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Significant ecological impact on the progression of fluoroquinolone resistance in *Escherichia coli* with increased community use of moxifloxacin, levofloxacin and amoxicillin/clavulanic acid

Oscar Cuevas[1], Jesús Oteo[1], Edurne Lázaro[2], Belén Aracil[1], Francisco de Abajo[3], Silvia García-Cobos[1], Adriana Ortega[1] and José Campos[1,4]* on behalf of the Spanish EARS-Net Study Group†

[1]*Antibiotic Laboratory, Bacteriology, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Carretera Pozuelo a Majadahonda, 28220 Majadahonda, Madrid, Spain;* [2]*Agencia Española del Medicamento y Productos Sanitarios, Ministry of Health, Madrid, Spain;* [3]*Unidad de Farmacología Clínica, Hospital Universitario 'Príncipe de Asturias', Departamento de Farmacología, Facultad de Medicina, Universidad de Alcalá de Henares, Madrid, Spain;* [4]*Consejo Superior de Investigaciones Científicas, Madrid, Spain*

*Corresponding author. Tel: +34-918223650; Fax: +34-915097966; E-mail: jcampos@isciii.es
†Members of the Spanish EARS-Net Study Group are listed in the Acknowledgements section.

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Objectives: To determine trends in ciprofloxacin resistance and co-resistance to other antibiotic classes in blood isolates of *Escherichia coli*, and to investigate if there is an ecological relationship to the community use of fluoroquinolones and other antibiotics.

Methods: Forty-two Spanish hospitals of the European Antimicrobial Resistance Surveillance Network collected ciprofloxacin and other antibiotic susceptibility data for non-duplicate consecutive *E. coli* isolates from patients with bacteraemia between 2001 and 2009. The nationwide ambulatory use of antibiotics between 1997 and 2008 was determined by WHO methods, and the co-evolution of both parameters was further analysed.

Results: Of the 28307 *E. coli* blood isolates, 27.9% were ciprofloxacin non-susceptible (CIPNS), increasing from 17.6% in 2001 to 32.7% in 2009. A continuous increase was observed between CIPNS and other resistances, including cephalosporin resistance due to the production of extended-spectrum β-lactamases (ESBLs) and non-susceptibility to both amoxicillin/clavulanic acid and tobramycin. Although the total use of antibiotics did not increase, community use of levofloxacin, moxifloxacin and amoxicillin/clavulanic acid increased by 307.2%, 62.6% and 70.1%, respectively. Yearly rates of CIPNS *E. coli* strongly correlated with the use of levofloxacin, moxifloxacin and amoxicillin/clavulanic acid ($r^2 > 0.80$; $P < 0.005$ in all cases).

Conclusions: The rapid increase in CIPNS *E. coli* causing bacteraemia was closely related to the increase in resistance to amoxicillin/clavulanic acid, production of ESBLs and resistance to aminoglycosides. Community use of fluoroquinolones (mainly moxifloxacin and levofloxacin) and of amoxicillin/clavulanic acid represents a significant driver in the progression of fluoroquinolone resistance in bacteraemic *E. coli*.

Keywords: antimicrobial susceptibility, invasive pathogens, *E. coli*

Introduction

Escherichia coli is one of the most prevalent microorganisms, and is known to cause both nosocomial and community-acquired infections.[1,2] Resistance to several antimicrobial agents is not uncommon for this pathogen.[3] Fluoroquinolone resistance and extended-spectrum β-lactamase (ESBL) production in *E. coli* have increased worldwide in the last decade.[1] In many countries, fluoroquinolones are one of the most used antibiotics.[4]

The European Antimicrobial Resistance Surveillance Network (EARS-Net) is focused on the surveillance of antimicrobial resistance in invasive pathogens. According to EARS-Net, the rate of fluoroquinolone resistance in blood isolates of *E. coli* varies among European countries (http://www.rivm.nl/earss).[4] While some studies have failed to identify a link or have identified a very weak association between fluoroquinolone resistance in *E. coli* and fluoroquinolone use, others have suggested that the variation in fluoroquinolone use is consistent with the occurrence of fluoroquinolone resistance at the country level.[5,6] Robust conclusions between resistance and usage may be difficult to achieve, due to confounding factors such as clonal dissemination and lack of statistical power.

