SUsceptibility and Resistance to Fosfomycin and other antimicrobial agents among pathogens causing lower urinary tract infections: findings of the SURF study

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Abbreviations

AMRHAI, antimicrobial resistance and healthcare associated infections

API, Analytical Profile Index

CLED, cysteine lactose electrolyte deficient

CLSI, Clinical and Laboratory Standards Institute

EMA, European Medicines Agency

ESBLs, extended-spectrum β-lactamases

EUCAST, European Committee on Antimicrobial Susceptibility Testing

MALDI-ToF, matrix-assisted laser desorption/ionization time-of-flight

MIC, minimum inhibitory concentration

NA, not applicable

REWIND, REal World INternational Database

SURF, Surveillance sUsceptibility and Resistance to Fosfomycin in comparison with other antimicrobial agents study

UTI, urinary tract infection

uUTI, uncomplicated urinary tract infection

1 **Abstract**

2 **Background:** Urinary tract infections (UTIs) are prevalent world-wide, particularly

3 among women. Their incidence increases with age, and treatment is increasingly

4 challenging owing to antibiotic resistance and the lack of new agents. We investigated

5 the susceptibility of current urinary isolates to fosfomycin and other antibiotics across

6 Europe.

7 **Methods:** This cross-sectional study collected consecutive urinary isolates from non-

8 hospitalised women at 20 centres in Belgium, UK, Italy, Spain and Russia. Bacteria were

9 tested by disk diffusion with relevant antibiotics. As a quality control, a central

10 laboratory re-tested, by agar dilution: (i) isolates found resistant to fosfomycin, and (ii)

11 every tenth isolate; all non-Russian sites were included.

12 **Results:** A total of 2848 isolates were analysed, principally *Escherichia coli* (2064,

13 72.5%), *Klebsiella* spp. (275, 9.7%) and 103 *Proteus* spp. (103, 3.6%). For *E. coli,* agents

14 active against >90% of isolates were nitrofurantoin (98.5%), fosfomycin (96.4%), and

15 mecillinam (91.8%). Fosfomycin and nitrofurantoin remained active against >90% of

16 cephalosporin-resistant *E. coli*. Among 143 *E. coli* recorded as susceptible locally by

17 disk tests, 138 (96.5%) were confirmed susceptible by MIC tests, however resistance

18 was only confirmed in 29/58 (50%) of those reported resistant by local disk tests.

19 **Conclusion:** *E. coli* was found to be the most common uropathogen isolated and was

20   highly susceptible to fosfomycin, nitrofurantoin and mecillinam, all used effectively for

21   more than 30 years. Guidelines advocating fosfomycin for uUTIs in women remain

22   microbiologically valid.

23

1 Introduction

Urinary tract infections (UTIs) – principally uncomplicated cystitis in women – are among the most common bacterial diseases in humans [1]. They are a significant cause of morbidity at all ages [2] but there is an increased prevalence in women aged 15–24 years and aged ≥45 years [3, 4]. The most prevalent pathogen is *Escherichia coli*, accounting for 80% of cases, but other Enterobacterales are also frequent, notably *Klebsiella pneumoniae* [5, 6]*.

If untreated, or if the treatment fails, cystitis can precipitate ascending infections, including pyelonephritis and sepsis, with renal damage [2]. The main reason for failure is resistance to the antibiotics used, which standardly include β-lactams, trimethoprim, and co-trimoxazole [7, 8]; fluoroquinolones also are still widely used, as revealed in the multi-national REWIND (REal World INternational Database) study [9], although they are no longer recommended in European or international guidelines. Resistance to these standardly used antibiotics is increasing, although its prevalence varies among countries [10-13]. Most resistance, except to fluoroquinolones, is determined via acquired plasmids, including those encoding extended-spectrum β-lactamases (ESBLs), which inactivate cephalosporins [8, 11, 14].

The challenge of resistance, along with the paucity of novel antibiotics, highlight the need to re-evaluate older alternatives [15]. These include fosfomycin, an agent known for over 40 years, which is available as an oral trometamol salt as well as in parenteral

46 formulations. A systematic review and meta-analysis has shown that a single dose of

47 fosfomycin trometamol was as effective as longer courses of alternative agents for

48 uncomplicated UTIs (uUTIs) in women [16].

