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Tristan Delory, Josselin Le Bel, Sylvie Lariven, Nathan Peiffer-Smadja, François-Xavier Lescure, et al.. Computerized Decision Support System (CDSS) Use for Surveillance of Antimicrobial Resistance in Urinary Tract Infections in Primary Care. *Journal of Antimicrobial Chemotherapy*, 2022, 77 (2), pp.524–530. 10.1093/jac/dkab392 . hal-03888700

HAL Id: hal-03888700

<https://hal.sorbonne-universite.fr/hal-03888700v1>

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1 **TITLE**

2 **Computerized decision support system (CDSS) to inform the surveillance of antimicrobial**
3 **resistance in urinary tract infections in primary care.**

4 **Short running title** (50 characters): CDSS for surveillance of AMR in primary care.

5 **Word count:** 2876

6

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31 **Abstract**

32 **Background**

33 Hospital-based surveillance of antimicrobial resistance may be irrelevant to guide antimicrobial use for
34 urinary tract infections (UTIs) in primary care.

35 **Objectives**

36 To highlight the value of online computerized decision support systems (CDSS) in informing
37 surveillance of antimicrobial resistance in community-acquired UTIs.

38 **Methods**

39 We report the susceptibility profile for key antibiotics by type of UTI involving *E. coli* from 2017 to
40 2020, using queries for UTI (Q-UTI) submitted to a French CDSS. We compare results to the MedQual
41 French surveillance system for community-acquired UTI and the European Antimicrobial Resistance
42 Surveillance Network (EARS-NET) for invasive infections.

43 **Results**

44 We collected 43,591 Q-UTI were collected, of which 10,192 (23%) involved *E. coli*: 40% cystitis, 32%
45 male-UTI, and 27% pyelonephritis. Resistance was 41.3% (95%CI, 40.3%-42.2%) for amoxicillin,
46 16.6% (95%CI, 15.9%-17.3%) for fluoroquinolones, 6.6% (95%CI, 6.1%-7.0%) for 3CG, and 5.7%
47 (95%CI, 5.2%-6.1%) for aminoglycosides. Resistance to amoxicillin was lower than that reported in
48 MedQual (42.7%, p -value=0.004), and in EARS-NET (55.2%, p -value<0.001). For fluoroquinolones,
49 resistance was higher than in MedQual (12.0%, p -value<0.001) and EARS-NET (15.8%, p -
50 value=0.041). In complicated pyelonephritis and male UTI, fluoroquinolones resistance peaked at
51 ~20%. For 3CG, all UTI had higher resistance than in MedQual (3.5%, p -value<0.001), but lower than
52 in EARS-NET (9.5%, p -value<0.001). Aminoglycosides resistance was not reported by MedQual, and
53 was lower than in EARS-NET (7.1%, p -value<0.001).

54 **Conclusion**

55 CDSS can inform in real-time the ecology and surveillance of *E.coli* resistance in community-acquired
56 UTI. In complicated upper UTIs, they underline the risk of empirical use of fluoroquinolones and
57 suggest preferential use of 3CG.

58 INTRODUCTION

59 A majority of countries worldwide have national action plans (NAPs) for the prevention of antimicrobial
60 resistance (AMR).¹ Surveillance of AMR is essential at every stage of the NAPs, from initial
61 description to monitoring effects, and subsequently inform clinical guidelines for antimicrobial use
62 (AMU). Routine surveillance of AMR often relies on samples collected in hospitals for individual patient
63 diagnosis with data contributed by hospital laboratories.^{2,3} These data may therefore not be
64 representative of the resistance level in the general population, and inappropriate for
65 recommendations at the community level.^{3,4} Improving AMR surveillance in primary care would be
66 more relevant, and is now recognized as an objective of interest.^{2,5,6}

67 Urinary tract infections (UTI) are clinical situations where hospital-based surveillance is likely to lead to
68 overestimate AMR, and to the inappropriate choices of antimicrobial therapy for community-acquired
69 infections.^{2,6} Indeed, hospital-based surveillance often reports for patients having fail initial empirical
70 therapy, with risks factors for antimicrobial resistance, complications or recurrence. Urinalysis
71 collected among these patients can also bias the reporting of resistance because of the wider range of
72 bacterial species involved in their UTI than in uncomplicated infections.² Yet the available AMR
73 surveillance data from the European Antimicrobial Resistance Surveillance System network (EARS-
74 NET) only reports hospital-based data aggregated over blood, and cerebrospinal fluid samples
75 irrespective of the underlying pathology (urinary tract infections, pneumonia, wound infections, ...).⁷
76 More relevant data is available from the French (MedQual) surveillance network for community-
77 acquired UTI in biological laboratories, but cannot be stratified by infection type or patient's
78 characteristics.⁸⁻¹⁰

