Background

Escherichia coli is the predominant cause of both community and nosocomial urinary tract infection (UTI). In the UK, trimethoprim or nitrofurantoin are usually recommended for empirical treatment of episodes of uncomplicated cystitis in the community [1], whilst parenteral cephalosporins and aminoglycosides are reserved for complicated infections or pyelonephritis. In North America a cut off point of 20% has been suggested as the level of resistance at which an agent should no longer be used empirically [2]. A UK study of the antimicrobial susceptibility of bacterial pathogens causing UTI in 1999 – 2000 showed high levels of resistance to trimethoprim, amoxicillin and oral cephalosporins [3] whilst a study of three collections of E. coli strains obtained from patients in East London in 1991, 1999 and 2004 showed rates of trimethoprim resistance of over 30% [4]. The emergence of strains producing extended spectrum β-lactamases
(ESBL’s) and others exhibiting quinolone resistance now threatens the empirical use of both cephalosporins and ciprofloxacin [5] seriously limiting treatment regimens. In order to determine current levels of resistance to antibiotics commonly used locally for empirical treatment, we reviewed susceptibility to ampicillin, amoxicillin/clavulanate, trimethoprim, nitrofurantoin, cefalexin, gentamicin, ciprofloxacin and cefpodoxime amongst all E. coli urinary isolates obtained in our laboratory over a 1 year period.

Methods
All E. coli isolates recovered from urine samples submitted for microscopy, culture and sensitivity to the laboratories of Barts and The London NHS Trust between 1st January and 31st December 2005 were included. Samples originating from General practice, Accident and Emergency or other primary care destinations were considered representative of community isolates whilst samples originating from patients hospitalised for 48 hrs or more on general or specialised wards were considered nosocomial.

Primary isolation of strains from urine specimens was performed using chromogenic agar (Mast diagnostics, Bootle, Merseyside) and bacterial counts quantified by inoculation of 0.3 μl of urine onto cystine lactose electrolyte deficient (CLED) agar (Mast diagnostics). Sensitivity testing was performed by the BSAC disc diffusion method using ampicillin (25 μg), cefalexin (30 μg), gentamicin (10 μg), ciprofloxacin (1 μg), nitrofurantoin (200 μg), trimethoprim (2.5 μg), amoxicillin/clavulanate (30 μg) and cefpodoxime (10 μg) discs and isosensitest agar.

Multi-drug resistance was defined in this analysis as resistance to three or more of the following antibiotics: ciprofloxacin, cefpodoxime, amoxicillin/clavulanate and gentamicin.

Differences in the prevalence of antibiotic resistance between groups were analysed using the χ² test. Strength of association was assessed by calculation of odds ratios with 95% confidence intervals.

Results
A total of 11,865 E. coli isolates were cultured from urine samples over the study period, of these 10,521 (88.7%) were considered community isolates while 1,344 (11.3%) were of nosocomial origin. 10,166 (85.7%) were from women and 1,656 (14.0%) from men (43 sex unknown). 1,227 (10.3%) were from children < 16 years of age. The frequency of antimicrobial susceptibility of all isolates to the eight antibiotics is shown in tables 1, 2, 3. Nitrofurantoin was the most active agent (94% susceptible) followed by gentamicin (93.7%) and cefpodoxime (92%). Ampicillin and trimethoprim were the least active agents with 55% and 40% of isolates exhibiting resistance respectively.

Isolates from men were significantly more resistant to all eight agents than isolates from women (Table 1). In particular, resistance to cefpodoxime, gentamicin, ciprofloxacin and cefalexin was observed more than twice as frequently in isolates from men (odds ratios = 2.5). A significant difference between paediatric and adult isolates was seen for all agents except amoxicillin/clavulanate. Resistance to cefalexin, ciprofloxacin, gentamicin, nitrofurantoin and cefpodoxime was more common in adults whilst ampicillin (OR 0.72) and trimethoprim (OR 0.76) resistance was associated with paediatric strains (Table 2).

Nosocomial isolates were more resistant than community isolates to all agents tested. The prevalence of gentamicin (OR 4.93), ciprofloxacin (OR 4.74), and cefpodoxime (OR 4.48) resistance exhibited the most marked differences (Table 3). Patterns of multi-drug resistance are shown in table 4. Ampicillin resistance in combination with trimethoprim resistance was more frequently observed than resistance to the single agent alone, the combination of ampicillin and trimethoprim resistance was also seen in combination with amoxicillin/clavulanate.
Lanate and ciprofloxacin. Resistance to all agents except nitrofurantoin was the most common multi-drug resistant phenotype and was observed in 1.3% of isolates.

