Ir J Med Sci (2017) 186:733–741
DOI 10.1007/s11845-016-1538-z

ORIGINAL ARTICLE

Antibiotic resistance patterns of *Escherichia coli* urinary isolates and comparison with antibiotic consumption data over 10 years, 2005–2014

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Received: 19 August 2016 / Accepted: 25 December 2016 / Published online: 4 January 2017

Abstract

Introduction *Escherichia coli* is a common cause of urinary tract infections (UTI). Reviews of antibiotic resistance of this organism can inform choice of empiric treatment of UTI and other infections and strategies for combating antimicrobial resistance. We reviewed laboratory and hospital pharmacy records to assess trends in non-susceptibility rates and the effect of antimicrobial stewardship interventions.

Methods A retrospective observational study of isolates of *E. coli* from MSU samples at a Dublin teaching hospital from inpatients and community, obtained from January 2005 to December 2014. Susceptibility to a panel of antibiotics was determined using the disc diffusion method, as well as extended-spectrum beta-lactamase (ESBL) production status. Trends in resistance were plotted graphically and analysed in a descriptive manner.

Results Except for nitrofurantoin and gentamicin, non-susceptibility increased for all antimicrobials tested. Co-amoxiclav non-susceptibility reached 48% in hospital and 32.6% in the community by 2014. Piperacillin–tazobactam non-susceptibility increased from 6.8 to 23.8% in hospital and from <1 to 12.5% in community, with similar increases for ESBL producing isolates. Ciprofloxacin non-susceptibility peaked at 25.5% in hospital in 2012 and 11.44% in the community in 2014.

Conclusion *Escherichia coli* isolates from community MSU samples have high rates of non-susceptibility to trimethoprim and co-amoxiclav. Nitrofurantoin remains the best empiric therapy for cystitis. Increasing non-susceptibility to co-amoxiclav and piperacillin–tazobactam in hospital isolates is concerning. Ciprofloxacin non-susceptibility is increasing faster in the community than in hospital. A sharp reduction in hospital fluoroquinolone consumption did not result in a significant reduction in ciprofloxacin non-susceptibility of hospital *E. coli* isolates.

Keywords Antibiotic resistance · Antibiotic consumption · *E. coli* · Epidemiology

Introduction

Escherichia coli (*E. coli*) is a common cause of urinary tract infection (UTI) and bloodstream infection in both hospitals and the community and may also cause wound, peritoneal, and respiratory tract infections. It belongs to the family Enterobacteriaceae and comprises part of the normal gastrointestinal tract flora of humans and animals [1]. The emergence of high rates of antimicrobial resistance (AMR) in *E. coli* has been a cause of concern internationally [2]. This trend is greatly facilitated by the ease with which *E. coli* can acquire mobile genetic elements carrying resistance determinants and also by the spread of particular pathogenic clones [3]. Important resistant determinants include genes encoding extended-spectrum beta-lactamase (ESBL) and carbapenemase enzymes, which can hydrolyse and render ineffective most beta-

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lactam antibiotics. This type of resistance is frequently accompanied by resistance to multiple other antibiotic classes, including fluoroquinolones and aminoglycosides, as seen in the internationally disseminated multi-drug-resistant ST-131 clone of *E. coli* [4].

Analysis of local *E. coli* AMR data may highlight emerging trends in resistance, which will inform empiric antimicrobial prescribing guidelines for urinary tract and other infections and guide antimicrobial prophylaxis regimens for certain urological procedures. This type of analysis may also inform broader strategies to mitigate the impact of AMR, by examining the relationship between antibiotic resistance trends and known drivers of resistance.

Antimicrobial resistance in *E. coli* is driven by the use of antimicrobials in people and animals, which exerts selection pressure on pathogenic and commensal bacteria resulting in the emergence and spread of resistant strains. Guidelines for empiric treatment of non-severe or lower UTI generally promote the use of narrow spectrum antimicrobials. In Irish and UK hospitals, recent antimicrobial stewardship (AMS) initiatives have promoted the use of beta-lactam/beta-lactamase inhibitor combination antibiotics, such as co-amoxiclav and piperacillin–tazobactam, in preference to third generation cephalosporins and fluoroquinolones, for the empiric treatment of severe sepsis and sepsis of urinary tract origin [5–7]. This approach is driven by a desire to reduce selection pressure for *Clostridium difficile* and Methicillin-resistant *Staphylococcus aureus* (MRSA); however, the increased use of beta-lactam/beta-lactamase inhibitor combinations may inadvertently drive selection of resistant gram-negative bacteria, such as *E. coli* [8].

