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1 **Prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in**
2 **community-onset urinary tract infections in France in 2013**

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16
17 Running title: ESBL-positive *E. coli* in UTI in France

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29

1 **Abstract**

2 **Objectives.** We sought to assess the importance of extended-spectrum beta-lactamase (ESBL)
3 producing Enterobacteriaceae in urinary tract infections in outpatients in France.

4 **Methods.** Retrospective laboratory based survey analysing susceptibility patterns of
5 *Escherichia coli* and *Klebsiella pneumoniae* isolates providing from urines collected from
6 outpatients during three months in 2013.

7 **Results.** 499 laboratories collected data on 51,643 *E. coli* and 3,495 *K. pneumoniae* isolates.
8 The overall proportion of ESBL-producing *E. coli* was 3.3%. The proportion was higher for
9 males (4.8%) than for females (3.0%) and increased with age: 2% for patients <20 years to
10 5.4% for those aged >80 years. More than 95% of isolates were susceptible to cefixime,
11 fosfomycin, and nitrofurantoin. In nursing homes, the ESBL-producing *E. coli* proportion was
12 12.1%. For *K. pneumoniae*, the proportion of ESBL-positive isolates was 6.6%, and this
13 proportion increased with age. Data from 2010 collected from a subset of the network showed
14 that the ESBL-producing *E. coli* proportion was 2.0%.

15 **Conclusion.** ESBL-producing isolates were rather frequent in urines in French outpatients in
16 2013. Males and persons residing in nursing homes were at higher risk of ESBL-positive
17 infection. Despite the increase in ESBL-positive isolates, the susceptibility to antibiotics used
18 to treat cystitis remains high.

19

20

21 Introduction

22 The worldwide rise of antimicrobial resistance conducted many countries to develop
23 national plans to control this public health threat.[1,2] After promising results of its first plans,
24 France is currently in the middle of its third antibiotic sparing plan.[3] In a majority of these
25 plans, surveillance of antibiotic resistance is recognised as a core issue. The goals for such
26 surveillance have been listed elsewhere. [4] In particular, surveillance data should help in
27 establishing guidelines for empirical treatment when antibiotic susceptibility tests results are
28 not yet available or will not be performed. In addition, up-to-date data are of interest to assess
29 the accuracy of already published guidelines.

30 Urinary tract infections (UTI) are among the most common bacterial infections that
31 are treated in the community by an empirical antibiotic treatment regimen. In many countries,
32 it is currently not recommended to perform urinalysis for cystitis before treatment, and the
33 choice of the antibiotic regimen relies on the epidemiology of antibiotic resistance.
34 *Escherichia coli*, which is a commensal species of the digestive tract, is the most common
35 bacterial species isolated in UTI. The increase in resistance of *E. coli* to extended-spectrum
36 cephalosporins (ESC) is now well documented, and is mainly due to the production of
37 extended-spectrum beta-lactamase (ESBL) in the hospital setting as well as in the
38 community.[1,5] In France for instance, there has been a 10-fold increase in the digestive
39 carriage of ESBL-producing *E. coli* in the community in the last years.[6] The increase in
40 ESBL-producing *E. coli* makes the treatment of community-onset UTI more complex because
41 such isolates are usually multidrug-resistant, which increases the risk of treatment
42 failure.[1,2,7] In addition, treating ESBL-positive infection is more costly than treating their
43 susceptible counterpart.[7] Therefore, it is of interest to gather up-to-date data on the
44 prevalence of antibiotic resistance of *E. coli* isolated from UTIs in the community.

45 Our main objective was to assess the prevalence of ESBL-producing *E. coli* amongst
46 all *E. coli* isolated from urine samples in the community in ambulatory care in 2013. Data on

47 *Klebsiella pneumoniae* the second most frequent Enterobacteriaceae isolated in community-
48 acquired UTIs and data from patients in nursing homes were also collected for comparison
49 purposes.

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50 **Materials and methods**

51 *Laboratories*

52 Private practice laboratories participating in one of the three pre-existing networks (EpiVille,
53 MedQual-ville, Aforcopi-Bio) of the national observatory for epidemiology of bacterial
54 resistance to antibiotics (ONERBA), and to a fourth network previously set-up for other
55 purposes than surveillance of bacterial resistance (BPR network) were asked to participate on
56 a voluntary basis. A special attention has been paid to national coverage of the network. A
57 total of 499 private practice laboratories distributed throughout metropolitan France, and that
58 referred urines clinical samples to 43 bacteriological centres participated into the network.