49 Fosfomycin has an inherently broad spectrum of activity; however, the European

50 Committee on Antimicrobial Susceptibility Testing (EUCAST) now only has breakpoints

51 (S <8, R >8 mg/L) for *E. coli* in respect of the trometamol formulation used for uUTI

52 [17].

53 The aim of the European-wide 'Surveillance sUsceptibility and Resistance to

54 Fosfomycin in comparison with other antimicrobial agents study' (SURF) was to

55 provide a current snapshot of the prevalence of resistance to fosfomycin compared

56 with that to other oral antibiotics frequently prescribed to treat uUTIs in women.

57 **2   Materials and methods**

58 **2.1   Study design and isolates**

59 SURF was a cross-sectional epidemiological study on bacteria isolated from urine

60 samples collected from women between April 2019 and November 2019. Twenty

61 laboratories located across five countries participated, comprising three in Belgium,

62 two in UK, five in Italy, four in Spain and six in Russia (see Acknowledgements). To

63 avoid selection bias, the study protocol required collection of urine samples from all

64 consecutively sampled non-hospitalised women who (according to clinical referral or

65   the International Classification of Diseases coding system) were believed to have a

66   lower UTI. No clinical data were collected and since the 'study subjects' were the

67   uropathogens, not the patients, only limited institutional review was required and

68   obtained.

69   **2.2   Sample processing and analysis**

70   Isolates were sub-cultured and streaked for single colonies on MacConkey or Cysteine

71   Lactose Electrolyte Deficient (CLED) agar. Local laboratories used the following

72   methods to identify the organisms: matrix-assisted laser desorption/ionization time-of-

73   flight (MALDI-ToF) mass spectroscopy (14 sites), Vitek or other automated systems (5

74   sites) or Analytical Profile Index (API) strips (1 site). Diffusion susceptibility tests were

75   performed for each isolate using disks containing fosfomycin (plus glucose-6-

76   phosphate) 200 µg, amoxicillin/clavulanate 20/10 µg, ampicillin 10 µg, cefpodoxime

77   10 µg, cefalexin 30 µg, ciprofloxacin 5 µg, trimethoprim 5 µg, mecillinam 10 µg and

78   nitrofurantoin 100 µg. These disks were obtained centrally from Thermofisher (Life

79   Technologies Italia Fil. Life Technologies Europe BV Via G.B. Tiepolo, 18 I-20900 Monza

80   MB, Italy) and distributed to the sites to ensure consistent quality. Sites used Mueller-

81   Hinton agar and confluent growth, following the test method shared by both EUCAST

82   and the CLSI. Disk diffusion zone diameters were interpreted according to current

83   EUCAST breakpoints (EUCAST 2021), following the amendments to guidance on

84   fosfomycin susceptibility testing [18].

85   Given that *E. coli* is the most commonly identified uropathogen and that EUCAST 2021

86   only provides zone diameter breakpoints for fosfomycin applied to *E. coli* [18]*,* our

87   analysis focused on this species.

88   **2.3   Quality control**

89   As a representative quality control sample, laboratories in all participating countries

90   except Russia sent a subculture of every tenth bacterial isolate to a central laboratory

91   (Antimicrobial Resistance and Healthcare Associated Infections [AMRHAI] Reference

92   Unit, Public Health England, now UK Health Security Agency) for re-testing. They also

93   sent all isolates, irrespective of species, with a zone diameter <24 mm, corresponding

94   to the then (and current) EUCAST disk breakpoint.

95   Isolates received by AMRHAI were re-identified by MALDI-ToF mass spectroscopy

96   (Biotyper, Bruker, Bremen Germany), then minimum inhibitory concentrations (MICs)

97   were determined using the CLSI agar dilution method [19]. Fosfomycin, glucose-6-

98   phosphate, nitrofurantoin, ampicillin, clavulanate, ciprofloxacin, trimethoprim and

99   cephalexin were purchased from Merck Life Sciences (Gillingham, UK); amoxicillin,

100   cefpodoxime and mecillinam were purchased from Alpha Aesar (Heysham, UK).