We present a 10 year review of AMR data for *E. coli* isolated from mid-stream urine (MSU) culture and for antimicrobial consumption at a large Dublin teaching hospital, from 2005 to 2014. We aimed to compare resistance rates in hospital and in the community over time and to use inpatient antibiotic consumption data to analyse the impact of AMS interventions on inpatient *E. coli* non-susceptibility rates.

Methods

We carried out a retrospective observational study of all isolates of *E. coli* from MSU samples at our institution from January 2005 to December 2014. Data were retrieved from the microbiology laboratory information system of the Mater Misericordiae University Hospital. MSU samples were defined as any urine samples not labelled as a catheter urine sample (which were excluded). We also excluded urine cultures indicating mixed growth or pathogens other than *E. coli*. A total of 264,905 MSU samples were submitted to the laboratory in this period. We included only the first isolate of *E. coli* from each patient, to avoid overestimation of resistance rates from repeat submission of urine specimens.

Each isolate was classified as being of community or hospital origin. Community samples included those originating from general practitioners in the surrounding catchment area and samples from hospital outpatients and long-term care facilities. Hospital samples included those submitted from the emergency department as well as from hospital wards.

Urine culture was undertaken for all submitted specimens, regardless of urine microscopy results. If pure growth of $\geq 10^4$ colony forming units of *E. coli* was obtained, then antimicrobial susceptibility testing (AST) was performed. Antimicrobial susceptibility was determined using the disc diffusion method according to guidelines of the Clinical and Laboratory Standards Institute (CLSI), in its respective current version, until June 30th 2012 [9]. Thereafter, disc diffusion testing was performed according to criteria recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), in its respective current version (http://www.eucast.org/ast_of_bacteria/disk_diffusion_methodology/). The following antimicrobials were tested: trimethoprim, nitrofurantoin, amoxicillin, co-amoxiclav, piperacillin–tazobactam, ciprofloxacin, and ertapenem. Cefpodoxime disc diffusion testing was performed for all isolates as a screening test for resistance to the third generation cephalosporins (3GCs).

If the cefpodoxime screen was positive, then the minimum inhibitory concentration (MIC) value for the 3GCs cefotaxime and ceftazidime was determined using Vitek II antimicrobial susceptibility testing (AST) card (bioMérieux, France). ESBL status was determined using either double disc synergy (Oxoid Diagnostics, UK) or a gradient method (Liofilchem MIC Test, Italy).

From January 1st 2006 through to June 30th 2012, results were interpreted using contemporaneous recommendations by CLSI [10]. From July 1st 2012, results were interpreted using criteria recommended by the EUCAST in its respective current version (http://www.eucast.org/clinical_breakpoints/). We defined non-susceptibility as an AST result of "intermediate" (I) or "resistant" (R), according to the interpretation criteria in use at the time of testing. From March 2014, the laboratory introduced a new antimicrobial susceptibility recommendation for co-amoxiclav if used to treat uncomplicated UTI only. This was in accordance with EUCAST recommendations that treatment success for "cystitis", as opposed to systemic infection, is likely even with relative resistance to co-amoxiclav. We included AST results calculated using both the "systemic" and "uncomplicated" UTI breakpoint separately in our analysis for 2014.

We determined the trend in isolation of multi-drug resistant (MDR) *E. coli*, defined as non-susceptibility to three or more of the following antibiotic classes: ampicillin, 3GCs, fluoroquinolones (ciprofloxacin), and aminoglycosides (gentamicin). Total hospital antibiotic consumption data, calculated as Defined Daily Dosages (DDD), were obtained from the pharmacy department.

Trends in resistance were plotted graphically and analysed in a descriptive manner for evidence of an effect of changes related to hospital AMS policies. Student's *T* Test was performed to assess for trends in resistance in consecutive years and between hospital and community samples, to assess for trends in resistance in consecutive years, to assess changes in hospital DDD antimicrobial consumption, and to assess changes between hospital antimicrobial consumption and rates of resistance. The average change of resistance for each antimicrobial was calculated.

Results

In total, 264,905 MSU samples were submitted to the laboratory for analysis over 10 years. A total of 20,475 single patient isolates of *E. coli* were eligible for analysis after application of our selection criteria, the majority of which were community isolates (76.7%, $n = 15,\ 695$). Figure 1a, b shows the number of MSU samples received from hospital and community, the proportion positive for *E. coli* and the rates of MDR and ESBL positive *E. coli* each year.

Trends in non-susceptibility rates for individual antibiotics are shown in Fig. 2a–g. Non-susceptibility rates were higher in hospital than the community for all antimicrobials tested.