79 Joint information on resistance level by type of UTI may however be readily obtained using the case
80 description submitted by practitioners to an online computerized decision support system (CDSS) for
81 antimicrobial prescribing.¹¹ In those, detailed information on the type of UTI and microbiology is input
82 at the point of care to assist clinical decision-making and improve antimicrobial prescription. It has the
83 potential to reduce the likelihood of recall bias related to surveillance based on the retrospective
84 collection of cases.

85 We hypothesized that data submitted to *Antibiocllic* – a French online guideline-based CDSS for
86 antimicrobial prescribing extensively used in primary care (<http://www.antibiocllic.com>) – would allow
87 describing resistance level by infection type in community-acquired UTI due to *E. coli*.¹²

88 Here, we report the susceptibility profile for key antibiotics by type of UTI involving *E. coli* from 2017 to
89 2020. We then compare it to that obtained by the MedQual French surveillance system for community-
90 acquired UTI, and by EARS-NET for invasive infections.

91 MATERIAL AND METHODS

92 Objectives

93 We aimed to highlight the added value of online computerized decision support systems (CDSS) for
94 antimicrobial prescribing in primary care to inform the surveillance of antimicrobial resistance in
95 community-acquired UTIs involving *E. coli*.

96 Study design

97 We conducted a cross-sectional analysis of *Antibiocliv* data, prospectively collected from November
98 2017 (week 47) to September 2020 (week 37).¹²

99 Description of the CDSS extension for UTI

100 *Antibiocliv* was developed by academics and released in October 2011. Its access and use are free of
101 charge. It relies on a Task-Network Model (TNM) to translate national guidelines into an easy-to-use
102 system described elsewhere.¹² An academic steering committee monitors official updates of national
103 guidelines for each pathology/infectious disease.

104 In late 2017, we extended *Antibiocliv* with a module for patient-specific recommendations of
105 antimicrobial therapy for UTI. Access to this module was possible upon registration. The UTI targeted
106 by the system included asymptomatic bacteriuria in pregnant women, cystitis (in children,
107 uncomplicated and complicated in adults), pyelonephritis (in children, uncomplicated and complicated
108 in adults), and male UTI. Users could input characteristics of patients, results of urine culture (when
109 available), and exposure to fluoroquinolone within the last 6 months to individualize the proposition for
110 antimicrobial therapy. In all cases, users were free to follow or not the CDSS proposition for
111 antimicrobial therapy. Previous cross-sectional surveys showed that 96% of users reported CDSS
112 assistance during the last consultation. *Antibiocliv* was systematically used for initiation of an antibiotic
113 course by 24% of users, and 93% reported having followed the CDSS recommendation for the latest
114 prescription. Most GPs were comfortable using the CDSS in front of a patient.¹²

115 Data

116 We defined a query for urinary tract infection (Q-UTI) as a query performed to the CDSS for the
117 antimicrobial therapy of a UTI. The data describing a Q-UTI included user's characteristics, patient's

118 characteristics (age group, type of UTI type, history of UTI, recent exposure to antibiotics,
119 hospitalization and travel abroad within the last year), and pathogen / antimicrobial resistance profile.
120 Q-UTI data were recorded at the point-of-care during CDSS consultation. Q-UTI were classified
121 according to guidelines of the European Association of Urology and the French Infectious Disease
122 Society (SPILF)^{13,14}. When urinalysis was not performed or registered for managing infection, the Q-
123 UTI was considered as not documented. Antimicrobial resistance profile of Q-UTI was established by
124 primary care laboratories working with physician using the CDSS. Susceptibility testing result was
125 reported by physician using the CDSS, according to guidelines from the French microbiology society
126 ("Comité de l'Antibiogramme de la Société Française de Microbiologie", CA-SFM) aligned on the
127 European Committee on Antimicrobial Susceptibility Testing (EUCAST).¹⁵

