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

**Supplementary data**

Box-Jenkins method

The Box-Jenkins method consisted of the following steps:

Each time series was checked for stationary requirements (constant mean, variance and autocorrelation through time), with the unit root test (augmented Dickey–Fuller test); Some series did not need any transformation while some series required suitable differencing or other types of transformations, e.g., logarithmic transformation, to obtain a stationary series; Once the series was stationary the sample autocorrelation function (ACF) and partial autocorrelation function (PACF) were used to identify the auto-regressive (AR), moving-average (MA) or mixed behaviour (ARMA). The ARIMA (p,d,q) model notation consists of *p,* the order of AR terms, *d,* the order of non-seasonal differencing operations, and *q,* the order of MA terms. Having constructed separate models for each antibiotic and resistance time series, we then diagnosed them for acceptability using the Akaike Information Criterion (AIK) and the Ljung- Box statistic for white noise for residuals.

Following the development of univariate ARIMA models, a linear transfer function modelling method [16,17] was used to investigate the dynamic relationship between antibiotic use and the incidence of resistant isolates, considering possible time delays (lag times). In this study the output or response was the percentage of AMR and the explanatory variable was AC. The cross-correlation function (CCF) between the residuals of the two ARIMA models was used to determine the correlations between the antibiotic use series and the incidence of resistant isolates. The transfer function model was then estimated with significance tests for parameter estimates at a *p* value of <0.05 used to eliminate unnecessary terms. The most parsimonious model was chosen, i.e. the model with the fewest parameters and highest biological plausibility. All final model residuals passed a ‘white noise’ test (based on the Ljung–Box statistics). For each model, the *R*2 coefficient was calculated as goodness-of-fit measure, expressing the fraction of the variance of the dependent variable explained by the dynamic regression model. For the purposes of this manuscript only the significant findings are reported.

**Supplementary Table I.** Chronology of important events in the hospital AMS programme

|  |  |  |
| --- | --- | --- |
| Year | Event/intervention | Effect and/or rational |
| 2007 | Appointment of an antimicrobial pharmacist | Establishment of a formal hospital AMS programme including annual point prevalence surveys and quarterly AC monitoring with feedback to hospital staff and at grand rounds |
| 2009 | Publication of the SARI Guidelines for antimicrobial stewardship in hospitals in Ireland [1] | Rationale for AMS in Irish hospitals and recommended AMS structures and interventions  |
| 2016 | SPC changes to piperacillin/tazobactam dosing recommendations for nosocomial infections & severe pneumonia from 8-hourly intervals to 6-hourly. | Increased consumption which has not been accounted for in revised versions of the WHO DDD values. |
| 2017 | World-wide supply shortage of piperacillin/tazobactam | Reduced availability and adjustment of antimicrobial prescribing guidelines |
| 2017-2018 | Procalcitonin feasibility study in the hospital [2,3] Investigation of its effect on antimicrobial prescribing in respiratory tract infections | Routine PCT testing has not yet been implemented |
| 2018 | The first hospital-acquired CPE case was identified in the study hospital in December 2017 with a further four cases identified in January 2018 [4]  | Universal screening commencement for CPE for all hospital inpatients and grand round presentation in 2018 |
| 2018 | JAMA [5] clinical trial comparing Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for patients with *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance | Increased use of meropenem to treat blood stream infections caused by *E coli* or *Klebsiella pneumoniae* resistant to ceftriaxone |
| 2018 | Update of hospital antimicrobial prescribing guidelines | Empiric guidelines included recommendations for the use of carbapenems for multi-drug resistant infections |
| 2019 | EUCAST clinical breakpoint (v 9.0, valid from 1 January 2019 [6] | Recommended changes included higher antimicrobial doses for the treatment of *Enterobacterales* (gentamicin) and *Pseudomonas* (piperacillin/tazobactam, ceftazidime, ciprofloxacin, amikacin and gentamicin)   |
| 2019 | The European Medicines Agency (safety committee PRAC) review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics [7] | A final legally binding decision by the European Commission in March 2019 recommended increased caution with usage |
| 2019 | Grand rounds presentation including presentation of a review of the restricted antimicrobial prescribing process | Update of the restricted antimicrobial prescribing policy |
| 2020 | March 9th 2020 1st in-patient diagnosed with Covid-19 | Reduced core AMS activity (in person ward rounds, audits, AMS meetings, education and training activities)HSE interim guidelines on COVID-19 treatment guidelines |

