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BRIEF REPORT

Modeling antibiotic resistance to project future rates: quinolone resistance in *Escherichia coli*

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Abstract While the development of resistance to a new antibiotic is expected, the time course and degree of resistance that will develop are uncertain. Some best projections of the future extent of resistance can be highly impactful for activities, such as antimicrobial development, that require significant lead time. We focus on the surge among hospital isolates in fluoroquinolone-resistant *Escherichia coli* and use data on resistance and consumption to explore and quantify trends in increasing resistance and their relationship to antibiotic use from 2001 to 2007. A mixed-effects logistic regression model produced a good fit to the observed resistance rates during this period in the United States and Europe. The model contained significant effects of time, consumption, and country on developing fluoroquinolone resistance in *E. coli*. There was a larger projected increase in resistance for high fluoroquinolone-consuming countries projected to 2013: 45% (95% confidence interval [CI]: 38%, 53%) for high consumers vs. 33% (95% CI: 25%, 41%) for low consumers. The model was also used to obtain regional projections of resistance that can be used by local prescribers. In order to better understand and predict trends in antimicrobial resistance, it is vital to implement and expand current surveillance systems.

The development of antimicrobial resistance eventually reduces or eliminates the effectiveness of nearly every antibiotic that is introduced. Beyond the general expectation that this phenomenon will occur, there are, however, unanswered questions, such as when and at what rate resistance will develop, and how it will be impacted by antibiotic consumption patterns. The time required to take a new chemical antimicrobial from entity discovery to marketed product can total a decade or more [1]. Thus, some best projections of the future extent of resistance are critical and can be highly impactful for activities, such as drug development, that require significant lead time. We are seeking ways to synthesize the available antibiotic resistance data and to use this information to quantitatively project future trends, accounting for the inherent uncertainty in these estimates.

There are many combinations of antibiotics and pathogenic microorganisms displaying resistance whose time course is important to understand. In this report, we focus on fluoroquinolone-resistant *Escherichia coli*. The development of resistance among fluoroquinolones was once thought to be unlikely due to the synthetic nature of this class [2]. However, there has been a surge among hospital isolates in quinolone-resistant *E. coli* specifically, and in gram-negative bacteria in general, during this decade, accompanied by an apparent dearth of antimicrobials currently in development to treat these targets. Our goal is to develop a model to provide statistical estimates of future resistance rates, while accounting for regional differences and quinolone use.

The European Antimicrobial Resistance Surveillance System (EARSS) provides validated antimicrobial susceptibility data for various pathogen and drug resistance combinations for invasive hospital isolates (blood and cerebrospinal fluid [CSF]) by country [3]. The data used in this report on annual observed fluoroquinolone resistance rates in *E. coli* were obtained from the EARSS interactive database for Europe (http://www.rivm.nl/earss/) in January 2009. The data on fluoroquinolone resistance rates in *E.*

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coli from the United States were obtained from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) surveillance system [4]. The data on annual human standard unit fluoroquinolone consumption was obtained from Intercontinental Marketing Services (IMS, Plymouth Meeting, PA). The time period from 2001 to 2007 was chosen in order to maximize the number of countries with available data on both resistance and consumption. For an oral solid molecule, the standard unit factor is one tablet or capsule; for an injectable molecule, it is one ampoule or vial. The sum total of all standard units for each country was used in this analysis. Standard unit consumption information was divided by the population size for each country and year, to yield a per capita measure, using data from the US Census (http://www.census.gov/) for the United States and from the US Census International Data Base (IDB) by country for Europe. Countries represented in the statistical model were those with data on both resistance (either EARSS or MYSTIC) and consumption (IMS).

A logistic mixed-effects model was developed to fit the existing data on resistance and consumption and to predict future trends in resistance. A logistic functional form is one that has been considered appropriate for describing emerging antibiotic resistance, as it allows for the slow initial rise, period of rapid increase, and final leveling off that have been observed [5, 6]. Both the lme4() library in the R package [7] and the nlmixed procedure in SAS [8] were used to fit the model reported here, and provided consistent results. Note that, while the fluoroquinolone usage in the current year was used as the consumption covariate, the form of the causal effect is likely to be a cumulative or lagged consumption effect. However, because each country's per capita standard unit consumption was fairly constant over time, the consumption in each year should provide a proportional representation of the relative consumption over time by each country.

Figure 1 shows the relationship between the per capita standard unit fluoroquinolone consumption and fluoroquinolone resistance in *E. coli* by country for the US and Europe in 2001 and 2007. A univariate logistic regression model was fitted separately for each year, with consumption as the explanatory variable and the proportion of resistant samples as the response variable. The line indicates the model-predicted resistance for a given consumption level. Data from both 2001 and 2007 display statistically significant relationships between fluoroquinolone consumption and resistance (both $P<0.0001$). However, in 2001, the model predicts an average rate of resistance of 4.4% (95% confidence interval [CI]: 3.8%, 5.0%) for a consumption of 0.5 standard units and an average rate of resistance of 15.7% (95% CI: 14.3%, 17.3%) for a consumption of 2 standard units. By 2007,