Most isolates of *E. coli* (>95%) remained susceptible to nitrofurantoin throughout the period. Average trimethoprim non-susceptibility was stable in both hospital and community (37.8 and 31.4%).

We observed non-susceptibility to amoxicillin of 70.5% in hospital and 62.4% in the community by 2014. Co-amoxiclav non-susceptibility increased to 48% in hospital and 32.6% in the community by 2014. Applying the EUCAST "lower UTI" breakpoint for 2014, rather than the "systemic infection" breakpoint, resulted in somewhat lower co-amoxiclav non-susceptibility rates of 35.8 and 24.2%, respectively.

Piperacillin–tazobactam non-susceptibility increased in hospital isolates from 6.9% in 2006 to 23.9% in 2014 and from <1 to 12.5% in the community. We observed a similar increase in for ESBL producing and MDR *E. coli* isolates from hospital samples. These trends correlated with an increase in the total hospital consumption of beta-lactam/beta-lactamase inhibitors (33 536 DDD in 2014), but not 3GCs (3575 DDD in 2014). Oral co-amoxiclav dosing increased locally from twice to three times daily from 2010, contributing to the raised consumption of beta-lactam/beta-lactamase inhibitors. Carbapenem non-susceptibility was rare, with one resistant isolate detected from hospital and community, respectively.

Gentamicin non-susceptibility remained low throughout, averaging 9.5% in hospital and 4.2% in the community. Ciprofloxacin non-susceptibility peaked at 25.5% in hospital in 2012 and has declined slightly since, but has continued to increase in the community, reaching 11.4% by 2014. Ciprofloxacin restriction was implemented in 2008, due to concerns about increasing fluoroquinolone resistance nationally, and was accompanied by a decline in hospital fluoroquinolone consumption (Fig. 3).

Rates of non-susceptibility to trimethoprim, amoxicillin, and gentamicin were significantly greater in hospital compared with community isolates ($p < 0.001$, Table 1), and for co-amoxiclav ($p = 0.023$), but not for piperacillin–tazobactam ($p = 0.08$). Ciprofloxacin was the only antimicrobial for which the change in non-susceptibility was significantly greater in the community than hospital (average increase per year 0.40 versus −0.26%, $p < 0.001$).

Discussion

Our review found increasing non-susceptibility of urinary *E. coli* isolates to beta-lactam/beta-lactamase inhibitors and quinolones in both hospital and community and a large increase in the consumption of beta-lactam/beta-lactamase inhibitors in our institution. On-going surveillance of AMR in *E. coli* can enable clinicians to make informed decisions when choosing empiric antibiotics for urinary tract infections and other infections likely to be caused by this organism [11]. A recent UK review of AMR highlighted that monitoring of antimicrobial usage is a key component of effective surveillance, as it illustrates the link between antibiotic consumption and resistance [12]. The authors of this report called for a surveillance system that encompasses antibiotic consumption and resistance and on-going surveillance of different "drug/bug" combinations, as well as identification of key resistance mechanisms, such as ESBL production.

Current Irish guidelines for antimicrobial prescribing in primary care (http://www.antibioticprescribing.ie/) recommend nitrofurantoin, trimethoprim, and fosfomycin as first-line therapy for adult uncomplicated UTI. Our community nitrofurantoin resistance remains very low, supporting its recommendation in the guideline. Community trimethoprim non-susceptibility rates are stable at 31.4%, similar to trimethoprim resistance rates in the west of Ireland in 1995