Spain has high rates of both antibiotic resistance and antibiotic use, and might be an acceptable setting for the

investigation into whether or not the use of fluoroquinolones and other antibiotic families is influencing the rapid increase in fluoroquinolone resistance in *E. coli*. In this study, we hypothesized that, although the rapid evolution of fluoroquinolone resistance in *E. coli* is likely a multifaceted event, the burden of antibiotic use by the general population is a definitive factor from the ecological standpoint.

The aims of this study included: (i) determination of trends in ciprofloxacin resistance and co-resistance to other antibiotic classes in blood isolates of *E. coli* collected by Spanish hospitals of the EARS-Net over a 9 year period (2001–09); (ii) analysing trends in the community use of fluoroquinolones and other antibiotics over a 12 year period (1997–2008); and (iii) investigating the ecological relationship between the progression of fluoroquinolone resistance in *E. coli* causing bacteraemia and the community use of antibiotics.

Materials and methods

Antibiotic resistance

Forty-two Spanish hospitals participating in the EARS-Net collected antibiotic susceptibility data for all first blood *E. coli* isolates from each patient from 2001 to 2009. Selection of these hospitals was performed according to EARS-Net criteria and selected hospitals were evenly distributed across the country.[1,3] These hospitals serve ~13 million people, which represents ~30% of the total Spanish population.

Each laboratory identified strains and tested their susceptibilities according to standard microbiological procedures, by using commercial microdilution broth systems.[7] Results were scored as susceptible, intermediate or resistant, according to criteria established by the CLSI.[8] For ciprofloxacin-non-susceptible (CIPNS) strains, multidrug resistance was defined as resistance to an additional two or more of the following antibiotics: ampicillin; cefotaxime; gentamicin; and co-trimoxazole. A quality assurance exercise (UK National External Quality Assessment Scheme) was performed annually to ensure comparable results among the hospital laboratories.

Nosocomial infections were defined according to the EARS-Net definition as infections acquired ≥48 h after hospital admission. Patients with community-acquired infections were identified as those who had positive *E. coli* cultures at the time of or within 48 h of hospitalization. All susceptibility data were compiled and analysed with WHONET (http://www.who.int/drugresistance/whonetsoftware/en/).

Antibiotic use

Data regarding the nationwide ambulatory use of antibiotics between 1997 and 2008 were provided by the Spanish Agency for Medicines and Medical Devices (Ministry of Health and Social Policy) and obtained from the Especialidades Consumo de Medicamentos database of retail pharmacy sales of all medicines acquired with National Health System prescriptions. This strategy covered nearly 100% of the Spanish population. The information was tabulated per year and the number of units was converted into defined daily doses (DDDs) of each antibiotic following WHO methodology.[9] We then expressed the number of DDDs per 1000 inhabitants per day (DIDs) for each of the active drug ingredients.

Statistical analysis

The significance of the antimicrobial resistance trends was calculated by the χ^2 test. Trends in antibiotic use were examined by regression model analysis. Statistical analysis of predictors of infection was performed using univariate and multivariate analysis. Variables for which *P* values were <0.1 in the univariate analysis were further examined in the multivariate model using logistic regression. The strength of the association between antibiotic use and ciprofloxacin resistance was determined by linear regression analysis. The proportion of resistance was transformed to the natural logarithm of the odds of resistance. The log odds of resistance (as the dependent variable) was expressed as a simple linear function of the independent variable (antibiotic use).[6] Ciprofloxacin resistance for 2001–09 was correlated with the antibiotic use in the year before. All differences for which *P* values were <0.05 were considered statistically significant. Data were analysed using the SPSS 13.0 software package.

Results

Patients and isolates

The 42 participating hospitals reported data on 28307 consecutive *E. coli* blood infections, corresponding to the same number of patients; 14352 patients (50.7%) were males and 27231 (96.2%) were adults (>14 years). The *E. coli* isolated from 16361 (57.8%) patients caused community-acquired infections. The blood cultures were obtained from patients in the following locations: emergency room (39.2%); internal medicine (30.3%); surgery (6.9%); intensive care units (6.6%); paediatrics (2.1%); and other departments (14.9%).

