁴ | 4 to 10 | [0.27 - 0.29] |
| | Fluoroquinolones ² | 0 to 1 | [0.25 - 0.26] |
| | Carbapenems ⁷ | 6 | -0.25 |
| | Other cephalosporins ⁶ | 5 and 8 | [-0.26 - -0.27] |
| | Penicillins and beta-lactamase inhibitor ⁵ | 0 and 5 | [-0.24 - 0.27] |
| | Carbapenems ⁷ | 0 | 0.30 |

¹ r = correlation coefficient;

² ofloxacin, norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin;

³ ceftipime;

⁴ piperacillin-tazobactam, ticarcillin-clavulanic acid;

⁵ amoxicillin-clavulanic acid, ampicillin-sulbactam;

⁶ ceftriaxone, cefotaxime, ceftazidime;

⁷ meropenem, imipenem, ertapenem;

⁸ amoxicillin, piperacillin

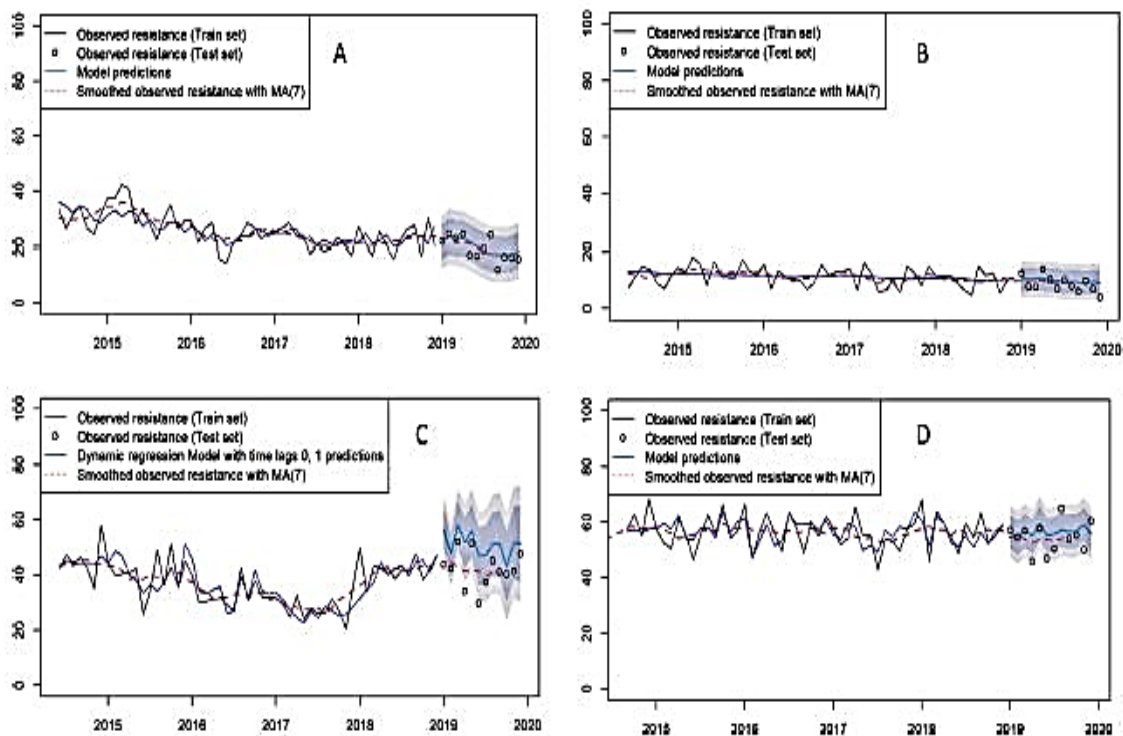


Figure 1. Resistance rates in *Escherichia coli* in a French University Hospital between 2014 and 2018, observed resistance rates in 2019 and forecasted resistance rates in 2019 using dynamic regression models: for fluoroquinolones (A), cephalosporins (B), penicillins/beta-lactamase inhibitors (C) and penicillins (D).

The current study results are in agreement with those of Mahamat et al., who reported that an increase in 1 DDD/10 0 0 inpatient-days of ofloxacin, ciprofloxacin and norfloxacin increased

E. coli resistance to ofloxacin by 0.81%, 0.65% and 0.53%, respectively, with lag times of 4 to 6 months [21]. Similar correlations between fluoroquinolone consumption and resistance have been reported both in hospital settings and in the community [22–24], and appear to be mainly related to the selection for *gyr* and *par* mutant strains of *E. coli* [25]. Thus, the current study confirmed the usefulness of limiting the use of fluoroquinolones to decrease the rate of resistance to this class [26].

In accordance with previous studies [27,28], a correlation was found between fluoroquinolone consumption and resistance to cephalosporins and PBIs. The cross-selection pressure effect that is, at least in part, mediated by fluoroquinolone resistance genes carried on beta-lactamase plasmids, such as *bla CTX-M*, supports this finding [29]. However, the effect of decreased cephalosporin consumption in limiting fluoroquinolone resistance in *E. coli* needs to be confirmed [11, 22]. On the contrary, the negative correlation of AAPBI consumption with resistance to fluoroquinolones and cephalosporins strengthens the current study result, highlighting the potential activity of tazobactam on extended-spectrum beta-lactamase (ESBL) [11, 30]. Similarly, the negative correlation between cephalosporin resistance and consumption of fourth-generation cephalosporin is supported by its activity on AmpC beta-lactamase [32].