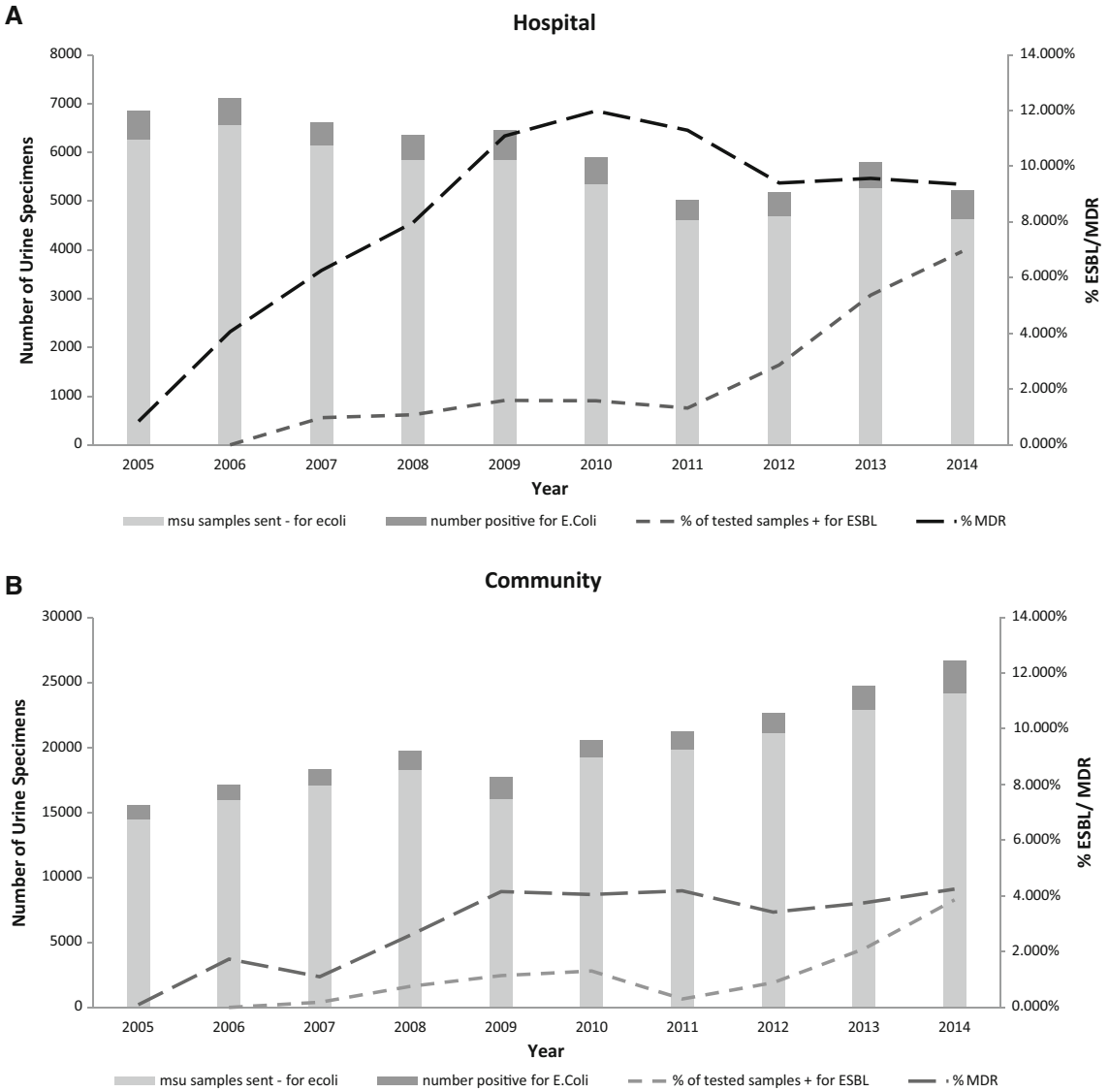

Fig. 1 **a** Total number of urine specimens received and proportion (%) positive for *E. coli* (*bar chart*) from inpatient hospital patients between 2005 and 2014 is shown. The percentage of these samples with extended-spectrum beta-lactamase activity (ESBL) or meeting criteria for multi-drug resistance (MDR) is represented by the dotted and dashed lines, respectively. **b** Total number of urine specimens received and proportion (%) positive for *E. coli* (*bar chart*) from community specimens between 2005 and 2014 is shown. The percentage of these samples with extended-spectrum beta-lactamase activity (ESBL) or meeting criteria for multi-drug resistance (MDR) is represented by the *dotted* and *dashed lines,* respectively

[13]. However, international guidelines on the treatment of UTI discourage using an agent for empiric therapy where resistance rates exceed 20% [14]. Given our finding of persistently high non-susceptibility rates, trimethoprim should only be considered an appropriate choice for selected patients for whom empiric nitrofurantoin is contra-indicated due to intolerance, allergy, or reduced renal function, or in cases of nitrofurantoin resistance identified by culture, e.g. inherent resistance in *Proteus mirabilis* or acquired resistance in *E. coli.*

The use of co-amoxiclav or ciprofloxacin for empiric treatment of lower UTI in primary care is to be discouraged, even in the setting of low resistance rates, as they are more likely to select for resistance. Ciprofloxacin in particular has been identified as a driver for the selection and dissemination of multi-drug resistant *E. coli* ST131 strain [15]. Co-amoxiclav non-susceptibility rates now exceed 20% in our community, compared to 10.1% resistance in a Dublin community setting previously [16], despite the 2014 implementation of a less stringent laboratory definition of resistance to co-amoxiclav for treating uncomplicated UTI. The significant likelihood of treatment failure with empiric co-amoxiclav is another reason to limit its use in UTI treatment. Community non-susceptibility