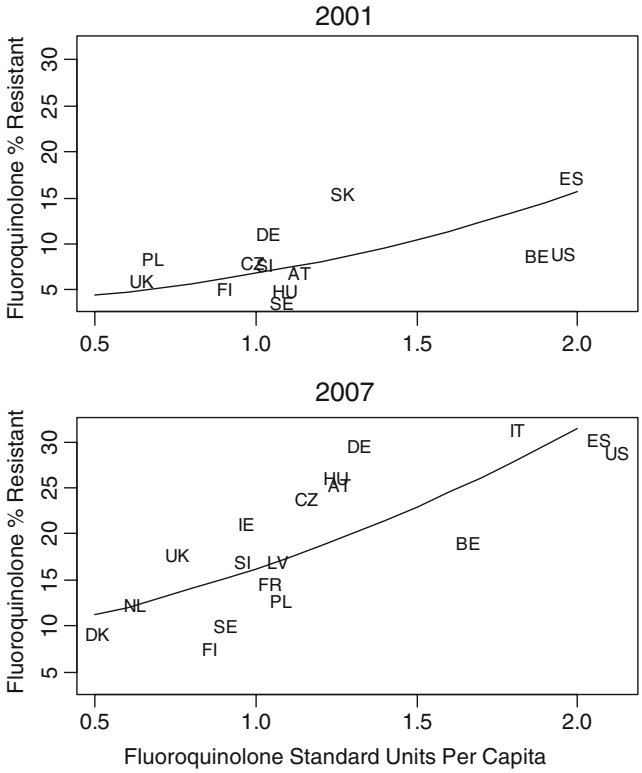

Fig. 1 Relationship between per capita standard unit fluoroquinolone consumption and fluoroquinolone resistance in *Escherichia coli* by country in 2001 and 2007. Country abbreviations: Austria (*AT*), Belgium (*BE*), Czech Republic (*CZ*), Denmark (*DK*), Finland (*FI*), France (*FR*), Germany (*DE*), Hungary (*HU*), Ireland (*IE*), Italy (*IT*), Latvia (*LV*), Poland (*PL*), Slovakia (*SK*), Slovenia (*SI*), Spain (*ES*), Sweden (*SE*), The Netherlands (*NL*), United Kingdom (*UK*)

these rates have at least doubled, with a predicted average rate of resistance of 11.2% (95% CI: 10.7%, 11.6%) for a consumption of 0.5 standard units and an average rate of resistance of 31.4% (95% CI: 30.3%, 32.5%) for a consumption of 2 standard units.

Plots of year and consumption against the logit function of resistance probabilities indicated linear terms to be appropriate to describe these effects.

A more complex model allowing the consumption effect to change in different years did not appear to be necessary, as the additional model parameters were not statistically significant. Thus, the final model used to predict future fluoroquinolone resistance rates in *E. coli* was:

$$\mathrm{Ln}\left(\mathrm{R_{ij}}/\left(1-\mathrm{R_{ij}}\right)\right)=(\beta_0+\mathrm{b_{0i}})+(\beta_1+\mathrm{b_{1i}})\mathrm{T_{ij}}+\beta_2\mathrm{C_{ij}}+\varepsilon_{\mathrm{ij}}$$

where i indexes countries and j indexes time in years. R_{ij} is the proportion of resistant isolates for the ith country in the jth year, and β_0, β_1, β_2 are fixed parameters to measure the intercept (β_0), average slope associated with time (β_1), and fluoroquinolone consumption (β_2). The random coefficients, b_{0i} and b_{1i} allow the model to estimate a different intercept and time slope for each country.

The logistic mixed-effects model indicated significant effects of both time ($P<0.0001$) and consumption ($P=0.0004$) on developing fluoroquinolone resistance in *E. coli* during the period from 2001 to 2007 in the US and Europe. The random country effects, as represented by an offset ($P=0.01$) and slope by year ($P=0.03$) term, also appeared to be significant. One way that this model can be used is to examine and project resistance by consumption patterns on a global scale. To do this, fluoroquinolone consumption was classified as either low (0.6 standard units per year), medium (1 standard unit per year), or high (1.7 standard units per year). Due to the significant relationship between fluoroquinolone consumption and resistance, there is a larger overall projected increase in resistance for high-consuming countries projected to 2013: 45% (95% CI: 38%, 53%) for high consumers vs. 33% (95% CI: 25%, 41%) for low consumers and 37% (95% CI: 30%, 45%) for medium consumers. Thus, even among low-consuming countries, the level of projected resistance rates in 2013 would raise concern for the use of empiric fluoroquinolone therapy for a suspected *E. coli* infection.

This type of model can also be used to obtain regional projections of resistance for local prescribers. This provides an alternative to each country assessing its resistance scenario separately, as the strength of data from multiple regions, such as the effect of consumption, can be incorporated into regional estimates. Figure 2 displays the observed percentages of fluoroquinolone-resistant samples by country over time (solid squares), along with the model predictions extrapolated to 2013 (solid lines) and 95% CIs (dashed lines). For the majority of countries, the correspondence indicates a good fit of the model to the observed resistance rates. To obtain future predictions, it was assumed that the fluoroquinolone consumption per capita remains constant at 2007 levels for the period 2008–2013 (with the exception of Slovakia, whose consumption was assumed to be constant at 2005 levels for the period 2006–2013).