Abbreviations: SARI-Strategy for the control of Antimicrobial Resistance in Ireland

SPC-Summaries of Product Characteristics

EUCAST- European Committee on Antimicrobial Susceptibility Testing

PRAC-Pharmacovigilance Risk Assessment Committee of the European Medicines Agency

References

1 SARI Guidelines for Antimicrobial Stewardship in Hospitals in Ireland, 2009. [https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/infectioncontrolandhai/guidelines/File,4116,en.pdf](https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/infectioncontrolandhai/guidelines/File%2C4116%2Cen.pdf).

2 O'Riordan et al. J Antimicrob Chemother 2019;74(11):3352-61.

3 O'Riordan et al. Int J Clin Pharm 2021;43(3):532-40.

4 Fahy et al. Infection Prevention in Practice 2020;2(4):100100.

5 Harris et al. Jama 2018;320(10):984-94.

6 EUCAST. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters., 2019. http://www.eucast.org 2019

7 EMA. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics, 2019. <https://www.ema.europa.eu/en/news/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone>

**Supplementary Table II**: Annual antimicrobial consumption trends for in-patient antibiotic use in the study hospital 2017-2020 (Mean annual DDD/100 bed days)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Antimicrobial | 2017 | 2018 | 2019 | 2020 | Trend | p-value of trend |
| Third Generation cephalosporin |
| Ceftriaxone | 1.8 | 2.27 | 2.8 | 4.59 | Increasing | 0.0006 |
| Carbapenems |
| Ertapenem | 0 | 0 | 0.0497 | 0.212 | Increasing | 0.011 |
| Meropenem | 2.75 | 2.76 | 2.98 | 3.53 | Increasing | 0.054 |
| Fluroquinolones |
| Ciprofloxacin | 7.1 | 6.11 | 6.24 | 5.24 | Decreasing | 0.0012 |
| Levofloxacin | 1.01 | 1.01 | 2.89 | 1.61 | Increasing | 0.076 |
| Aminoglycosides |
| Gentamicin | 4.45 | 5.32 | 4.38 | 3.88 | Decreasing | 0.057 |
| Broad spectrum penicillin combination |
| Piperacillin- tazobactam | 11.7 | 14.2 | 13.8 | 16.8 | Increasing | 0.03 |
| Other antimicrobials |
| Aztreonam | 0.18 | 0.0422 | 0.0347 | 0.296 | Increasing | 0.371 |
| Co-trimoxazole | 1.07 | 0.902 | 0.966 | 2.03 | Increasing | 0.15 |
| Vancomycin | 3.41 | 3.71 | 3.15 | 3.64 | Stable | 0.86 |

**Supplementary Table III**: Percentage of non-duplicate clinical isolates of *E.coli* antibiotic resistance trends in the MUH (Annual mean quarterly resistance %)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Antibiotics | 2017 | 2018 | 2019 | 2020 | Trend | p-value of trend |
| Number of Isolates | 233 | 258 | 255 | 211 |  |  |
| Ceftriaxone | 21 | 15.8 | 13.2 | 14.2 | Decreasing | 0.136 |
| Ciprofloxacin | 32.5 | 31.5 | 27.8 | 25.7 | Decreasing | 0.138 |
| Levofloxacin | 35 | 36.6 | 31.7 | 29.4 | Decreasing | 0.233 |
| Co-trimoxazole | 31 | 38.3 | 32.3 | 34.4 | Stable | 0.69 |
| Ertapenem | 1.39 | 1.59 | 1.12 | 0 | Stable | 0.32 |
| Meropenem | 0 | 0.39 | 0 | 0 | Stable | 0.467 |
| Piperacillin-tazobactam | 23.9 | 26.1 | 21.6 | 18 | Stable | 0.143 |
| Gentamicin | 12.7 | 10.4 | 11.4 | 9.09 | Stable | 0.206 |
| Aztreonam | 22.6 | 17 | 14.8 | 16.5 | Decreasing | 0.07 |