Ciprofloxacin resistance

Of the 28307 *E. coli* tested, 7898 (27.9%) were CIPNS; 27.2% were resistant and 0.7% were intermediate. In 2009, the percentage of CIPNS *E. coli* was 32.7% (interhospital range 14%–45%; SD 7%).

Among CIPNS isolates, non-susceptibility to other antibiotics was 85.8% for ampicillin, 28.3% for amoxicillin/clavulanic acid, 63.8% for co-trimoxazole and 23.9% for gentamicin. Of the CIPNS isolates, 19.3% were ESBL producers. In 7216 of the 7898 CIPNS isolates (91.4%), information on the five selected antibiotics (see the Material and methods section) was available. Multidrug resistance was present in 5050 (70%) of those isolates. The most prevalent phenotypes included resistance to ampicillin and co-trimoxazole [detected in 2203 CIPNS *E. coli* isolates (43.6% of multiresistant strains and 7.8% of isolates overall)], and resistance to ampicillin, co-trimoxazole and gentamicin [detected in 879 isolates (17.4% of multiresistant strains and 3.1% of strains overall)]. Multidrug resistance was more prevalent in nosocomial CIPNS isolates (78.5%) than in community-acquired CIPNS isolates (67.4%) [odds ratio (OR) 1.77; 95% confidence interval (CI) 1.59–1.97; $P<0.0001$].

Ciprofloxacin and other antibiotic resistance trends

The annual rates of CIPNS *E. coli* increased from 17.6% (2001) to 32.7% (2009) (χ^2 for trend 315.1; $P<0.0001$). The percentage of CIPNS increased in all participating hospitals. This increase was observed in isolates causing both nosocomial infections (13.8% change; χ^2 for trend 115.2; $P<0.0001$) and community-acquired infections (17.3% change; χ^2 for trend 217; $P<0.0001$). CIPNS *E. coli* causing community-acquired infections increased faster than nosocomial isolates.

The proportion of CIPNS *E. coli* producing an ESBL or non-susceptible to amoxicillin/clavulanic acid or tobramycin continually increased between 2003 and 2009 (Figure 1). Of the CIPNS

