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1 **Resistance to third-generation cephalosporins in *Escherichia coli* in the French**
2 **community, The Times They Are A-Changin'?**

3

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23

24 **Running title:** Resistance of *E. coli* to third-generation cephalosporins in outpatients

25 **Abstract**

26 **Introduction.** Since the early 2000s, *E. coli* resistance to third-generation cephalosporins
27 (3GCs) has been increasing in all European countries, mainly due to the spread of extended
28 spectrum β -lactamases (ESBL). We present here a retrospective study that combines
29 resistance of *E. coli* to 3GCs and quinolones and the antibiotic use in the community in a
30 region of Northeastern France.

31 **Materials and Methods.** Since 2012, we conducted an observational surveillance of
32 antimicrobial resistance and antibiotic use in the community: data of antibiotic resistance in
33 *E. coli* isolates were collected from 11 private laboratories, and consumption data from the
34 three main healthcare insurances.

35 **Results.** A significant decrease of resistance prevalence to 3GCs (from 5.6 to 3.9%, $p <$
36 0.001), nalidixic acid (16.7 to 14.8%, $p = 0.004$) and ciprofloxacin (10.9 to 8.1%, $p < 0.001$)
37 was reported between 2015 and 2017. Although the total antibiotic consumption did not
38 vary significantly between 2012 and 2017, we observed a decrease of the consumption of
39 3GCs (-32%, $p < 0.001$) and fluoroquinolones (-25%, $p < 0.001$).

40 **Conclusion.** We report here a decrease of the prevalence of *E. coli* isolates resistant to 3GCs
41 and quinolones in outpatients in a context of significant decreasing consumptions of these
42 two antibiotic classes.

43

44 **Keywords:** *E. coli*; third-generation cephalosporins; quinolones; resistance; outpatients.

45

46

47 **1. Introduction**

48 High rates of antimicrobial resistance in *Escherichia coli* are an important global
49 public health concern [1]. Indeed, *E. coli* constitutes a major cause of both community-onset
50 and hospital-acquired infections [2]. Since the early 2000s, *E. coli* resistance to third-
51 generation cephalosporins (3GCs) has been increasing in hospital and community settings of
52 all European countries, mainly due to the spread of extended spectrum β -lactamases (ESBL)
53 [1,3,4]. In 2017, EARS-net report showed that the rate of resistance of *E. coli* to 3GCs
54 reached 14.9 % in bacteremias in hospital setting and upward trends were observed in
55 almost all European countries in the last decade [1]. Besides these hospital data, several
56 surveillances have also reported an increasing trend of resistance to 3GCs in *E. coli* from the
57 community [5,6]. This spread combines dissemination of epidemic clones such as ST131 -
58 C1/H30-R and C2/H30-Rx clades, as well as horizontal transfers of plasmid-borne *bla*_{ESBL} [7].
59 The possibility that ESBL rates reach that of penicillinase within this species is clearly a
60 matter of major concern.

61 ESBL-producing *E. coli* isolates are often resistant to other antibiotics such as
62 fluoroquinolones and aminoglycosides, further complicating the management of patients
63 infected with ESBL-producing *Enterobacteriaceae* [6,7]. Indeed, combined resistance to
64 3GCs, fluoroquinolones, and aminoglycosides was 6.3 % in 2017 in the EU, but did not
65 significantly change during the period 2014–2017 [1]. Moreover, up to 70 % of ESBL-
66 producing isolates were resistant to fluoroquinolones in community-onset infections [6]. The
67 spread of ESBL-producing *E. coli* within the community is mainly driven by antimicrobial
68 exposure, notably previous use of fluoroquinolones and oral 3GCs, which have a high
69 ecological impact [8]. In that context, we implemented in our region an antimicrobial
70 resistance stewardship program that monitored the antibiotic use in outpatients.

71 We present here a retrospective study that combines the resistance of *E. coli* to 3GCs

72 and quinolones and the antibiotic use in the community in a region of Northeastern France.