**Supplementary Table IV:** Percentage of non-duplicate clinical isolates of *Klebsiella pneumoniae*

antibiotic resistance trends (Annual mean quarterly resistance %)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Antibiotics** | **2017** | **2018** | **2019** | **2020** | **Trend** | **p-value of trend** |
| Number of Isolates | 72 | 63 | 51 | 59 |  |  |
| Ceftriaxone | 19.6 | 17.8 | 11.9 | 10.8 | Decreasing | 0.043 |
| Ciprofloxacin | 22.4 | 23.3 | 8.01 | 12.5 | Decreasing | 0.014 |
| Levofloxacin | 25.1 | 35.4 | 17.7 | 15.4 | Decreasing | 0.0255 |
| Co-trimoxazole | 20.4 | 19.6 | 13.6 | 11.5 | Decreasing | 0.053 |
| Ertapenem | 0 | 1.39 | 0 | 1.92 | Increasing | 0.471 |
| Meropenem | 0 | 1.39 | 0 | 1.92 | Increasing | 0.471 |
| Piperacillin-tazobactam | 44.8 | 44.3 | 29.9 | 24.7 | Decreasing | 0.012 |
| Gentamicin | 17.8 | 14.6 | 10 | 3.85 | Decreasing | <0.01 |
| Aztreonam | 19.6 | 17.8 | 10 | 10.8 | Decreasing | 0.0462 |

The most frequently isolated other *Enterobacterales* species were:

2017 –165 isolates (Citrobacter (21), Enterobacter(55), Proteus(28), Serratia(21))

2018-151 isolates (Citrobacter (20), Enterobacter(39), Proteus(35), Serratia(20))

2019-167 isolates (Citrobacter (16), Enterobacter(59), Proteus(30), Serratia(22))

2020-133 isolates (Citrobacter (12), Enterobacter(34), Proteus(36), Serratia(21))

**Supplementary Table V:** Study hospital percentage of non-duplicate clinical isolates of other *Enterobacterales*species antibiotic resistance trends (Annual mean quarterly resistance %)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Antibiotics** | **2017** | **2018** | **2019** | **2020** | **Trend** | **p-value of trend** |
| Number of Isolates | 165 | 151 | 167 | 133 |  |  |
| Ceftriaxone | 16  | 13.3  | 19.3  | 18.7  | Stable | 0.231 |
| Ciprofloxacin | 13.8  | 11.2  | 10.2  | 16.1  | Fluctuating | 0.571 |
| Levofloxacin | 15.2  | 11.5  | 13.8  | 18.2  | Fluctuating | 0.353 |
| Co-trimoxazole | 8.28  | 13.9  | 11.2  | 12.8  | Increasing | 0.353 |
| Ertapenem | 0.581 | 1.35  | 1.47 | 5.19 | Increasing | 0.003 |
| Meropenem | 0  | 0.676 | 0  | 0  | Stable | 0.918 |
| Piperacillin-tazobactam | 15.5  | 16.3  | 21.8  | 17.2  | Increasing | 0.426 |
| Gentamicin | 3.3  | 5.29  | 4.76 | 5.51 | Increasing | 0.44  |
| Aztreonam | 14.5  | 12  | 20  | 17.2  | Fluctuating | 0.3  |

**Supplementary Table VI** : Multivariate transfer function model of piperacillin/tazobactam use and temporal relationship with the incidence of non-duplicate clinical isolates of *E.coli* resistant to ceftriaxone

|  |  |
| --- | --- |
|  | (1) |
| (Intercept) | 53.930 \*\*\* [9.003] |
| Piperacillin/tazobactam lag 0 | -1.333 \*\* [-4.564] |
| Piperacillin/tazobactam lag 1 | -0.488 [-2.246] |
| Moving average term 2 | -0.839 \*\*\* [-6.509] |
| N | 12  |
| R squared | 0.864  |
| logLik | -23.135  |
| AIC | 56.270  |
|  \*\*\* p < 0.001; \*\* p < 0.01; \* p < 0.05. T statistics in brackets. |