128 We collected the 2017 to 2019 data on *E. coli* resistance to key antibiotics (amoxicillin, third-
129 generation cephalosporin – 3CG, fluoroquinolones – FQ, and aminoglycosides) from the EARS-NET
130 for invasive infections and the French MedQual network for primary care urine cultures (last data
131 available for both networks)⁷⁻¹⁰. EARS-NET reports aggregated resistance issued from blood and
132 cerebrospinal fluid, regardless of the underlying pathology (urinary tract infections, pneumonia, wound
133 infections...).⁷ EARS-NET for France relied on three networks cumulating a maximum of 59 health
134 institutions laboratories over surveyed period: 23 from teaching hospitals, 30 general hospitals, 3
135 military hospitals, and 3 private hospitals. Duplicates are eliminated, data aggregated and sent to
136 EARS-NET for external quality assessment in collaboration with the United Kingdom National External
137 Quality Assessment Service (NEQAS-EARS).¹⁶ The representativeness for national population
138 coverage of hospitals and population was ranging from 20% to 22% over study period.^{7,8} The
139 MedQual network reports aggregated resistance issued from random urine culture performed in
140 primary care, regardless of the underlying pathology and does not report on aminoglycosides.
141 MedQual relied on 610 to 1016 private practice laboratories in all 13 regions of France during survey
142 period, with 18% to 25% representativeness of private practice laboratories, and population. Regional
143 resistance levels for fluoroquinolones, and 3CG in *E. coli* are only available for year 2019. Results of
144 susceptibility tests are monthly collected in the MedQual database centre for validation and analysis.

145 ⁸⁻¹⁰

146 **Statistical analysis**

147 We restricted the analysis to Q-UTI performed by primary care users, involving *E. coli* and regarding
148 cystitis, pyelonephritis in adults except for pregnant women, and male UTI. We first described the
149 characteristics of patients by type of UTI. Then we computed the 95% confidence interval (95%CI) for
150 the percentage of resistance to amoxicillin, 3CG, FQ, and aminoglycosides in *E. coli*, in data issued
151 from our CDSS-extension. We compared the resistance level to the one issued from MedQual and
152 EARS-NET, using crude prevalence ratio and the chi-squared test. All tests were two-tailed and the
153 level of significance was set at 5%. Analysis was performed on R, version 4.0.1 (R Foundation for
154 Statistical Computing, Vienna, Austria).

155 **Ethics, policies, and funding**

156 *Antibiocllic* is edited and administered by a not-for-profit organization which is not linked to any
157 pharmaceuticals companies, neither for the contents of the CDSS nor for funding. The steering
158 committee members are volunteers and conflicts of interest of members are disclosed on the website.
159 The funding used to develop the CDSS-extension was obtained from a competitive call of Paris area
160 health authorities. None of the collected data are shared with private companies. The confidentiality
161 policy is fulfilling with European General Data Protection Regulation. The study has been approved by
162 the ethics committee of the CNGE (N° 16051997).

163 RESULTS

164 CDSS registered users

165 During the three years of study, 3,494 medical doctors registered to the CDSS-extension, of which
166 2,996 (86%) were general practitioners (GPs), and 2,622 (75%) were from the Ile-de-France area.
167 Users were 52 years old in median [IQR, 40 to 61], and 1,861 (53%) were women. Most were working
168 in group practices or health centers (2,256 – 65%). Compared to national data, GPs characteristics
169 were similar for age, with a higher rate of females (53% versus 48%) and GPs-trainer (29% versus
170 8%).^{17,18} Two-third users (2,385 – 68%) reported using the previous version of the CDSS (before
171 2017) and consulting the CDSS in 40% [IQR, 15 to 70] of cases in which they initiated an antibiotic
172 therapy.

173 UTI due to *E.coli* in CDSS-extension

174 The registered users submitted 43,591 Q-UTI to the system during the study period, with a median of
175 8 Q-UTI [IQR, 2 to 32] per user. A total of 38,862 Q-UTI (91%) concerned adult patients, 16,249 (42%)
176 were documented by a urine culture, and 10,192 (64%) involved *E. coli*, and were therefore included
177 in the statistical analysis: cystitis in 4,174 (41%), male UTI in 3,226 (32%), and pyelonephritis in 2,792
178 (27%). Table 1 shows the characteristics of patients by type of UTI involving *E. coli*. More than a third
179 of Q-UTI (4,066 – 40%) occurred in the elderly (age ≥ 65 years), 2,081 (20%) in patients who had
180 received antibiotic therapy in the 3 months before, and 831 (8%) in patients who presented repeated
181 UTI. In complicated cystitis, complicated pyelonephritis or male UTI, patients were older, likely to live
182 in nursing homes, had higher rate of repeated UTI, had been recently hospitalized, or recently
183 received antibiotics (Chi-squared tests, *p*-values <0.001).