73

74

75 **2. Materials and methods**

76 Since 2012, we conducted an observational surveillance (the OSCAR network) of
77 antimicrobial resistance and antibiotic use in the community in Franche-Comté region, a
78 Northeastern area of France with 1.2 million inhabitants.

79 3GCs and quinolones (nalidixic acid and ciprofloxacin) resistance data were collected
80 during six years (2012-2017) from eleven private laboratories. All resistance data concerning
81 nursing homes or clinics were excluded. For one patient, one isolate per susceptibility profile
82 and per year was considered.

83 Antimicrobial consumption data were provided by the three main healthcare
84 insurances of Franche-Comté and their beneficiaries represented 88% of the total
85 population. These antibiotic reimbursement data for ambulatory care, based on antibiotics
86 dispensed in community pharmacies, were available since 2012. The consumption data were
87 expressed in defined daily dose (DDD) per 1000 beneficiaries per day for each antibiotic for
88 systemic use (ATC group J01): tetracyclines (J01A), β -lactams (J01C and J01D), sulfamide and
89 trimethoprim (J01E), macrolides (J01F), aminoglycosides (J01G), fluoroquinolones (J01M)
90 and associations and other antibiotics (J01R+J01X) [9].

91 We tested the variation in the prevalence of *E. coli* isolates resistant to 3GCs, nalidixic
92 acid, and ciprofloxacin, using the χ^2 test. The trend of consumption of each antibiotic class
93 over the period 2012 to 2017 was tested by using a negative binomial model for which the
94 DDD were considered as counting data. The relative change, also calculated here, consists of
95 the variation of consumption of each antibiotic class between the two years 2012 and 2017.

96

97

98 **3. Results**

99 **3.1 Antimicrobial resistance in *E. coli***

100 A total of 34,767 *E. coli* isolates have been tested for their susceptibility between 2012 and
101 2017. Trend in resistance prevalence of *E. coli* to 3GCs, nalidixic acid, and ciprofloxacin, are
102 shown in Figure 1a. Resistance rate for 3GCs was 3.9% in 2012, reached 5.9% in 2015 and
103 significantly decreased between 2015 and 2017, from 5.9 to 4.2% ($p < 0.001$). Although the
104 evolution of the prevalence of resistance to nalidixic acid differed from that to 3GCs and
105 ciprofloxacin between 2012 and 2015, a significant decrease of the prevalence of resistance
106 to quinolones was also reported between 2015 and 2017, from 16.7 to 14.8% for nalidixic
107 acid ($p = 0.004$) and from 10.9 to 8.1% for ciprofloxacin ($p < 0.001$). Among *E. coli* isolates
108 resistant to 3GCs collected between 2012 and 2017, the prevalence of nalidixic acid and
109 ciprofloxacin resistance decreased in parallel between 2015 and 2017, from 73.8 to 64.2%,
110 and from 66.8 to 52.9%, respectively (Figure 1b).

111

112 **3.2 Antibiotics consumption**

113 Although the total antibiotic consumption did not vary significantly between 2012 and 2017,
114 the use of penicillins (J01C), and that of the broad-spectrum penicillins (J01CA) such as
115 amoxicillin (J01CA04), increased significantly ($p < 0.001$) over the study period (Table 1).
116 Except for tetracyclines (J01A) and associations and other antibiotics (J01R+J01X), we found
117 a significant downward trend of consumption for the others studied group of antibiotics
118 (Table 1). We notably observed a decrease of the 3GCs (J01DD, -32.1%, $p < 0.001$) and
119 fluoroquinolones consumption (J01M, -25.5%, $p < 0.001$) over the study period (Table 1,
120 Figure 1a).