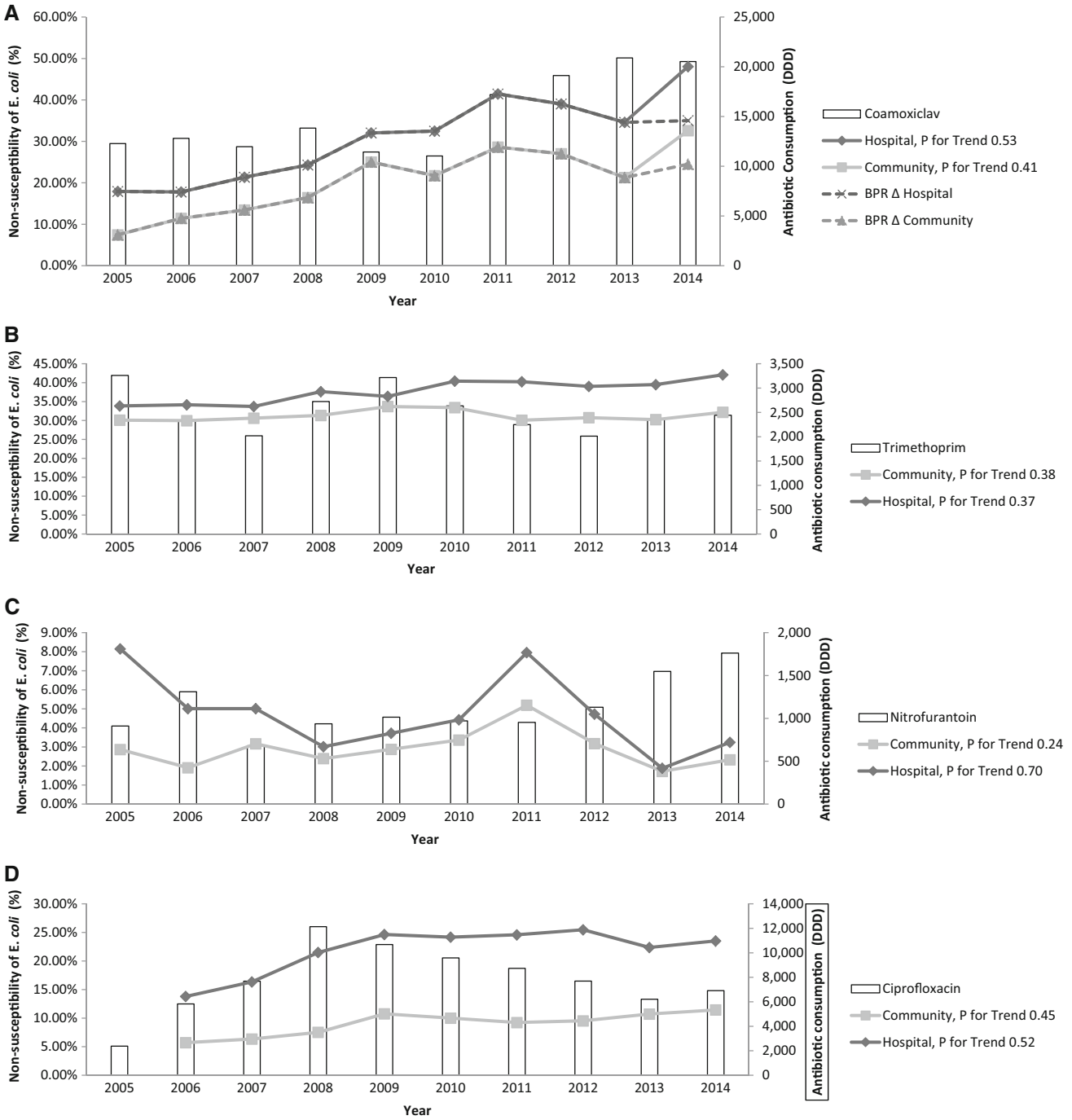

Fig. 2 **a**–**g** Non-susceptibility (%) of *E. coli* isolated from urine specimens from hospital and community samples to each of the following antibiotics: **a** co-amoxiclav, **b** trimethoprim, **c** nitrofurantoin, **d** ciprofloxacin, **e** amoxicillin, **f** gentamicin, and **g** piperacillin/tazobactam (*lines*). The defined daily dose (DDD) consumption of the respective antibiotic by hospital inpatients over the same period (2005–2014) is represented by *bars*. *p* value for the trend in non-susceptibility for the respective antibiotics in community and hospital is displayed in each panel. Student's *T* Test for Hospital versus Community non-susceptibility over the study period was also performed; the respective *p* values were as follows: **a** co-amoxiclav, $p = 0.02$, **b** trimethoprim, $p < 0.01$, **c** nitrofurantoin, $p = 0.24$, **d** ciprofloxacin, $p < 0.01$, **e** amoxicillin, $p < 0.01$, **f** gentamicin, $p < 0.01$, and **g** piperacillin/tazobactam, $p = 0.07$; where $p < 0.05$ is considered to demonstrate a significant difference between non-susceptibility between Hospital and Community *E. coli* isolates. BPRΔ: break point resistance change in 2014 for Co-amoxiclav