184 Resistance to key antibiotics

185 Among the 10,192 *E. coli* strains described in the Q-UTI, resistance to amoxicillin was present in
186 4,208 (41.3%; 95%CI, 40.3 to 42.2%), to fluoroquinolones in 1,691 (16.6%; 95%CI, 15.9 to 17.3%), to
187 3CG in 681 (6.6%; 95%CI, 6.1 to 7.0%), and to aminoglycoside in 578 (5.7%; 95%CI, 5.2 to 6.1%).
188 Overall, cross-resistance to 3CG and fluoroquinolones was present in less than 10% of Q-UTI. The
189 resistance increased in complicated upper UTIs, reaching ~20% for fluoroquinolones in complicated
190 pyelonephritis and male UTI (Figure 1).

191 **Comparison with surveillance networks for antimicrobial resistance**

192 The resistance levels to the antibiotics were stable over the years within our CDSS and established
193 surveillance systems (Cochran-Armitage tests, p -values >0.050). Figure 1 shows the resistance level
194 of studied antibiotics by type of UTI within our CDSS, and in other surveillance systems.

195 ***Amoxicillin***

196 The overall resistance to amoxicillin in *E. coli* identified in our system (41.3%) was lower than that
197 reported in MedQual (42.7%, prevalence ratio = 0.93 (95%CI, 0.96 to 0.98), p -value = 0.004), and in
198 EARS-NET (55.2%, prevalence ratio = 0.75 (95%CI, 0.74 to 0.76), p -value <0.001).

199 ***Fluoroquinolones***

200 For fluoroquinolones, overall resistance (16.6%) was higher than in MedQual (12.0%, prevalence ratio
201 = 1.38 (95%CI 1.38 to 1.39), p -value <0.001) and EARS-NET (15.8%, prevalence ratio = 1.05 (95%CI
202 1.05 to 1.06), p -value = 0.041). This higher resistance for fluoroquinolones was found in all types of
203 UTIs but uncomplicated cystitis, and ranged from 14.3% to 20.4%. The prevalence ratios ranged
204 between 0.91 and 1.70.

205 ***Third generation cephalosporins***

206 For 3CG, all types of UTI had higher resistance rate than in MedQual (6.6% versus 3.5%, prevalence
207 ratio = 1.90 (95%CI, 1.90 to 1.91), p -value <0.001). It ranged from 4.8% to 10% and corresponded to
208 prevalence ratios of 1.37 to 2.86. Conversely, resistance to 3CG was lower than that reported by
209 EARS-NET (6.5% versus 9.5%, prevalence ratio = 0.68 (95%CI, 0.68 to 0.69), p -value <0.001).

210 ***Aminoglycosides***

211 Overall, resistance to aminoglycosides was lower in our system than in EARS-NET (5.7% versus
212 7.1%, prevalence ratio = 0.80 (95%CI, 0.79 to 0.80), p -value <0.001). Most significant variation were
213 for uncomplicated cystitis (4.4%, p -value <0.001) and pyelonephritis (4.5%, p -value <0.001), while it
214 was similar to EARS-NET for other UTIs (Figure 1). MedQual was not reporting resistance to
215 aminoglycosides.

216 **DISCUSSION**

217 Community-acquired UTI involving *E. coli* submitted to our CDSS showed a gradient of resistance
218 from uncomplicated cystitis to complicated pyelonephritis and male UTI. Antimicrobial resistance was
219 higher than that derived from random urine cultures but close to EARS-NET for invasive infections.
220 We found a concerning rate of resistance to fluoroquinolones in complicated pyelonephritis and male
221 UTI, around 20%.