In this report, we present an analysis of the publicly available surveillance data on fluoroquinolone resistance in *E. coli* and examine their relationship with information on fluoroquinolone annual consumption. We develop a

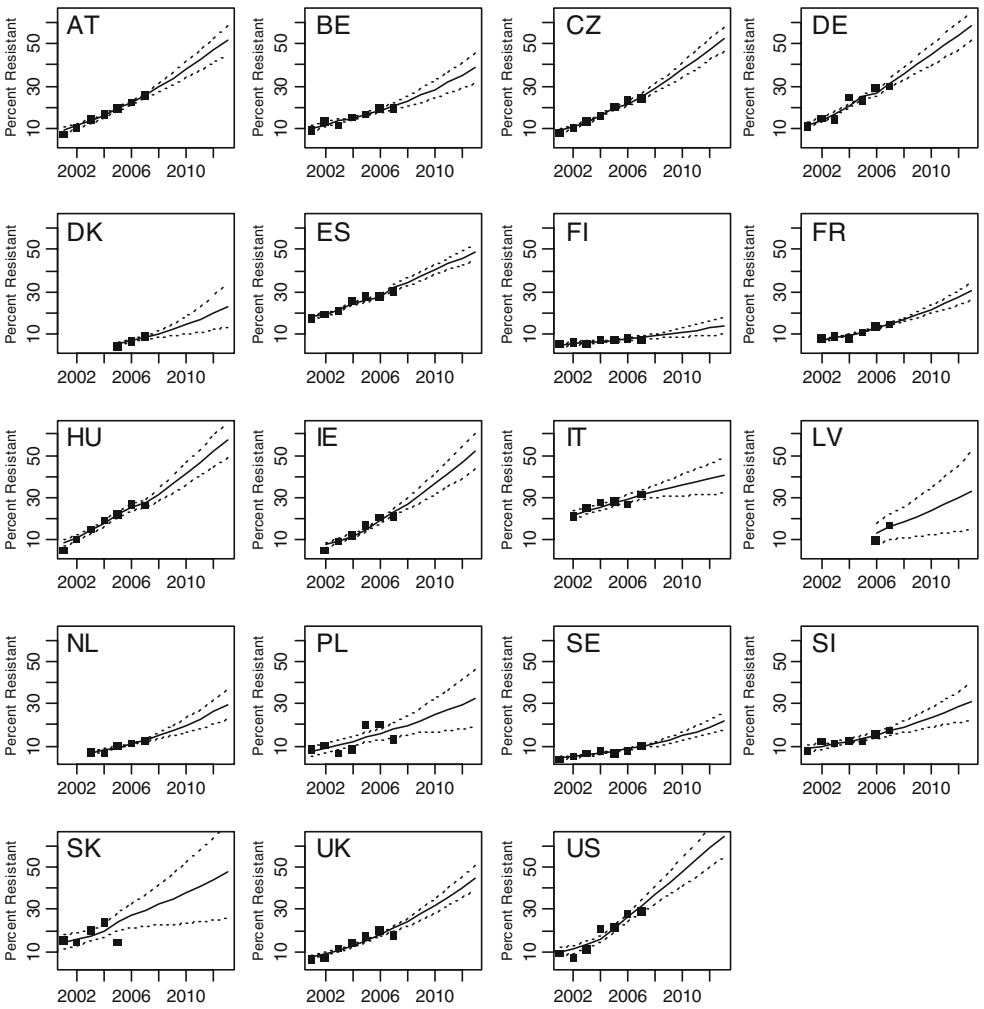

Fig. 2 Observed and model-predicted fluoroquinolone resistance rates in *E. coli*, 2001–2013. The *solid squares* are observed fluoroquinolone resistance rates, the *solid lines* are model-predicted rates, and the *dashed lines* are 95% confidence intervals. Country abbreviations: Austria (*AT*), Belgium (*BE*), Czech Republic (*CZ*), Denmark (*DK*), Finland (*FI*), France (*FR*), Germany (*DE*), Hungary (*HU*), Ireland (*IE*), Italy (*IT*), Latvia (*LV*), Poland (*PL*), Slovakia (*SK*), Slovenia (*SI*), Spain (*ES*), Sweden (*SE*), The Netherlands (*NL*), United Kingdom (*UK*)

logistic mixed-effects model to provide statistical estimates of future resistance rates based on observed consumption and resistance levels. The logistic model fitted to the resistance observed in hospital isolates for the US and Europe presented in this paper projects a period of increasing resistance through to the year 2013, with predictions of up to 45% resistant isolates. Our ability to understand time trends in developing resistance to antimicrobial agents depends heavily on the amount and quality of serial surveillance data that is collected. Currently, the EARSS system is leading the way with information on resistant invasive hospital isolates in Europe. There remains a critical unmet need to understand hospital resistance trends in the rest of the world and community resistance everywhere. This information is indispensable to antimicrobial prescribers, drug developers, and, ultimately, anyone in need of antibiotic therapy.

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