101   **2.4   Statistical analysis**

102   All statistical analyses were conducted using SAS® release 9.4 (SAS Institute, Inc., Cary,

103   NC, USA). No formal hypothesis was formulated; rather the analyses were exploratory

104 and contained analytical and descriptive aspects. No formal sample size estimation

105 was computed. Categorical data are presented as absolute and relative frequencies (n

106 and %). Chi-squared tests were used to compare proportions of resistant and

107 susceptible isolates between countries; data validation/sensitivity analyses considered

108 all isolates with paired (local and central laboratory) results.

109 Results were assigned to a not applicable (NA) category when there was no EUCAST

110 breakpoint defined for a particular organism/antibiotic combination, or when there

111 were missing values.

3   Results

3.1   Isolates collected and tested

114 A total of 2848 isolates were collected and tested: 473 (16.6%) in Belgium, 581 (20.4%)

115 in Italy, 565 (19.8%) in Spain, 393 (13.8%) in the UK and 836 (29.4%) in Russia (Figure

116 1). Among the 2012 non-Russian isolates, 543 (19.1%) were sent to the central

117 laboratory for re-testing as part of the quality control, and 542 (19.0%) were re-tested

118 there, with MICs determined. Ultimately, a total of 534 isolates (18.8%) had matching

119 paired local and central laboratory susceptibility results, comprising 116 (21.7%) from

120 Belgium, 150 (28.1%) from Italy, 150 (28.1%) from Spain and 118 (22.1%) from the UK

121 (Figure 1). Of the 534 paired isolate samples, 333 had been sent for central analysis

122 because they had an inhibition zone diameter measurement of <24 mm for fosfomycin

123 and 201 as part of the representative 10% sampling (26 fulfilled both criteria and, to

124 avoid double inclusion, are counted only within the 10% sample).

125 The most prevalent uropathogen was *E. coli* (n= 2064, 72.5%), followed, among

126 Enterobacterales, by *Klebsiella* spp. (n=275, 9.7%) and Proteeae (n=103, 3.6%);

127 substantial groups among the remaining 406 (14.3%) included *Enterococcus* spp.

128 (n=134)*, Streptococcus* spp. (n=45), *Staphylococcus* spp. (n=28) and *Pseudomonas*

129 *aeruginosa* (n=21)*.*

130 **3.2   Susceptibility and resistance among eligible *E. coli* isolates**

131 Based on the disk diffusion tests by local laboratories, only three agents –

132 nitrofurantoin, fosfomycin and mecillinam – were active against >90% of *E. coli*

133 isolates, with resistance rates of 0.5%, 3.6% and 8.2%, respectively. Of these, only

134 nitrofurantoin and fosfomycin retained activity against over 90% of the 348 (16.9%) *E.*

135 *coli* isolates that were resistant to cefpodoxime and which accordingly were inferred to

136 be ESBL producers or AmpC hyperproducers. Mecillinam appeared active against

137 84.2% of these cefpodoxime-resistant isolates, though its clinical efficacy against ESBL

138 producers remains contentious [20, 21] even when these appear susceptible *in vitro*.

139 Cephalosporins, amoxicillin/clavulanate and ciprofloxacin were active against around

140 80% (79.2–83.1%) of all *E. coli* isolates, whereas trimethoprim and ampicillin inhibited

141 fewer than 70%. Under 60% of the cefpodoxime-resistant *E. coli* isolates were

142 susceptible to agents besides fosfomycin, nitrofurantoin and mecillinam.

143   Comparisons covering all species are challenging due to the lack of fosfomycin and

144   nitrofurantoin breakpoints, except for *E. coli*. Among agents with breakpoints for all

145   uropathogens, only mecillinam remained active against >90% of isolates;

146   cephalosporins, amoxicillin/clavulanate and ciprofloxacin were active against 80–

147   83.9%, trimethoprim against 71%, and ampicillin against 48.2% (Table 1).