59

60 *Bacteriology*

61 Laboratories participating in this new network called « ONERBA-Ville » complied with
62 national recommendations regarding antibiotic susceptibility testing ([www.sfm-](http://www.sfm-microbiologie.org)
63 [microbiologie.org](http://www.sfm-microbiologie.org)), which are very similar to EUCAST recommendations
64 (http://www.eucast.org/ast_of_bacteria), derived from ONERBA's recommendations for
65 surveillance of bacterial resistance.[4,8]

66 Antibiotic susceptibility test methods were chosen locally and included liquid media
67 automated systems (n= 35 for Vitek-2, BioMérieux; n=4 for BD Phoenix system, BD
68 Biosciences; n=4 for Microscan WalkAway, Siemens Healthcare diagnostics) and the disk
69 diffusion method (n=6). ESBL-production was determined according to national
70 recommendations as described elsewhere. [9]

71 Isolates were considered susceptible to tested antibiotics by using the following breakpoints:
72 $\leq 4/2$ mg/L for amoxicilline/clavulanate, ≤ 1 mg/L for cefixime, ≤ 0.5 mg/L for ciprofloxacin,
73 ≤ 32 mg/L for fosfomicin, ≤ 64 mg/L for nitrofurantoin, and $\leq 2/38$ mg/L for cotrimoxazole.

74

75 *Database*

76 Data were retrospectively collected for each *E. coli* or *K. pneumoniae* strain isolated from
77 urines routinely collected for diagnosis of community-onset urinary tract infections in
78 outpatients or those in nursing home during September to November 2013. Data included
79 patient's age, gender, and susceptibility tests results including ESBL production. In case of
80 duplicates, only the first isolate was retained for the study. Whenever possible and for
81 comparison purpose, similar data were collected for 2010.

82

83 *Data analysis*

84 Data have been analysed by using STATA 11 (StataCorp, College Station, TX, USA).
85 Fisher's exact test was used to compare proportions. The Chi2 test for trend has been used to
86 assess the impact of age on the proportion of ESBL-producing isolates. A p-value < 0.05 was
87 considered as statistically significant.

88

89 **Results**90 *E. coli* isolated from outpatients in 2013

91 Data on 51,463 *E. coli* isolates were collected from urine samples of outpatients during the 3-
92 month study period. The median age of the patients was 60 years and 86.4% were females.

93 Among all isolates, 1,694 (3.3%) were ESBL-positive. Patients with ESBL-producing isolates
94 were older (median, 70 years) than those with ESBL-negative isolates (median, 60 years;
95 $p<0.001$). The proportion of ESBL-producing *E. coli* was higher in males (4.8%) than in
96 females (3.0%, $p<0.001$). The proportion of patients harbouring ESBL-producing isolates
97 increased with age (Table 1): from 2.0% among patients under 20 years, to 5.4% among those
98 over 80 years ($p<0.001$, chi-square test for trend). This significant trend was observed after
99 stratified analysis by gender (Table 1).

100 As expected, ESBL-producing isolates were significantly less frequently susceptible to
101 antibiotics than ESBL-negative isolates: 22.7% against 67.6% for co-amoxiclav, 47.5%
102 versus 80.8% for cotrimoxazole, 44.0% against 91.0% for ciprofloxacin, 4.0% against 98.0%
103 for cefixime, 93.7% against 98.9% for fosfomycin, 95.4% against 98.9% for nitrofurantoin
104 (Table 2). Overall, 6.0% of the isolates were resistant to at least 3 of the 6 drugs.

105 *E. coli* isolated in nursing homes in 2013

106 A subset of 17 technical centres analysing samples for 237 laboratories provided data on 908
107 *E. coli* isolates from patients located in nursing homes during the study period. The median
108 age of patients in nursing homes (88 years) was higher than for outpatients (60 years;
109 $p<0.001$). The proportion of ESBL-producing isolates was higher in nursing homes in 2013
110 (12.1%) than in outpatients (3.3%; $p<0.001$). Of interest, the proportion of ESBL-producing
111 isolates in nursing homes, did not differ significantly according to gender (14.0% in males
112 versus 11.7% in females; $p=0.5$). The percentage of susceptibility to ciprofloxacin was lower
113 for *E. coli* isolated in nursing homes than for those from outpatients for isolates taken as a

114 whole (73.8% versus 89.5%, respectively; $p<0.001$) or when considering only ESBL-
115 producing isolates (17.4% versus 44.0%, respectively; $p<0.001$).