121

122 4. Discussion

123 After several years of constant rise, we report here a significant decrease of the
124 prevalence of *E. coli* resistant to 3GCs and quinolones in outpatients from Franche-Comté
125 between 2015 and 2017. Regarding the resistance to 3GCs, our results confirm those
126 collected by another French surveillance network (Medqual) which nevertheless reported a
127 lower decrease between 2015 and 2017 (from 4.5% in 2015 to 4% in 2017 *versus* 5.9% to
128 4.2% in Franche-Comté) [10]. These trends observed in the community coincided with those
129 recorded in EARS-net database, the national survey of *E. coli* isolated from blood culture in
130 French hospitals (11% in 2015 to 10.2% in 2017) [1]. Although this national downward trend
131 was not significant, the decrease reported in Franche-Comté could be more general in
132 France.

133 Concerning fluoroquinolones, the decrease of resistance reported here was also highlighted
134 by EARS-net data in France (from 17.7% in 2015 to 15% in 2017) [1]. The same trend was
135 described by the Medqual network in community-onset infections for nalidixic acid.

136 However, the decrease of the resistance rate of ciprofloxacin in *E. coli* was less pronounced,
137 from 10.1% in 2015 to 9.6% in 2017 *versus* 10.9% to 8.1% in Franche-Comté [10]. According
138 to other studies, we described here high resistance rates of quinolones in isolates resistant
139 to 3GCs [6,11].

140

141 Interestingly, the decrease of the prevalence of *E. coli* resistant to 3GCs in
142 community-onset infections reported here occurred in a context of a significant decrease of
143 the consumption of 3GCs and fluoroquinolones, despite a significant increase of penicillins
144 consumption. Many studies have described the high-ecological impact of 3GCs and
145 fluoroquinolones. For instance, recent phylogenic studies using whole genome sequencing

146 identified the most recent common ancestor of successful epidemic clones, thus strongly
147 suggesting that fluoroquinolones had played an important role in the global expansion of the
148 major pathogens *Escherichia coli* ST131 H30-Rx, methicillin-resistant *Staphylococcus aureus*
149 EMRSA-15, *Pseudomonas aeruginosa* ST235 in the mid-1980s, and that of *Clostridium*
150 *difficile* 027 in the early 1990s [12–15].

151

152 Although this is not statistically demonstrated, the decrease of the use of
153 fluoroquinolones and 3GCs, which began in 2013 in our region, presumably played a major
154 role in the trend of resistance to 3GCs among community *E. coli* isolates. However, the
155 reducing consumption of antibiotics is not immediately followed by the decrease of
156 antibiotic resistance. Some studies reported that once the resistance to an antimicrobial is
157 well established in a population of *E. coli*, a reduction in the use of that antimicrobial is
158 unlikely to influence to resistance rates in the short-to-medium term [2,16]. This could be
159 explained by two effects. The first one may be due to the prolonged carriage of multidrug-
160 resistant *E. coli* even in the absence of antimicrobial selection pressure, described for *E. coli*
161 ST131 [17]. Hence, it may take several years to achieve a sufficient patient turnover and to
162 observe the effect of antibiotic use reduction [16]. The second one is the nonlinear
163 relationship between the antibiotic use and resistance ; other parameters could be involved
164 such as dissemination of resistant strains by cross-transmission [18]. A recent study has
165 calculated antibiotic consumption thresholds below which the resistance rates are
166 independent from the consumption. For instance, minimum thresholds were estimated for
167 selected antibiotics and the rates of ESBL-producing or cefepime-resistant *E. coli* [18].

168

169 This study has several limitations. First, our data did not establish a significant
170 relationship between the decrease of antibiotic resistance rate and their consumption. Then,
171 we missed the genotyping data that could have allowed the understanding of the decrease
172 of resistance reported here. However, we could speculate that the decrease in prevalence of
173 the major multidrug-resistant clone *E. coli* ST131 H30-Rx participated, at least in part, to the
174 decrease of the resistance in the species. OSCAR network surveillance must be continued to
175 confirm the trend in resistance prevalence and antibiotics consumption reported here.