148   Resistance rates differed significantly (p<0.01) between countries for all the antibiotics

149   studied except trimethoprim. Fosfomycin and nitrofurantoin nonetheless retained

150   activity against >90% of *E. coli* in all the countries (Table 2), while mecillinam only

151   narrowly failed to do so, with resistance rates of 10.0–10.8% in Italy, Belgium and the

152   UK. Overall, the highest resistance rates were seen in Italy (highest for five of nine

153   antibiotics tested) and the UK (highest for four antibiotics); Russia had the lowest

154   resistance rates for five of the nine agents included. Resistance prevalence rates for

155   cefpodoxime and cephalexin closely tracked each other across countries, being highest

156   (27.5% and 26.3%, respectively) in the UK and lowest (6.4% and 8.0%, respectively) in

157   Spain (Table 2).

158   **3.3   Data validation**

159   Two hundred and one *E. coli* isolates were sent to the central laboratory for MIC

160   testing (Table 3). Among the 143 isolates submitted as fosfomycin susceptible, based

161   on zone diameters >24 mm, 138 were confirmed susceptible by MIC tests, with MICs

162   <8 mg/L, indicating a false susceptible rate from local laboratories of 3.5%. Four of the

163   five isolates sent as susceptible but found resistant by the central laboratory were

164   inhibited by fosfomycin at 16–32 mg/L, with only one isolate found substantially more

165   resistant (MIC 64 mg/L). The rate of false susceptible results was also low ($\leq$5%) for

166   cefpodoxime, cephalexin, ciprofloxacin, trimethoprim and nitrofurantoin, but was 9.3%

167   for mecillinam (17/183), 15.5% (14/90) for ampicillin and 21.6% (34/157) for

168   amoxicillin/clavulanate.

169   False resistance rates were higher. Only half (29/58, 50%) of the *E. coli* submitted as

170   'fosfomycin resistant', based on zones <24 mm were confirmed as resistant by dilution

171   testing (MIC >8 mg/L), whereas the other 29 isolates were found susceptible, 22 of

172   them with MICs of $\leq$1 mg/L; for nitrofurantoin, 4/5 isolates submitted as resistant were

173   found susceptible, indicating a false resistance rate of 80%, albeit based on a tiny

174   group. Mecillinam (7/18, 39%), cefpodoxime (10/46, 22%), trimethoprim (10/71, 14%)

175   and cephalexin (5/44, 11%) also had false resistance rates >10%, whereas rates were

176   under 10% for amoxicillin/clavulanate, ampicillin and ciprofloxacin.

177   Three hundred and thirty-three non-*E. coli* isolates were re-tested for susceptibility to

178   fosfomycin at the central laboratory (Table 4), 36 with zones equal to or larger than

179   the *E. coli* breakpoint of 24 mm and 297 with smaller zones. Among the former 36,

180   'susceptible' MICs $\leq$8 mg/L were confirmed for 14, including 3/4 *Klebsiella* spp. and 6/7

181   Proteeae, though only for 5/25 isolates of other species. MICs >8 mg/L were seen for

182   248/297 non-*E. coli* reported to give zones <24 mm, including 20/23 Proteeae and

183   116/123 'others'; 'discordances' of an MIC **<**8 mg/L but a zone <24 mm were

184   predominantly seen for *Klebsiella* spp. (39 cases among 151 Klebsiella tested with

185   zones <24 mm).

186   **4   Discussion**

187   This study aimed to identify the pathogens responsible for community uUTIs in women

188   and to assess their current antimicrobial resistance profiles across Europe, including

189   Russia. *In vitro* susceptibility is a strong predictor of the likely success of antimicrobial

190   treatment in uUTI [22]. Although most resistance-contingent treatment failures are not

191   seriously consequential, a minority do lead to more severe disease, mostly in the

192   elderly; in particular, *E. coli* bacteraemias are strongly associated with failure of

193   therapy of prior UTIs [23].

194   A total of 2848 isolates were analysed and, as expected, considerably the most

195   common uropathogen was *E. coli* (72.5%), followed by *Klebsiella spp*. (9.7%) and

196   *Proteus* spp. (3.6%). The dominance of *E. coli* is consistent with prior studies [12, 24,

197   25], especially in Europe and the USA [12].