**Discussion**

In the UK most uncomplicated urinary tract infections are treated in the community with short courses of empirical antibiotics. This relies on susceptibility data from local surveillance schemes as in many cases urine samples are only sent for microbiological evaluation following treatment failure, recurrent or relapsing infection. Although the levels of resistance we observed amongst community isolates may therefore overestimate the true rate of resistance in the community, the high levels of resistance to ampicillin and trimethoprim raise concerns over the use of these agents. This was particularly evident amongst isolates from children, which were more likely to exhibit resistance to ampicillin and trimethoprim compared to those from adults. Increased resistance to the other agents in adults is likely to reflect their wider use both empirically and as second line therapies in relapsing, complicated or nosocomial infection. The higher rates of resistance to all agents observed in males is likely to reflect their wider use both empirically and as second line therapies in relapsing, complicated or nosocomial infection. The rise in the number of CTX-M producing strains of *E. coli* which have disseminated widely throughout Europe post 2000 [9] with those producing CTX-M-15 being most widespread in the UK [10].

**Conclusion**

Nitrofurantoin remained the most active agent and as it can be administered orally and is highly concentrated in urine, it may therefore be the most appropriate agent for empirical use in uncomplicated UTI. Empirical treatment for nosocomial UTI or infection with multi-drug resistant isolates remains challenging with many authorities recommending parenteral carbapenems (imipenen, ertapenem or meropenem) [11] especially where ESBL isolates are present.

### Table 2: Frequency of antibiotic susceptibility in relation to age

| Antibiotic          | < 16 years | ≥ 16 years | P   | OR (CI95%) |
|---------------------|------------|------------|-----|------------|
|                     | n  | n (%) Resistant | n  | n (%) Resistant | |
| Ampicillin          | 1225  | 763 (62.3) | 10484  | 5694 (54.3) | ≤0.001  | 0.72 (0.64–0.81) |
| Amoxicillin/clavulanate | 1109  | 143 (12.9) | 9480  | 1296 (13.7) | NS | 1.07 (0.89–1.29) |
| Cefalexin           | 1225  | 100 (8.2) | 10462  | 1104 (10.6) | ≤0.01 | 1.33 (1.07–1.64) |
| Ciprofloxacin       | 1224  | 72 (5.9) | 10468  | 1334 (12.7) | ≤0.001  | 2.34 (1.83–2.99) |
| Gentamicin          | 1226  | 44 (3.6) | 10482  | 693 (6.6) | ≤0.001  | 1.90 (1.39–2.59) |
| Nitrofurantoin      | 1224  | 46 (3.8) | 10462  | 643 (6.1) | ≤0.001  | 1.68 (1.24–2.28) |
| Trimethoprim        | 1223  | 566 (46.3) | 10471  | 4129 (39.4) | ≤0.001  | 0.76 (0.67–0.85) |
| Cefpodoxime         | 1064  | 43 (4.0) | 8787  | 691 (7.9) | ≤0.001  | 2.03 (1.48–2.78) |

### Table 3: Frequency of antibiotic susceptibility among community and nosocomial isolates

| Antibiotic          | Community | Nosocomial | P   | OR (CI95%) |
|---------------------|-----------|------------|-----|------------|
|                     | n  | n (%) Resistant | n  | n (%) Resistant | |
| Ampicillin          | 10509  | 5663 (53.9) | 1339  | 870 (65.0) | ≤0.001  | 1.59 (1.41–1.79) |
| Amoxicillin/clavulanate | 9564  | 1145 (12.0) | 1145  | 307 (26.8) | ≤0.001  | 2.69 (2.33–3.11) |
| Cefalexin           | 10498  | 876 (8.3) | 1327  | 340 (25.6) | ≤0.001  | 3.78 (3.29–4.36) |
| Ciprofloxacin       | 10488  | 974 (9.3) | 1341  | 441 (32.9) | ≤0.001  | 4.79 (4.20–5.46) |
| Gentamicin          | 10505  | 482 (4.6) | 1342  | 260 (19.4) | ≤0.001  | 5.00 (4.24–5.88) |
| Nitrofurantoin      | 10492  | 556 (5.3) | 1332  | 139 (10.4) | ≤0.001  | 2.08 (1.71–2.53) |
| Trimethoprim        | 10492  | 4103 (39.1) | 1341  | 649 (48.4) | ≤0.001  | 1.46 (1.30–1.64) |
| Cefpodoxime         | 8868  | 504 (5.7) | 1103  | 238 (21.6) | ≤0.001  | 4.57 (3.85–5.41) |
producing isolates may be involved. The increasing rates of resistance to uropathogenic *E. coli* isolates reported worldwide [12,13] warrants evaluation of other treatments such as fosfomycin [14] or possibly novel cephalosporin/inhibitor combinations [15].

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

All authors contributed equally to data extraction, analysis and drafting of the manuscript.

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