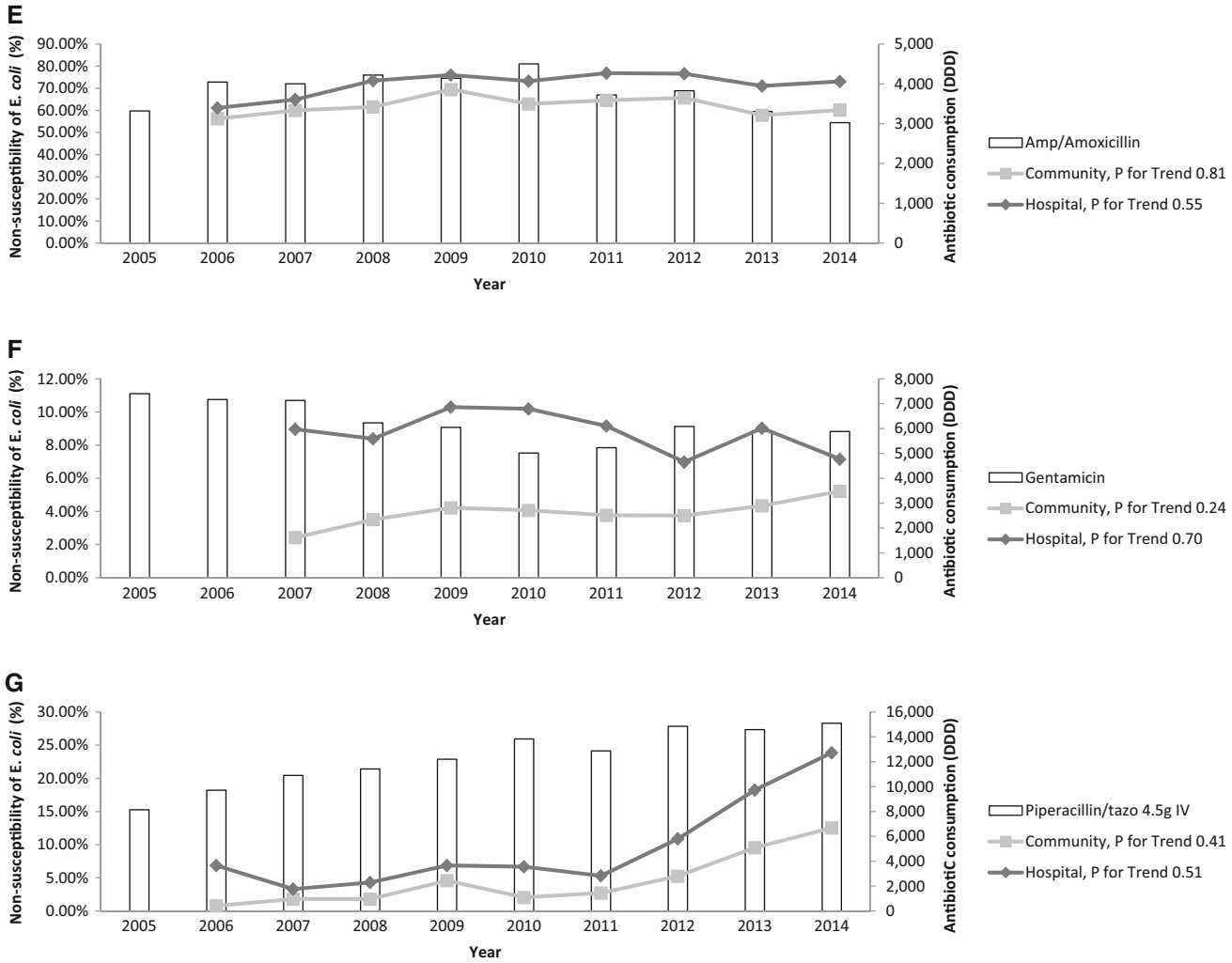

Fig. 2 continued

rates for ciprofloxacin are 11.4%, but it is concerning that our data show that resistance rates are rising faster in the community than in hospital, which if sustained may jeopardise its important role as second-line treatment for UTI caused by resistant organisms.