198   Although the Infectious Diseases Society of America (IDSA) no longer advocates a

199   single threshold for the rate of resistance, as it previously did specifically for co-

200   trimoxazole [25], it is widely agreed that an antibiotic ceases to be appropriate as

201   empirical therapy for uUTI when the resistance rate reaches 15–20% [25-27]. A cut-off

202 of approximately 20% is also supported by cost-effectiveness studies [28, 29]. On this

203 criterion, the only agents considered here that retained acceptable activity were

204 nitrofurantoin, fosfomycin and mecillinam, with cefpodoxime, cephalexin,

205 ciprofloxacin and amoxicillin/clavulanate 20/10 µg marginal, having resistance rates

206 around 15–20% and trimethoprim and ampicillin unacceptable, owing to much higher

207 resistance rates. Ciprofloxacin is now also discouraged by the European Medicines

208 Agency owing to toxicity concerns [30].

209 The resistance of *E. coli* to antimicrobials has increased in both developed and

210 developing countries [31], partly owing to spread of the sequence type (ST)131

211 lineage, which is often fluoroquinolone resistant and carries cephalosporin-hydrolysing

212 ESBLs along with the inhibitor-resistant OXA-1 penicillinase [32, 33]. Among the

213 present 2848 isolates, 14% were cefpodoxime resistant, suggesting likely ESBL

214 production and, among these, over 90% remained susceptible to fosfomycin and

215 nitrofurantoin.

216 Resistance rates among *E. coli* isolates differed between countries, being highest in

217 Italy and the UK and lowest in Russia and Belgium. These patterns are somewhat

218 counterintuitive: resistance rates for bloodstream isolates are generally highest in

219 Mediterranean Europe rather than, for example, the UK [34]. This dissonance may

220 reflect either differences in antimicrobial use between countries, or differences in the

221 extent of testing biases: treatment is often empirical, with culture reserved for first-

222 regimen failures. Consequently, laboratory testing may be biased towards recurrent

223 and recalcitrant infections, more likely to harbour resistant bacteria [35]. We do not

224 know the extent of this confounder in different countries, nor how much it varied

225 between them. Nevertheless, despite its effect, over 90% of *E. coli* isolates were

226 susceptible to fosfomycin and nitrofurantoin in *all* countries, supporting their broad

227 utility, and consistent with the results of other recent surveys [36].

228 Site-to-site reproducibility is a challenge for all decentralised surveys of antimicrobial

229 susceptibility; moreover, fosfomycin is a challenging drug to test in the laboratory,

230 requiring addition of glucose-6-phosphate to the disks and the discounting of isolated

231 colonies within inhibition zones [37]. We addressed these issues by central re-testing,

232 using the reference agar dilution method, for every tenth isolate and for all those that

233 gave zones <24 mm. For *E. coli* the results were reassuring: only 5 of the 143 re-tested

234 isolates that had given zones $\geq$24 mm proved resistant at 8 mg/L and only one of these

235 5 were resistant at the pre-2021 EUCAST fosfomycin trometamol breakpoint of 32

236 mg/L. 'False susceptibility' was a greater issue for amoxicillin/clavulanate and

237 mecillinam, with incidence rates of 34/157 and 17/183 respectively. The more

238 frequent error in the case of fosfomycin was that resistance was over-estimated by

239 disk diffusion, being confirmed by MIC testing in only half (29/58) *E. coli* isolates where

240 it was claimed from disk testing. No other agent had such a degree of resistance over-

241 estimation, except nitrofurantoin, where resistance was extremely rare.

242   When this project was initiated, EUCAST had an S ≤32/R >32 breakpoint for fosfomycin

243   trometamol with *all* Enterobacterales; while the SURF study was in progress, this

244   breakpoint was lowered to S ≤8/R >8 and narrowed to *E. coli*. The present data support

245   the view that disk testing has little reliability beyond *E. coli*, with poor MIC/zone

246   concordance found. Moreover, MIC distribution collated by EUCAST indicate that

247   modal values for fosfomycin for other relevant pathogens besides *E. coli* either equal

248   (*Klebsiella* spp.) or exceed (*Enterococcus* spp., and *Staphylococcus* spp.) an 8 mg/L

249   breakpoint [38]. The one notable and pertinent exception to these generalisations,

250   from the present data, is that the *E. coli* susceptibility criteria potentially might be

251   extended to Proteeae, where 6/7 collected isolates with zones >24 mm were

252   confirmed inhibited at 8 mg/L whereas 20/23 with zones <24 mm were confirmed

253   resistant at 8 mg/L (Table 4). Further zone/MIC correlation studies, along with

254   outcome data, are needed to resolve this issue and the role for fosfomycin trometamol

255   in uUTIs involving Proteeae.