Overall, the impact of beta-lactam consumption on AMR seemed limited in the current study. These results are in agreement with the literature, in which few studies have reported correlations between the consumption of beta-lactams and the acquisition of resistance to this class in *E. coli* [22, 31]. Thus, beta-lactams seem to generate less resistance in *E. coli* than fluoroquinolones, which seem to have the greatest influence on the emergence of AMR.

To the best of our knowledge, this study was the first to assess the potential of DR models as AMR forecasting tools. Herein are reported the results of an external validation, showing an error percentage for AMR prediction ranging from 8% to 34%. Thus, within the framework of ASP development, the current study results underlined the need to consider the uncertainty of AMR estimates when DR models are used to plan restriction strategies targeting the AMC with the greatest impact.

This study has some limitations. First, its single-centre retrospective design may limit the generalisability of the results. Second, AMC was low in our hospital [11, 22, 33], below the reported threshold inducing AMR, which may have led to misestimating some correlations [34]. Third, the current study model did not include some mechanisms of AMR acquisition (colonisation pressure and out-hospital AMC), nor individual factors (co-morbidities, antimicrobial dose and duration) [35], and it focused only on *E. coli*, which could have underestimated the impact of AMC on global AMR [36]. However, DR models are reputed to be more informative than other methodologies [12], to assess the link between AMC and AMR, explaining the fraction of AMR related to AMC [35] and accounting for autocorrelation of dependent resistance rates series and lag times. Finally, the COVID-19 pandemic restricted the availability of AMC data for 2020 and 2021, and therefore limited the external validation of the model [37]. Although the predictive abilities were suboptimal, the results highlighted the antibiotics most at risk for AMR, prompting physicians to limit their use in future ASPs.

Table 4
Parameters of multivariate dynamic regression models.

| Model | Lag time | Adjustment after principal component analysis | Parameter (SE ¹) | AIC ² | 2019 RMSE ³ | 2019 MAPE ⁴ | R ² |
|--|----------|---|------------------------------|------------------|------------------------|------------------------|----------------|
| Fluoroquinolones resistance | | | | | | | |
| Moving average | 1 | - | 0.35 (0.16) | 334 | 3.04 | 12% | 54% |
| Fluoroquinolones ⁵ | 0 to 5 | Adjustment in 2 principal components | 1.7 (0.3) | | | | |
| AAPBI ⁶ | 0 to 3 | | 0.59 (0.6) | | | | |
| Penicillins with beta-lactamase inhibitors resistance | | | | | | | |
| Moving average | 1 | - | 0.8 (0.13) | 360 | 10.1 | 34% | 53% |
| Moving average | 2 | - | 0.3 (0.2) | | | | |
| Seasonal moving average | 1 | - | 0.8 (0.47) | | | | |
| PBI ⁷ | 0 | - | 0.17 (0.09) | 318 | 5.5 | 20% | 36% |
| PBI ⁷ | 1 | - | 0.20 (0.09) | | | | |
| Penicillins resistance | | | | | | | |
| Autoregressive resistance | 1 | - | 0.28 (0.13) | 292 | 2.7 | 8% | 15% |
| Seasonal autoregressive resistance | 1 | - | 0.34 (0.14) | | | | |
| Other cephalosporins ⁸ | 5 and 8 | Adjustment in 2 principal components | -2.24 (0.46) | | | | |
| PBI ⁷ | 0 and 5 | | -0.6 (0.52) | | | | |
| Carbapenem ⁹ | 0 | - | - | | | | |
| Cephalosporins resistance | | | | | | | |
| Fourth-generation cephalosporin ¹⁰ | 0 | Adjustment in 1 principal component | 0.37 (0.20) | | | | |
| AAPBI ⁶ | 0 to 2 | | | | | | |
| Fluoroquinolones ⁵ | 0 to 4 | | | | | | |

¹ SE, standard error;

² AIC, Akaike Information Criterion;

³ RMSE, root-mean-square error;

⁴ MAPE, Mean Absolute Percentage Error;

⁵ ofloxacin, norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin;

⁶ AAPBI, anti-pseudomonal activity penicillins and beta-lactamase inhibitor, piperacillin-tazobactam, ticarcillin-clavulanic acid;

⁷ PBI, penicillins and beta-lactamase inhibitor, namely, amoxicillin-clavulanic acid and ampicillin-sulbactam;

⁸ ceftazidime, ceftazidime, ceftazidime;

⁹ meropenem, imipenem, ertapenem;

¹⁰ cefepime;

R², determination coefficient

5. Conclusions

Over a six-year period in a French teaching hospital, the increase in AMC was mainly driven by the increase in consumption of extended-spectrum penicillin (namely amoxicillin) and AAPBI (namely piperacillin-tazobactam), whereas the use of fluoroquinolones dramatically decreased. Among *E. coli* strains isolated during this period, there was a decrease in resistance to fluoroquinolone and cephalosporin, which was correlated with the decrease in fluoroquinolone use and the increase in AAPBI use. Resistance to penicillin remained stable and was correlated with penicillin consumption.

The current study results underlined the complex relationship between AMC and AMR, indicating that it involves multiple mechanisms and depends on antimicrobial classes, and highlighted the burden of fluoroquinolone use. The study also showed that DR models are potentially helpful in ASP development. Nevertheless, the margin of error of the models should prompt clinicians to interpret the forecasted results with caution. Further studies focusing on other bacteria, in one or more hospitals, are mandatory to confirm and extend the current study results.

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Competing Interests

None.

Ethical Approval

This study was conducted according to the guidelines of the Declaration of Helsinki. The Institutional Review Board of Nimes University Hospital approved the study (No. 210307).

Sequence Information

Not applicable.

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