176

177

178 **5. Conclusion**

179 We report here a decrease of the prevalence of *E. coli* isolates resistant to 3GCs and to
180 quinolones in a context of decreasing consumptions of these two antibiotic classes. The
181 stewardship programs can efficiently decrease the antimicrobial resistance, making the
182 progression to multi-resistance not inevitable. However, actions improving antimicrobial
183 prescription should be continuous because of their delayed effect.

184

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187 the use of its antibiotic resistance data.

188

189 **Declarations**

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191 Bourgogne-Franche-Comté).

192 **Competing Interests:** None

193 **Ethical Approval:** Not required

194

195 **Author contributions.** Conceived and designed the experiments: XB, CBS, and JL. Performed
196 the experiments: CBS, HB, and HGH. Analyzed the data: CBS, HB, AJ, and HGH. Wrote the
197 paper: AJ, CBS, and XB.

198

199

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259 Prolonged colonisation with *Escherichia coli* O25:ST131 versus other extended-
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265 population antibiotic use and rates of resistance. *Nat Microbiol* 2019; 4:1160-72.
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267 **Figure captions**

268 **Figure 1.** Resistance prevalence of *E. coli* isolated from community-onset infections to third-
269 generation cephalosporins and quinolones between 2012 and 2017 in Franche-Comté
270 (Northeastern France). **(a)** Trend in resistance rate of *E. coli* isolated from community-onset
271 infections to third-generation cephalosporins (3GCs), nalidixic acid (NA) and ciprofloxacin
272 (CIP) associated to 3GCs and quinolones consumption between 2012 and 2017 in the
273 Northeastern France. Prevalence of resistance to 3GCs, NA and CIP are represented by dark
274 grey, light grey and black lines, respectively. The prevalence of *E. coli* resistant to these
275 antibiotics decreased between 2015 and 2017 (χ^2 test). Consumptions of 3GCs and
276 fluoroquinolones (FQs) are represented by dark grey and light grey bars, respectively. **(b)**
277 Trend in resistance rate to nalidixic acid (NA) and ciprofloxacin (CIP) of *E. coli* isolates resistant
278 to third-generation cephalosporins (3GCs-R) between 2012 and 2017 in the Northeastern
279 France. The bars represent the number of *E. coli* isolates 3GCs-R between 2012 and 2017.
280 Light grey and dark grey lines represent the percentage of 3GCs-R *E. coli* isolates resistant to
281 NA and CIP, respectively.