256   Due to the dominance of *E. coli* and low rates of antimicrobial resistance, fosfomycin is

257   recommended as first-line treatment in many European countries, including Belgium

258   and Italy, and also in Russia and Brazil [9]. In addition, fosfomycin is recommended as a

259   first-line treatment for uUTIs in the latest European Association of Urology and IDSA

260   guidelines on urological infections [25, 39, 40]. The present results support such

261   guidance.

262   A strength of this study is that it included a large sample, covering five countries

263   (Belgium, Italy, Russia, Spain and UK), and should prove to be a useful source of quality

264   data on antibiotic resistance to guide empirical therapy. Limitations are that it

265   recruited consecutive laboratory isolates, rather than consecutive women presenting

266   with uUTI, and that individual patient characteristics were not collected. This

267   precluded exploration of reasons for differences in resistance rates between countries

268   and, as discussed earlier, raises questions on whether the extent of routine testing –

269   and the contingent sample bias towards difficult cases – may vary between countries.

270   Lastly, only four of the five participating countries sent samples to the central

271   laboratory to be re-tested.

272   In summary, stewardship is crucial to maintaining the utility of antibiotics, and should

273   be a key consideration for physicians managing UTIs. Good stewardship has two key

274   aspects: (i) ensuring that patients who need antibiotics swiftly receive active,

275   proportionate ones, and (ii) preventing over-use and disproportionate use of

276   antibiotics. In this context, fosfomycin and nitrofurantoin represent important tools for

277   the management of uUTIs owing to their low prevalence of resistance.

278   **5   Conclusion**

279   *E. coli* remains the most common causative uropathogen in all countries included in

280   this study. Due to the high susceptibility rates and acceptable resistance, especially

281   against *E. coli* isolates, fosfomycin, like nitrofurantoin, seems to be a good candidate to

282   effectively address antibiotic-resistant UTIs Europe-wide.

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Conflicts of interest

316   DML: Advisory Boards or ad hoc consultancy Accelerate, Antabio, Centauri, Entasis,

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328   **Author contributions**

329   **MT** contributed to study design and management, preparation of the manuscript,

330   review of all drafts and approval

331   **TEBJ** contributed to study design, preparation of the manuscript, review of all drafts

332   and approval

333   **TC** contributed to study design, preparation of the manuscript, review of all drafts and

334   approval

335   **SM** led the central laboratory 'quality control' testing and interpretation of results, and

336   reviewed drafts

337   **DML** contributed extensively to study design, review of results, and writing of this

338   manuscript

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451

452   **Figure legend**

453   **Figure 1.** Disposition of samples by country and by laboratory in the analysis

454   population.

455

Tables

Table 1. Number and percentages of resistant and susceptible isolates (eligible and cefpodoxime-resistant isolates)

Antibiotic	All *E. coli*		Cefpodoxime-resistant *E. coli*		All isolates	
	N^a	Resistant isolates, n (%)	N^a	Resistant isolates, n (%)	N^a	Resistant isolates, n (%)
Nitrofurantoin 100 μg	2060	31 (0.5)	348	15 (4.3)	2766	EUCAST breakpoints only for *E. coli*
Fosfomycin 200 μg	2062	74 (3.6)	348	28 (8.0)	2816	EUCAST breakpoints only for *E. coli*
Mecillinam 10 μg	2061	169 (8.2)	348	61 (17.6)	2804	203 (7.2)
Cefpodoxime 10 μg	2062	348 (16.9)	348	348 (100.0)	2813	454 (16.1)
Cephalexin 30 μg	2062	358 (17.4)	348	319 (91.7)	2811	500 (17.8)
Amoxicillin/clavulanate 20/10 μg	2062	383 (18.6)	348	165 (47.4)	2830	506 (17.9)
Ciprofloxacin 5 μg	2062	428 (20.8)	348	208 (59.8)	2841	568 (20.0)
Trimethoprim 5 μg	2062	632 (30.6)	348	172 (49.4)	2824	820 (29.0)
Ampicillin 10 μg	2062	1007 (51.2)	348	333 (95.7)	2827	1463 (51.8)