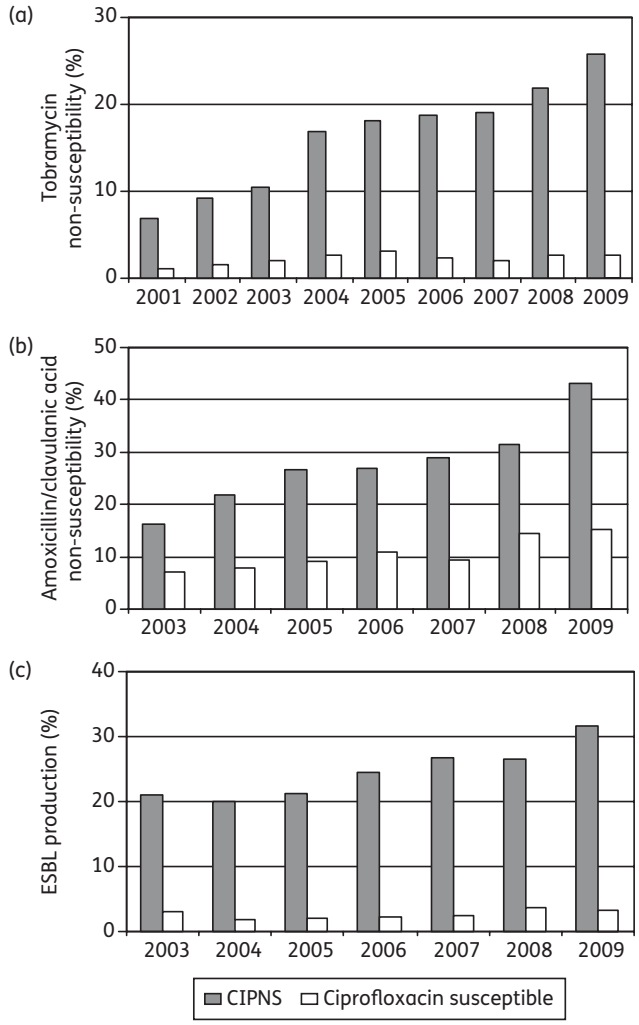

Figure 1. Relationships between ciprofloxacin susceptibility in blood isolates of *E. coli* and evolution of ESBL production (a), amoxicillin/clavulanic acid non-susceptibility (b) and tobramycin non-susceptibility (c).

E. coli, 19.3% produced ESBLs in comparison with 2.4% of the ciprofloxacin-susceptible isolates (OR 9.76; 95% CI 8.77–10.87; $P<0.0001$). In addition, the proportion of CIPNS isolates also producing ESBL consistently increased over time, from 6.8% in 2001 to 25.8% in 2009 (χ^2 for trend 116.1; $P<0.001$). In ciprofloxacin-susceptible *E. coli*, ESBL production also increased from 1.1% in 2001 to 2.9% in 2009 (χ^2 for trend 16.34; $P=0.04$). Similarly, of the CIPNS *E. coli*, 28.3% were non-susceptible to amoxicillin/clavulanic acid compared with 10.7% of ciprofloxacin-susceptible isolates (OR 3.295; 95% CI 3.04–3.57; $P<0.0001$). In CIPNS isolates, non-susceptibility to amoxicillin/clavulanic acid continuously increased from 16.4% in 2003 to 43.1% in 2009 (χ^2 for trend 153.8; $P<0.0001$). In ciprofloxacin-susceptible *E. coli*, non-susceptibility to amoxicillin/clavulanic acid also increased from 7.2% in 2003 to 15% in 2009 (χ^2 for trend 34.17; $P<0.0001$). In contrast, among CIPNS *E. coli*, multidrug resistance showed a non-significant increase from 69.5% in 2001 to 73.3% in 2009 (χ^2 for trend 2.53; $P=0.11$). In a recent multicentre study carried out in Spain, CTX-M-15-producing *E. coli* were detected in 70.4% of the EARS-Net hospitals; of these, almost 28% were also tobramycin resistant, 13.4% were gentamicin resistant and 16.4% were resistant to amoxicillin/clavulanic acid.[10]

Predictors of infection with CIPNS

Males and adults over age 65 years had a higher risk of infection from CIPNS isolates (Table 1). By univariate analysis, patients admitted to the internal medicine service had a higher risk of infection with CIPNS *E. coli*, but this association was not confirmed by multivariate analysis (Table 1).

E. coli infections acquired after 48 h of admission were significantly associated with a higher risk of being identified as CIPNS. Also, *E. coli* producing ESBLs or non-susceptible to amoxicillin/clavulanic acid or aminoglycosides (gentamicin and/or tobramycin) had a higher risk of being identified as CIPNS in all cases (Table 1).

Community antibiotic use

Community use of fluoroquinolones (WHO code J01M) increased in Spain from 2.184 DIDs in 1997 to 2.424 DIDs in 2008 (11.0% increase; $r^2=0.89$; $P<0.0001$). No significant changes were observed for ciprofloxacin use (1.032 DIDs in 1997 and 1.117 DIDs in 2008; $r^2=0.33$; $P=0.169$), but the use of levofloxacin and moxifloxacin strongly increased over time. Levofloxacin use was 0.138 DIDs in 2001 and 0.562 DIDs in 2008 (307.2% increase; $r^2=0.98$; $P<0.0001$). Moxifloxacin use was 0.214 DIDs in 2001 and 0.348 DIDs in 2008 (62.6% increase; $r^2=0.85$; $P=0.008$).

During the study period, amoxicillin/clavulanic acid was the most widely used antibiotic in Spain at the community level, increasing from 4.445 DIDs in 1997 to 7.562 DIDs in 2008 (70.1% increase; $r^2=0.91$; $P<0.0001$). Nonetheless, the total antibiotic use decreased from 21.337 DIDs in 1997 to 19.704 DIDs in 2008.