222 ***Gradient of resistance***

223 The existence of a gradient of resistance in *E. coli*, suggests that the location (lower versus upper) and
224 the type (uncomplicated versus complicated) of UTI could be used as a proxy for levels of resistance.
225 Resistance is likely to occur in upper complicated UTIs. ^{19–22} These parameters could inform the
226 choice of empirical therapies in primary care and accelerate prescription of more potent antimicrobial
227 therapy. This is of interest, considering that in elderly patients experiencing UTI in primary care, a
228 deferred antimicrobial therapy increases bloodstream infection rate and all-cause mortality. ²³

229 ***Resistance to fluoroquinolones and 3CG***

230 Consistent with surveillance data and the literature, resistance to fluoroquinolones and 3CG increased
231 from uncomplicated cystitis to complicated upper UTIs ^{3,7–10,20,24–27}. The high frequency of resistance to
232 fluoroquinolones in complicated upper UTIs (~20%) raises concerns regarding the empirical use of
233 oral fluoroquinolones for managing these infections in primary care ^{19,28}. It highlights that resistance
234 level in clinically relevant infection in primary-care may be close to that observed in hospital settings.
235 Primary care driven data issued from CDSS could inform stakeholders for monitoring the effect of
236 NAPs on AMR, and developing guidelines on AMU in community-acquired UTI. ^{1–3,6} Indeed, injectable
237 3CG and oral fluoroquinolones are often both recommended as first-line antibiotics in uncomplicated
238 and complicated upper UTIs. ^{6,13,14} The preferential use of injectable 3CG over oral fluoroquinolones is
239 recommended whenever the resistance to fluoroquinolones reaches 10% or higher. ^{6,13,14} Such
240 guidelines are developed in a hospital-based perspective where physicians are aware of the local
241 resistance rate, and have access to susceptibility testing. They may be not suitable for primary care,
242 where GPs can be unaware of national and local resistance rates, and lack access to point-of-care
243 susceptibility testing. ²⁹ One may then suggest that dual recommendations can mislead GPs towards
244 the prescription of an oral antibiotic over an infused antibiotic. Reducing the FQ/3CG ratio in primary

245 care is thereby unlikely, as illustrated by the high use of oral fluoroquinolones for UTI in primary care.
246 ^{30,31}

247 ***Limits to comparisons between surveillance systems***

248 The rate of empirical antimicrobial prescriptions was lower (60% versus 97%) than in a recent French
249 survey enrolling women with a similar rate of documented UTI. ³² GPs may indeed consult the CDSS
250 less frequently in infections without urine culture, as the guidelines are simpler than when a
251 documentation is available. This preferential use of the platform for challenging situations could
252 overestimate resistance in our system. The sampling properties of the surveillance systems used are
253 ill characterized, and the differences in sampling methods across surveillance systems can bias
254 resistance estimates and comparisons. ^{1-3,6,24} It is acknowledged that in EARS-NET, underreporting of
255 susceptible isolates can occur for blood cultures, resulting in an overestimation of resistance. ¹⁶ Also,
256 UTIs are not specifically targeted in EARS-NET, while in France the urinary tract is the most frequent
257 portal of entry for bloodstream infection. EARS-NET may represent a worst-case scenario for
258 resistance in the community. Its use may reduce the likelihood of misinforming guidelines on AMU in
259 primary care, but data like we provide are more relevant. ³³ Looking at Q-UTI submitted to our CDSS
260 allows describing the nature and frequencies of UTIs seen in general practice, where the prescription
261 is required. In our system, Q-UTI are submitted by participating GPs prospectively, which limits recall
262 bias. It jointly described the pathology and the germs, providing more details than in two other
263 systems. Despite differences in sampling, the resistance levels were in the range observed between
264 random urine cultures, and invasive infections. ⁷⁻¹⁰ The comparison of resistance levels between
265 networks is also hampered by the differences in periods for data collection, with older data for
266 MedQual and EARS-NET when our estimates are nearly real-time. The resistance levels to the
267 antibiotics were stable over the years within our system and established surveillance systems.
268 Combined with the slow change in antimicrobial resistance in France, this support that recent changes
269 are unlikely to explain the differences between these data sources. ⁷⁻¹⁰ Finally, most users of the
270 CDSS were concentrated in the "Ile-de-France" area, where antibiotic consumption is larger than in
271 France as a whole: 23.8 defined-daily doses per 1000-inhabitants in Ile-de-France versus 22.5 for the
272 rest of the country in 2018 for primary care. ³⁴ However, 2019 resistance data from the national
273 program for surveillance of antimicrobial resistance in primary care shows that resistance levels in our
274 system falls in the range observed among *E. coli* at regional level; from 6.8% to 15.3% for

275 fluoroquinolones (11.0% in “Ile-de-France”), and from 2.4% to 5.8% for 3CG (5.3% in “Ile-de-France”).
276 ¹⁰ Resistance levels observed within our CDSS are thereby likely to be paralleled to the French
277 situation.