116 *K. pneumoniae* isolated from outpatients in 2013

117 A subset of 41 technical centres analysing samples for 493 laboratories provided data on
118 3,495 *K. pneumoniae* isolates from outpatients. Patients harbouring *K. pneumoniae* were older
119 than those harbouring *E. coli* (median, 67 versus 60 years; $p<0.001$), and were more
120 frequently male (17.8% versus 13.6%; $p<0.001$). The proportion of ESBL-producing *K.*
121 *pneumoniae* was 6.6% as compared to 3.3% for *E. coli* ($p<0.001$). As for *E. coli*, the
122 proportion of ESBL-producing *K. pneumoniae* was higher among males than females (11.6%
123 versus 5.6%; $p<0.001$), and increased with age (Table 1). Regarding antibiotic susceptibility
124 (Table 2), *K. pneumoniae* isolates were significantly less frequently susceptible than *E. coli*
125 isolates to cefixime (93.2% versus 95.0%), fosfomycin (74.4% versus 98.7%), and
126 nitrofurantoin (71.0% versus 98.8%). On the contrary, *K. pneumoniae* isolates were
127 significantly more susceptible than *E. coli* isolates to ciprofloxacin (91.2% versus 89.5%), and
128 cotrimoxazole (88.4% versus 79.6%). Overall, 5.9% of the isolates were resistant to at least 3
129 of the 5 drugs.

130

131 *E. coli* isolated from outpatients in 2010

132 A subset of 27 centres analysing samples for 222 laboratories provided data on 15,658 *E. coli*
133 isolates from outpatients from September to November 2010. The proportion of ESBL-
134 producing isolates was 2.0% in 2010 as compared to 3.3% in 2013 ($p<0.001$). The proportion
135 of ESBL-producing isolates increased with patients' age in 2010, 1.5% before 60 years old to
136 2.6% in patients over 60 years ($p<0.001$). Overall, isolates were significantly more susceptible
137 to cefixime and cotrimoxazole in 2010 (96.5% and 82.9%, respectively) than in 2013 (95.0%
138 and 79.6%, respectively; $p<0.001$ for both comparisons). Isolates were slightly less
139 susceptible to fosfomycin in 2010 compared to 2013 (97.7% and 98.7%, respectively;

140 p<0.001). The susceptibility to ciprofloxacin and nitrofurantoin was similar in 2010 and 2013.
141 The susceptibility of ESBL-producing isolates to these antibiotics didn't change between
142 2010 and 2013.

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143 **Discussion**

144 We conducted a retrospective survey on the proportion of ESBL-producing *E. coli* and
145 *K. pneumoniae* isolated from urines of ambulatory or nursing home patients in 2010 and
146 2013. We showed that the proportion of ESBL-producing isolates was rather high and
147 increased with age, was higher for males as compared to females and increased since 2010.
148 Nevertheless, the proportions of susceptible isolates remain elevated for most antibiotics used
149 in the treatment of uncomplicated *E. coli* UTI.

150 The 3.3% proportion of ESBL-producing *E. coli* in urine samples in France in 2013 is
151 lower than what was reported in numerous European countries such as Spain (7,6%) Italy,
152 United-Kingdom and Germany (all circa 6%) between 2008 and 2011.[10–13] On the
153 opposite, a lower proportion (1.7%) of ESBL-producing *E. coli* was reported from outpatients
154 in Switzerland in 2009-2010.[14] These differences may be explained by variations in
155 populations surveyed, use of systematic urinalysis for UTI diagnosis, or by levels of antibiotic
156 use in the community.[14,15]

157 We report a significant increase in the proportion of ESBL-producing *E. coli* from
158 2010 to 2013. This is in accordance with previous findings in France showing that the
159 proportion of ESBL-producing *E. coli* was 0.3% in 1999 and 1.1% in 2006.[5,16] In addition,
160 during the same period of time, there was a 10-fold increase in the prevalence asymptomatic
161 carriers of ESBL-producing *E. coli* in the community.[6] However, these studies have been
162 conducted with different methodologies, and comparisons should be interpreted with caution.
163 The significant upward trend in ESBL-producing isolates with age as been previously
164 reported.[17,18] In addition, we confirmed that men have a higher risk of ESBL-positive
165 infections than women.[18,19] These findings underline the importance of age and gender
166 stratification for correct interpretation of resistant data and for comparisons between
167 populations in different settings. It suggests also that guidelines for the treatment of UTI
168 should be adapted to age and gender.