Table 2. Number and percentage of resistant *E. coli* isolates by antibiotic and country (eligible isolates)

	Fosfomycin	Amoxicillin/ clavulanate	Ampicillin	Cefpodoxime	Cephalexin	Ciprofloxacin	Trimethoprim	Mecillinam	Nitrofurantoin
Italy (N=325)[a]	**27 (8.3)**	**91 (28.0)**	169 (52.0)	71 (21.8)	70 (21.5)	**105 (32.3)**	101 (31.1)	**35 (10.8)**	**8 (2.5)**
Spain (N=435)	20 (4.6)	70 (16.1)	225 (51.7)	*28 (6.4)*	*35 (8.0)*	73 (16.8)	132 (30.3)	37 (8.5)	*0*
United Kingdom (N=240)	7 (2.9)	66 (27.5)	**153 (63.8)**	**66 (27.5)**	**63 (26.3)**	36 (15.0)	**87 (36.3)**	24 (10.0)	5 (2.1)
Belgium (N=367)[a]	*7 (1.9)*	82 (22.3)	176 (48.0)	43 (11.7)	46 (12.5)	*53 (14.4)*	110 (30.0)	37 (10.1)	5 (1.4)
Russia (N=695)	*13 (1.9)*	*74 (10.6)*	*332 (47.8)*	140 (20.1)	144 (20.7)	161 (23.2)	*202 (29.1)*	*36 (5.2)*	13 (1.9)
Chi square	<.0001	<.0001	0.0005	<.0001	<.0001	<.0001	0.3496	0.0068	0.0067

N = total number of isolates per country; *E. coli* resistance data are presented n (%) of samples. Percentages are computed on eligible isolates tested for each antibiotic within each country.

[a] Numbers of isolates tested are one or two lower than N in some cases owing to failed tests

Bold: highest rates; *italic*, lowest rates for each antibiotic

Table 3. Comparison of central and local results for *E. coli* (n=201) retested as a QC sample.

	Isolates categorised as susceptible at local laboratory			Isolates categorised as resistant at local laboratory		
	Total submitted to central lab.	Central lab found susceptible	Central lab found resistant	Total submitted to central lab.	Central lab found susceptible	Central lab found resistant
Fosfomycin 200 µg	143	138	5	58	29	29
Amoxicillin/clavulanate 20/10 µg	157	123	34	44	4	40
Ampicillin 10 µg	90	76	14	111	7	104
Cefpodoxime 10 µg	155	148	7	46	10	36
Cephalexin 30 µg	157	152	5	44	5	39
Ciprofloxacin 5 µg	147[a]	137 + 8 found I[b]	2	50	4	46
Trimethoprim 5 µg	130	128	2	71	10	61
Mecillinam 10 µg	183	166	17	18	7	11
Nitrofurantoin 100 µg	196	196	0	5	4	1

[a]   Includes isolates found 'I', defined by EUCAST as high-dose susceptible.

[b]   I, high dose susceptible.

Concordance between local and central laboratory results for each tested uropathogen by antibiotic (paired isolates subgroup)

Table 4. Concordance between local and central laboratory results for fosfomycin only,

shown for non-*E. coli* bacteria

Local Laboratory	Central Laboratory	
	MIC $\leq$8 mg/L Susceptible, n	MIC >8 mg/L Resistant, n
All non-*E. coli*		
Zone $\geq$24 mm, Susceptible	14	22
Zone <24 mm, Resistant	49	248
***Klebsiella* spp.**		
Zone $\geq$24 mm, Susceptible	3	1
Zone <24 mm, Resistant	39	112
Proteeae (i.e. *Proteus*, *Morganella* and *Providencia* spp.)		
Zone $\geq$24 mm, Susceptible	6	1
Zone <24 mm, Resistant	3	20
Other		
Zone $\geq$24 mm, Susceptible	5	20
Zone <24 mm, Resistant	7	116