A recent Irish cluster randomised trial of complex interventions to improve primary care UTI prescribing achieved encouraging results, through a combination of practice education sessions, monthly laboratory feedback and electronic reminders [17]. There was a sustained increase (minimum 30%) in the proportion of patients prescribed nitrofurantoin, which was mainly due to replacement of trimethoprim or co-amoxiclav and an increase in the proportion of patients receiving any empiric antimicrobial. A secondary analysis of this trial showed that quinolones were more likely to be prescribed to males than females (11 versus 3%), that the rate of quinolone prescription was not reduced by the intervention, and that choosing nitrofurantoin as the empiric antimicrobial resulted in a lower rate of re-attendance compared to non-first-line antimicrobials, for both males and females [18].

A single dose of fosfomycin is an alternative recommendation in national guidelines for women with simple cystitis, but the ability of microbiology laboratories to routinely report susceptibilities for this agent is hampered by the current absence of EUCAST or CLSI guidelines on how to perform and interpret disc diffusion results. Primary care physicians may be reluctant to use an agent if AST results are not available routinely from their local laboratory, and lack of routine AST data may mean that emerging resistance is missed.

Our analysis of hospital samples demonstrated only a minor reduction in ciprofloxacin non-susceptibility rates in *E. coli*, which is disappointing given that significant hospital AMS interventions were undertaken which did reduce fluoroquinolone consumption. In 2008, a hospital wide

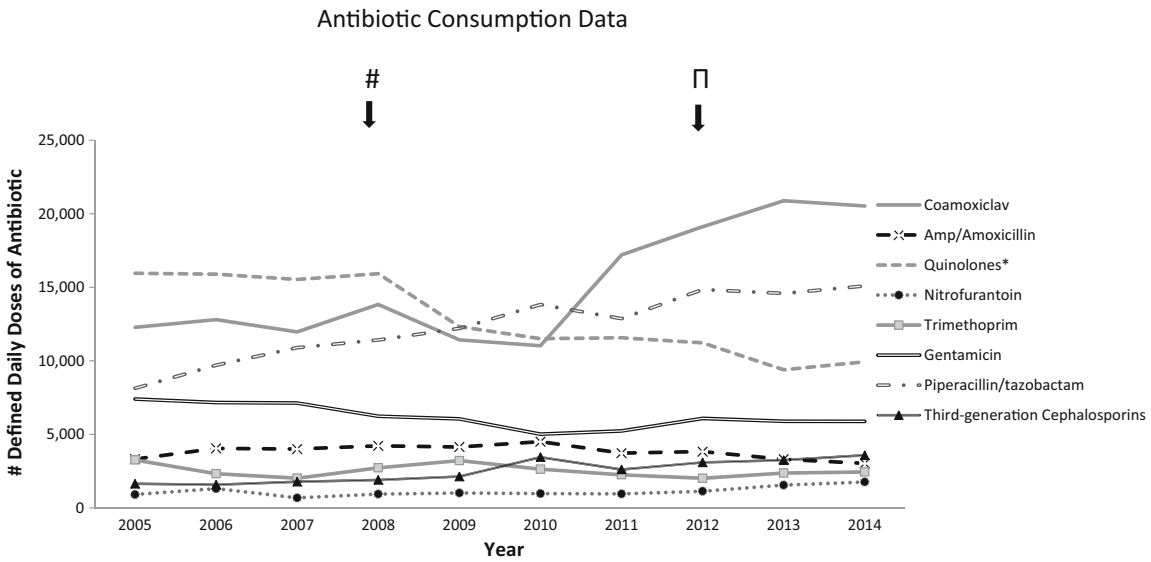

Fig. 3 Hospital antimicrobial use and timeline of relevant practice changes and stewardship decisions 2005–2014. # quinolone restriction. *Π* Community acquired pneumonia guideline change from quinolone + β Lactam to macrolide + β Lactam

Table 1 Trends in resistance for each studied antibiotic for the respective study 2005–2014

	T Test: trend of change in resistance (*p* value)			Average change in resistance/year		
	Community	Hospital	Community versus hospital	Community (%)	Hospital (%)	Community versus hospital (%)
Co-amoxiclav	0.41	0.54	0.023	2.79	3.35	0.55
Trimethoprim	0.38	0.38	<0.0001	0.23	0.92	0.68
Nitrofurantoin	0.24	0.7	0.241	−0.0	−0.55	−0.49
Ciprofloxacin	0.45	0.52	<0.0001	0.40	−0.26	−0.66
Amp/amoxicillin	0.81	0.55	0.001	0.72	1.21	0.50
Gentamicin	0.24	0.7	<0.0001	1.47	2.13	0.66
Piperacillin/tazobactam	0.41	0.51	0.079	0.49	1.50	1.01