169 *Antibiotic susceptibility*

170 Despite the rise of ESBL-producing isolates, *E. coli* and *K. pneumoniae* isolates remain
171 highly susceptible to fosfomicin, and nitrofurantoin, two drugs for which susceptibility rates
172 were not affected by ESBL production. These data reinforce the 2014 French guidelines for
173 empirical treatment of uncomplicated UTI, which recommend fosfomicin as first line drug
174 and nitrofurantoin as an alternative.[20,21] Desperately, we could not gather data regarding
175 pivmecillinam, which is recommended in the French guidelines. However, a high rate of
176 clinical failure has been reported recently for the treatment of ESBL-producing isolates with
177 this drug.[22] We report that 95.0% of all *E. coli* isolates were susceptible to cefixime.
178 However, this third generation cephalosporin is currently not recommended for the empiric
179 treatment of simple UTI mainly because of its ecological impact. In addition, the activity of
180 cefixime is highly susceptible to the production of ESBL, which is now more frequent.

181 *Limitations*

182 Our study has some limitations. First, we collected routine data on urinary samples without
183 information regarding clinical symptoms and risk factors. This is of importance in the context
184 of UTI in the community where urinalysis for uncomplicated cystitis is not recommended.
185 Therefore it is likely that urinalysis was partly performed for the most complicated UTI, and
186 the observed proportions of ESBL-producing isolates or of antibiotic resistance are likely to
187 overestimates “true” proportions. However, the observed trend, which is in accordance with
188 other studies, is likely to be real and calls for actions. The fact that we did not collect risk
189 factors of antibiotic resistance limits the interpretation of the results. Second, no specific
190 quality control was organized for the study. However, all French laboratories are now in the
191 process of national accreditation, which makes mandatory internal and external quality
192 controls such as the one annually organised by the French Medical Agency.

193 **Conclusion**

194 The retrospective study allowed assessing the magnitude of ESBL-producing isolates in the
195 outpatients settings. The observed proportion, which is ten times higher than the one observed
196 15 years ago is worrisome. Such study with a large network has to be repeated to assess trends
197 over time of antibiotic resistance and the impact of national plans against antibiotic resistance.

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199 **ONERBA-ville Network**

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213

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217

218 **Competing interest**

219 All authors declare no conflict of interest regarding the results of the study

220

221 **References**

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323

324

325 Table 1. Proportion of extended-spectrum beta-lactamase producing strains isolated from
 326 urines according to age in ambulatory patients in 2013

327

Variable	Age group					<i>P</i> value*
	0-20	21-40	41-60	61-80	> 80	
<i>Escherichia coli</i>						
- Total (n=51463)	2.0	1.9	2.5	3.9	5.4	0.001
- Female (42839)	2.0	1.9	2.3	3.6	5.1	0.001
- Male (6733)	2.9	1.7	3.6	5.5	6.8	0.001
<i>Klebsiella pneumoniae</i>						
- Total (n=3495)	3.4	4.1	4.8	6.5	10.3	0.001
- Female (n=2753)	2.4	3.8	3.3	4.3	10.7	0.001
- Male (n=594)	NA	9.1	11.7	13.7	7.6	0.001

328 NA: the number of isolates was <30;

329 * *P*-value: chi-square for trend

330

331

332

333 Table 2. Susceptibility (%) to the main antibiotics of strains isolated from urines in
 334 ambulatory patients in 2013
 335

Variable	Co-amox	Cefixime	Ciprofloxacin	Fosfomycin	Nitrofurantoin	Cotrimoxazole
<i>Escherichia coli</i> (n=51463)						
Total	66.1	95.0	89.5	98.7	98.8	79.6
Gender						
- Female	66.9	95.4	90.3	98.7	98.9	80.0
- Male	61.6	92.8	84.4	98.6*	98.1	77.5
ESBL production						
- ESBL-negative isolates	67.6	98.0	91.0	98.9	98.9	80.8
- ESBL-positive isolates	22.7	4.0	44.0	93.7	95.4	47.5
<i>Klebsiella pneumoniae</i> (n=3495)						
- Total	-	93.2	91.2	74.4	71.0	88.4

336 Co-amox: co-amoxiclav.

337 All differences between ESBL-positive and ESBL-negative isolates, between female and male
 338 patients, and between total *E. coli* and *K. pneumoniae* isolates are statistically significant
 339 ($p < 0.001$) but for *

The production of extended-spectrum beta-lactamase in Enterobacteriaceae has been associated with increased treatment failure and higher management costs.

The prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in urinary samples from outpatients has increased significantly in France to reach 3.3%.

The prevalence of extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* in the outpatient setting is circa twice than for *Escherichia coli*

The prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in nursing homes is circa 4 times higher than in the outpatient setting.

The prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in urinary samples increases significantly with patient's age.