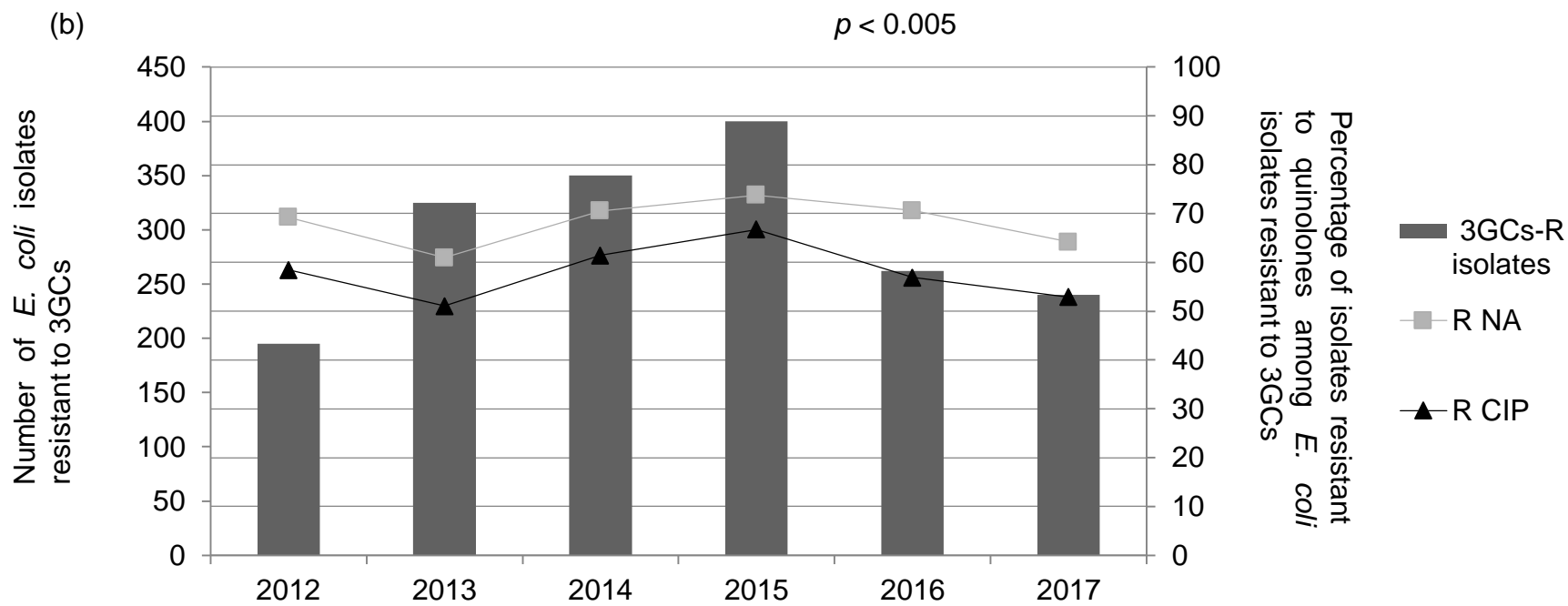
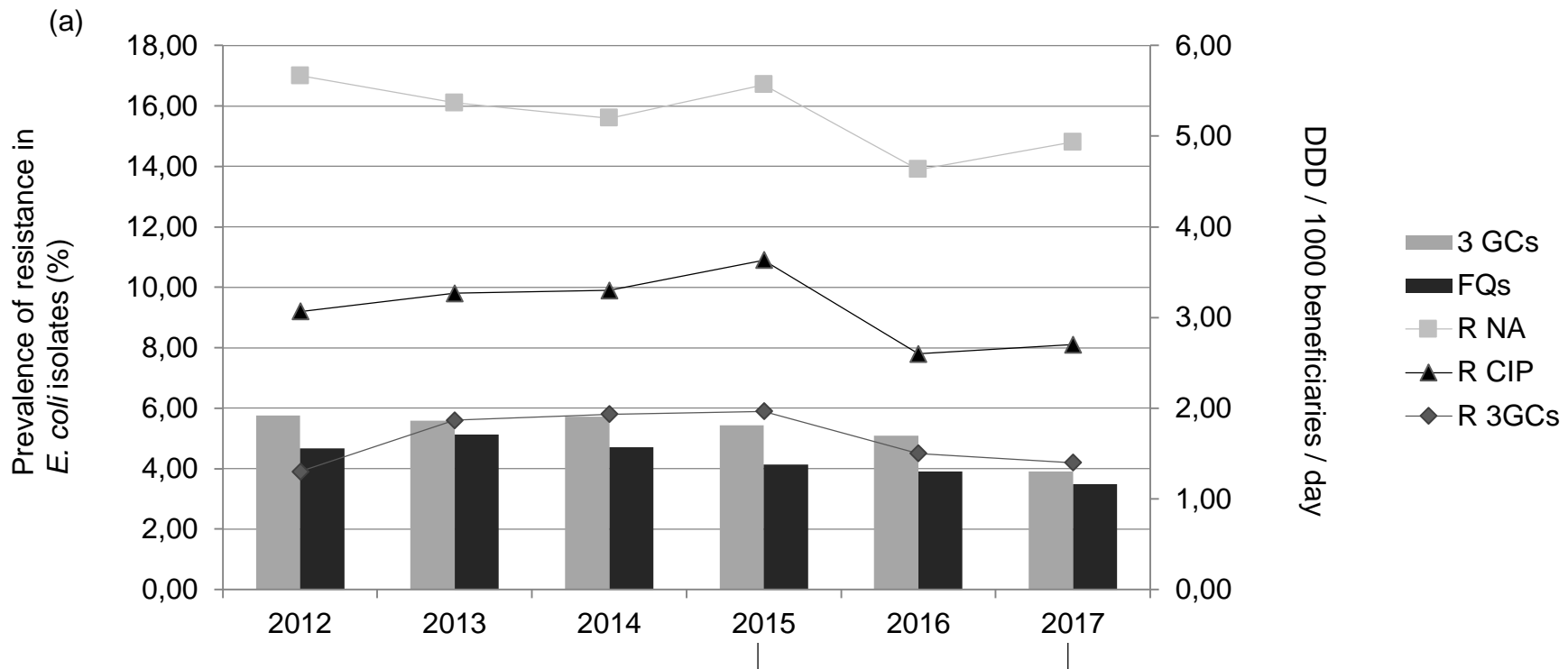