278 **Conclusion**

279 We presented data on *E. coli* resistance to antibiotics collected in primary care using a CDSS for
280 antimicrobial prescription. This can inform in real-time on the ecology and surveillance of *E.coli*
281 resistance in community-acquired UTI. Such data could be embedded in existing surveillance
282 systems. They underline the risk of empirical use of fluoroquinolones in complicated upper UTIs and
283 suggest a preferential use of 3CG in such settings. The future linkage between diagnosis, resistance,
284 and prescription is needed to better describe and inform antimicrobial use through individualized
285 guidelines for the prescription.

286 **TRANSPARENCY DECLARATION**

287 **Conflict of interest:** None to declare.

288 **Funding:** The CDSS-extension (*Antibiocliv+*) was funded by a grant from the Regional Health
289 Authorities of Ile-de-France (ARS Ile-de-France) obtained in 2016.

290 **Acknowledgment:** This work was selected to be presented at the 30th European Congress on
291 Clinical Microbiology and Infectious Diseases (ECCMID) – 2020. It is registered in the 30th ECCMID
292 2020, abstract book, under the number 3319.

293 We thank all the users for their positive feedback and their participation in the CDSS development. We
294 thank Gunther Groenewege for his help in ergonomics design. We thank the ANTIBIOCLIC+ study
295 group (alphabetical order): Emilie Ferrat, Jean Gaschignard, Nathan Moreau, Raphaël Lepeule,
296 Philippe Lesprit, Louise Rossignol, and Cécile Souty. We also thank the Paris Diderot University, the
297 SPILF, the CNGE, the CMG, the Regional Health Authorities of Ile-de-France (ARS Ile-de-France), as
298 well as the Health Insurance Agency of Ile-de-France (DRSM Ile-de-France) for their active
299 collaboration.

300 **Access to data:** Academic researchers can access the data for 12 months after the publication of
301 results. Transfer to countries outside of the EU is not allowed. A formal request had to be sent to the
302 corresponding author.

303 **Author's contribution:** TD: Conceptualization, Funding acquisition, Project administration, Data
304 Curation, Formal analysis, Visualization, Original Draft Preparation. JLB: Interpretation of data, Review
305 and editing. SL: Interpretation of data, Review and editing. NPS: Interpretation of data, Review and
306 editing. FXL: Interpretation of data, Review and editing. EB: Interpretation of data, Review and editing.
307 PJ: Interpretation of data, Review and editing. FT: Interpretation of data, Original Draft Preparation,
308 Supervision, Review and editing. PYB: Conceptualization, Interpretation of data, Original Draft
309 Preparation, Supervision, Review and editing