Correlation of CIPNS with community antibiotic use

Yearly rates of CIPNS *E. coli* showed a good correlation with outpatient use of fluoroquinolones ($r^2=0.68$; $P=0.006$) or amoxicillin/clavulanic acid in the previous year, with the strongest correlations being observed for moxifloxacin, levofloxacin and amoxicillin/clavulanic acid (Figure 2). CIPNS rates strongly correlated with the use of levofloxacin plus moxifloxacin ($r^2=0.93$), amoxicillin/clavulanic acid ($r^2=0.87$), moxifloxacin ($r^2=0.85$) and levofloxacin ($r^2=0.81$) (Figure 2). However, ciprofloxacin use did not show correlation with CIPNS ($r^2=0.06$; $P=0.51$). No correlation was detected between CIPNS *E. coli* and the overall antibiotic use ($r^2=0.40$; $P=0.07$) or the use of other antibiotic families.

Discussion

Although antibiotic resistance is a complex subject, the use and misuse of antibiotics are known to play pivotal roles in its development.[6] In addition to the use of fluoroquinolones, other factors, including clonal dissemination or transmission by the

Table 1. Predictors of infection with CIPNS *E. coli* causing bacteraemia

		Univariate analysis		Multivariate analysis	
	CIPNS (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Male	31.7	1.476 (1.398–1.558)	<0.0001	1.383 (1.286–1.488)	<0.0001
Adults >65 years old[a]	30.5	1.338 (1.261–1.419)	<0.0001	1.393 (1.286–1.510)	<0.0001
Internal medicine	31.6	1.357 (1.286–1.432)	<0.0001	0.990 (0.804–1.219)	0.922
Surgery	26.5	0.924 (0.829–1.029)	0.158	—	—
ICU admission	26.2	0.913 (0.819–1.019)	0.107	—	—
Emergency room	25.6	0.828 (0.784–0.874)	<0.0001	0.931 (0.847–1.024)	0.140
Paediatric wards	9.0	0.247 (0.199–0.306)	<0.0001	1.728 (0.267–11.161)	0.566
Infection >48 h after admission	31.0	1.292 (1.225–1.364)	<0.0001	1.239 (1.148–1.337)	<0.0001
ESBL producers	75.3	9.419 (8.446–10.504)	<0.0001	6.827 (5.841–7.980)	<0.0001
Amoxicillin/clavulanic acid NS	52.3	3.766 (3.475–4.081)	<0.0001	2.571 (2.325–2.843)	<0.0001
Aminoglycosides NS[b]	78.0	12.280 (11.153–13.523)	<0.0001	10.436 (9.209–11.827)	<0.0001

NS, non-susceptible strains.
[a]Patients >14 years old were included.
[b]Non-susceptibility to gentamicin and/or tobramycin.