Table 1: Consumption of antibiotics for the treatment of community-onset infections in the Northeastern France between 2012 and 2017.

Antibiotic class	Antibiotic consumption (DDD / 1000 beneficiaries / day)						Relative change ¹ (%)	Trend ² (p)
	2012	2013	2014	2015	2016	2017		
J01A - tetracyclines	2.57	2.93	2.64	2.47	2.61	2.52	- 1.8	0.208
J01C - β-lactams-penicillins	14.93	18.53	18.07	18.19	19.28	18.47	23.7	0.020*
J01CA - broad spectrum penicillins	7.92	10.38	10.25	10.68	11.69	11.68	47.5	< 0.001*
J01CR - penicillins associations	6.40	7.52	7.18	7.04	7.19	6.39	- 0,20	0.720
J01CR02 - amoxicillin-clavulanic acid	NA	NA	NA	7.03	7.18	6.38	NC	NC
J01D - other β-lactams	2.73	2.77	2.64	2.42	2.24	1.75	- 35.9	0.001*
J01DB - first-generation cephalosporins	0.22	0.035	0.16	0.015	0.015	0.007	- 96.8	< 0.001*
J01DC - second-generation cephalosporins	0.59	0.87	0.56	0.59	0.52	0.43	- 26.8	0.011*
J01DD - third-generation cephalosporins	1.92	1.86	1.91	1.81	1.70	1.30	- 32.1	0.001*
intravenous 3GCs	0.12	0.15	0.14	0.15	0.14	0.13	13.6	0.327
per os 3GCs	1.80	1.71	1.77	1.66	1.56	1.17	- 35.1	0.001*
J01E- sulfamide and trimethoprim	0.67	0.81	0.77	0.37	0.36	0.35	- 47.3	0.001*
J01F-macrolides	3.47	3.87	3.41	3.49	3.46	3.08	- 11.4	0.027*
J01FG01-pristinamycin	NA	NA	NA	0.98	0.90	0.90	NC	NC
J01G- aminoglycosides	0.04	0.042	0.035	0.033	0.031	0.025	- 36.4	< 0.001*
J01M- fluoroquinolones	1.56	1.71	1.57	1.38	1.30	1.16	- 25.5	< 0.001*
intravenous fluoroquinolones	0.00051	0.0007	0.00027	0.00049	0.00013	0.00052	- 3.0	0.438
per os fluoroquinolones	1.56	1.71	1.57	1.38	1.30	1.16	- 25.5	< 0.001*
J01R+J01X - Associations and other antibiotics	0.52	1.05	0.98	1.0	0.96	0.87	67.7	0.290
Total	26.91	31.70	30.10	29.35	30.24	28.24	4.9	0.905

NA: not available, NC: not calculated, *: significant trend (p < 0.05)

¹Relative change consists of the variation of consumption of each antibiotic class between the two years 2012 and 2017.

²The trend of consumption of each antibiotic class was determined over the period 2012 to 2017 by using a negative binomial model