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387 TABLES AND FIGURES

388 **Table 1: Patient's characteristics by type of UTI.**

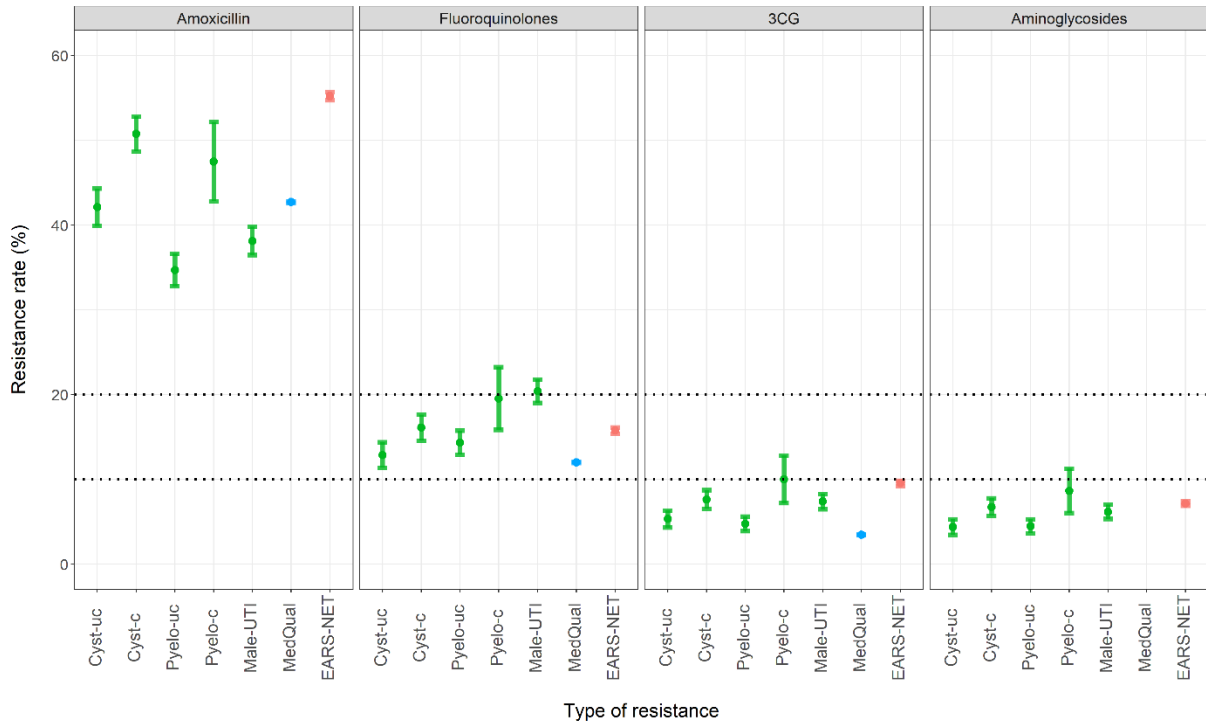
Patients' characteristics	Cystitis		Pyelonephritis		Male UTI	p-value ‡
	Uncomplicated	Complicated †	Uncomplicated	Complicated †		
	N = 1,919	N = 2,255	N = 2,352	N = 440	N = 3,226	
Age ≥ 65 years	539 (28.1%)	1,796 (79.6%)	304 (12.9%)	275 (62.5%)	1,152 (35.7%)	<0.001
Living in nursing home	23 (1.2%)	140 (6.2%)	12 (0.5%)	35 (8.0%)	46 (1.4%)	<0.001
Repeated UTI	176 (9.2%)	346 (15.3%)	113 (4.8%)	42 (9.5%)	154 (4.8%)	<0.001
Antibiotic intake within 3 months	445 (23.2%)	730 (32.4%)	302 (12.8%)	95 (21.6%)	509 (15.8%)	<0.001
Fluoroquinolones within 6 months	347 (18.1%)	568 (25.2%)	424 (18.0%)	139 (31.6%)	845 (26.2%)	<0.001
Traveled abroad within 12 months	30 (1.6%)	31 (1.4%)	54 (2.3%)	10 (2.3%)	82 (2.5%)	0.016
Hospitalization within 12 months	87 (2.3%)	372 (9.1%)	53 (1.9%)	57 (10.1%)	366 (7.2%)	<0.001

389 † Excluding infections in pregnant women.

390 ‡ Chi-squared comparison of patients' characteristics among uncomplicated cystitis (reference class) to other

391 types of UTI: complicated cystitis, uncomplicated pyelonephritis, complicated pyelonephritis, and male UTI.

392 **Figure 1: Resistance rate to amoxicillin, third-generation cephalosporin, fluoroquinolones, and**
 393 **aminoglycosides, in *E. coli*, by type of UTI in CDSS-extension and compared to MedQual and**
 394 **EARS-NET data.**



395 The estimation of resistance of *E. coli* to amoxicillin, fluoroquinolones, 3rd generation cephalosporin (3CG), and
 396 aminoglycosides are reported from three sources of data: CDSS-extension for documented urinary tract infection
 397 (green), MedQual for urine analysis in outsettings (blue), and EARS-NET for invasive infections (red). Estimates
 398 are shown with a 95% confidence interval. The dotted lines correspond to resistance rates of 10% and 20%,
 399 respectively. The following abbreviations are used: “Cys-uc” for uncomplicated cystitis; “Cys-c” for complicated
 400 cystitis; “Pyelo-uc” for uncomplicated pyelonephritis; “Pyelo-c” for complicated pyelonephritis; and “Male-UTI” for
 401 male urinary tract infection.
 402