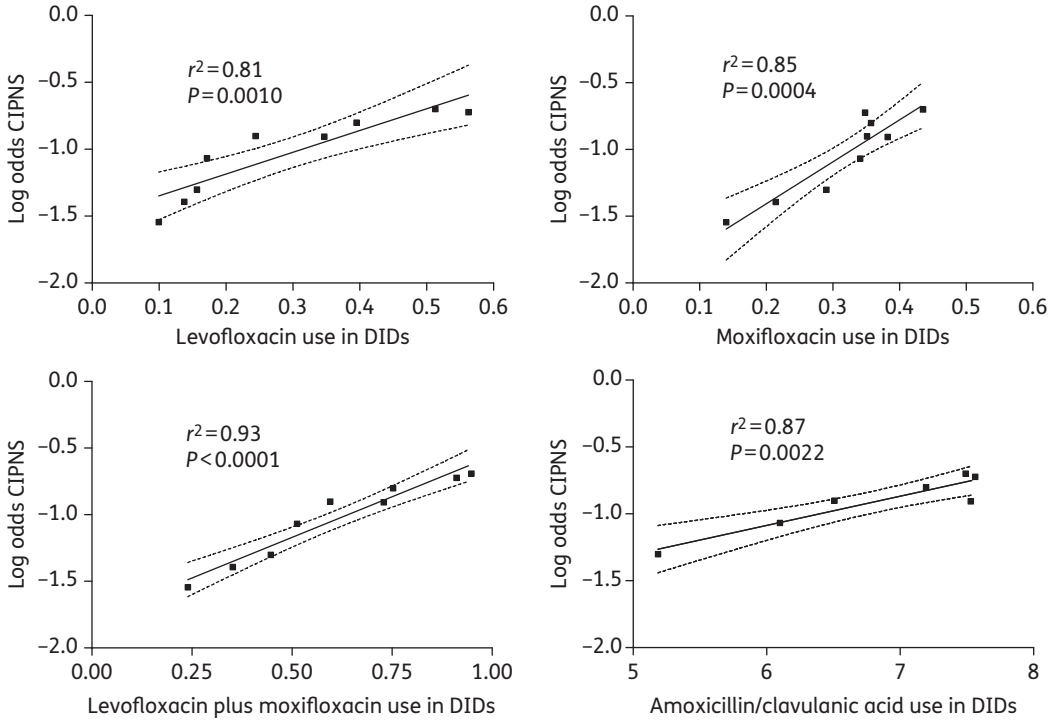

Figure 2. Occurrence of CIPNS in *E. coli* causing blood infections (years 2001–09), plotted against outpatient use of levofloxacin, moxifloxacin, levofloxacin plus moxifloxacin (years 2000–08) and amoxicillin/clavulanic acid (years 2002–08) in Spain with 95% CIs. DIDs, DDDs/1000 inhabitants/day; log odds, natural logarithm of the OR.

ingestion of contaminated food from animals, can be implicated in the spread of ciprofloxacin resistance in *E. coli*. In Europe, ecological studies based on routine surveillance data have shown a relationship between antibiotic use and resistance, and promote interventions to reduce antimicrobial use at a national level.[6] Although community use of antibiotics constitutes ~90% of the total human use,[4] a limitation of this study was that national representative data of hospital and veterinary use were not available.

In urinary pathogens, prolonged use of low doses of fluoroquinolones, such as ciprofloxacin or levofloxacin, was identified as a significant risk factor for the acquisition of fluoroquinolone

resistance.[11] CIPNS *E. coli* causing bacteraemia increased from 8.2% in 2001 to 25.6% in 2006 in the UK and Ireland.[12] A multicentre study from Finland failed to demonstrate an association between fluoroquinolone use and fluoroquinolone resistance in *E. coli*.[5] It has been suggested that co-selection of resistance can be the consequence of the use of different antimicrobial families.[13] In a recent study performed in France, the authors suggest that ciprofloxacin resistance in *E. coli* in hospital is linked to the consumption of fluoroquinolones within the hospital and its surrounding community, and, among all fluoroquinolones, levofloxacin use was found to be the most important factor.[14]

In this study, we report a number of findings of potential epidemiological, clinical and public health interest, including: (i) CIPNS *E. coli* causing bacteraemia constitute an extraordinary and rapidly progressing problem at both the community and nosocomial level; (ii) the rapid progress of CIPNS *E. coli* is closely related to the progression of resistance to amoxicillin/clavulanic acid and aminoglycosides, and the production of ESBLs; (iii) for the first time, we have shown that increased amoxicillin/clavulanic acid use (the most used antibiotic in Spain and other countries) correlates with an increased resistance to ciprofloxacin in blood isolates of *E. coli*—this finding is probably due to a co-selection event;[13] (iv) increased community use of fluoroquinolones (mainly moxifloxacin and levofloxacin) and amoxicillin/clavulanic acid correlates with ciprofloxacin resistance in *E. coli*; and (iv) current and future actions addressed at the improvement of fluoroquinolone resistance in *E. coli* should be focused on the prudent use of antibiotics, paying special attention to the use of moxifloxacin and levofloxacin, as well as other antibiotic families.

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Members of the Spanish EARS-Net Study Group

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Transparency declarations

None to declare.

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