Student's *T* Test was performed to assess for trends in resistance in consecutive years for community and hospital samples, and between hospital and community samples. The average change of resistance for each of the antibiotics was calculated

AMS programme focused on reducing inappropriate fluoroquinolone use, and in 2012, guidelines for treatment of community acquired pneumonia were changed from a combination of a fluoroquinolone and beta-lactam/beta-lactamase inhibitor to a macrolide and beta-lactam/beta-lactamase inhibitor. Our findings are consistent with the previous studies which indicate that once resistance to an antimicrobial is well established in a population of *E. coli,* a reduction in the use of that antimicrobial is unlikely to reduce resistance rates in the short-to-medium term [19, 20]. This highlights the need to act on emerging trends early before resistance becomes established.

High rates of gentamicin susceptibility support its role in local guidelines as adjunctive therapy for severe sepsis of urinary tract origin and prophylaxis for at risk groups undergoing Trans Rectal Ultrasound Guided (TRUS) biopsy. Local review of an active surveillance system for post-TRUS infection, operating since 2013, revealed no infections due to gentamicin resistant gram-negative bacteria.

Our data reveal an increased rate of *E. coli* from hospital isolates that are non-susceptible to co-amoxiclav (>35%, using both systemic and UTI breakpoints) compared to 13.9% in a previous Dublin study [21] and 12.5% in the west of Ireland [13]. Ciprofloxacin non-susceptibility rates in hospital are higher in our study than recent urinary *E. coli* data for hospitalised patients in Austria, and nearly double the rate in English hospitals, although low gentamicin non-susceptibility rates (<10%) are similar in all three countries [22, 23]. Co-amoxiclav and piperacillin–tazobactam non-susceptibility rates are markedly higher in our study than in Austria.

Our ESBL producing *E. coli* rate has increased and is similar to the incidence of 3GC resistance in England [22].

This increase occurred despite low rates of hospital consumption of 3GCs, after implementation of a strict restriction policy to reduce infection by *C. difficile*. Our ESBL and MDR rates are consistent with national data on invasive *E. coli* infections submitted to the European Antimicrobial Resistance Surveillance System network (EARRS-Net) in 2014 (10.6% ESBL producers and 15% MDR nationally) [24].

We identified a marked increase in the consumption of beta-lactam/beta-lactamase inhibitors in our hospital, concurrent with a reduction in fluoroquinolone usage, and maintenance of low level of 3GC usage. This finding is consistent with what is known as "squeezing the balloon effect", whereby restriction of particular antimicrobial classes, such as cephalosporins and fluoroquinolones, may drive increased consumption of other broad spectrum antimicrobials [25].

Our study had several limitations. Our data are from a single centre and analysed urinary isolates of *E. coli* only, with a maximum of one isolate per patient. Susceptibility data were predominantly from community rather than hospital, and antibiotic consumption data were only available for the hospital. However, the hospital resistance patterns identified are similar to those seen in national data for *E. coli* bloodstream infections reported through EARSS-Net. We did not explore broader issues impacting on resistance rates in humans, such as community AMS interventions, the impact of hospital infection control, and AMR in animals.

In conclusion, our data indicate high rates of non-susceptibility of community *E. coli* urinary isolates to trimethoprim and co-amoxiclav and confirm that nitrofurantoin remains the most appropriate first-line empiric therapy. For hospital isolates, non-susceptibility to co-amoxiclav, piperacillin–tazobactam, and ciprofloxacin is increasing compared to the previous Irish studies and recent reports from England and Austria. We observed a reduction in ciprofloxacin use in our hospital after AMS interventions, accompanied by a rise in the consumption of beta-lactam/beta-lactamase inhibitors, but did not see a similar reduction in ciprofloxacin resistance. Specific stewardship interventions to reduce broad spectrum penicillin usage in our hospital are required, along with efforts to audit both the effectiveness of this intervention and the impact on other prescribing trends and AMR.

Compliance with ethical standards

Conflicts of interest DL: No conflicts of interest to declare. PS: No conflict of interest to declare. RW: No conflict of interest to declare. NS: No conflict of interest to declare. MH: No conflict of interest to declare. FO'K: No conflict of interest to declare. ML: No conflict of interest to declare.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent For this type of study, formal consent is not required.

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