Temporal trends of extended-spectrum cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolates in in- and outpatients in Switzerland, 2004 to 2011

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Citation style for this article:
Kronenberg A, Hilty M, Endimiani A, Mühlemann K. Temporal trends of extended-spectrum cephalosporin-resistant Escherichia coli and Klebsiella pneumoniae isolates in in- and outpatients in Switzerland, 2004 to 2011 . Euro Surveill. 2013;18(21):pii=20484. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20484

Article submitted on 13 July 2012 / published on 23 May 2013

Increasing trends for invasive infections with extended-spectrum cephalosporin-resistant (ESC-R) *Enterobacteriaceae* have been described in many countries worldwide. However, data on the rates of ESC-R isolates in non-invasive infections and in the outpatient setting are scarce. We used a laboratory-based nationwide surveillance system to compare temporal trends of ESC-R rates in *Escherichia coli* and *Klebsiella pneumoniae* for in- and outpatients in Switzerland. Our data showed a significant increase in ESC-R rates from 1% to 5.8% in *E. coli* (p<0.001) and from 1.1% to 4.4% in *K. pneumoniae* (p=0.002) during an eight-year period (2004–2011). For *E. coli*, the increase was significantly higher in inpatients (from 1.2% to 6.6%), in patients residing in eastern Switzerland (from 1.0% to 6.2%), in patients older than 45 years (from 1.2% to 6.7%), and in male patients (from 1.2% to 8.1%). While the increase in inpatients was linear (p<0.001) for *E. coli*, the increase of ESC R *K. pneumoniae* isolates was the result of multiple outbreaks in several institutions. Notably, an increasing proportion of ESC-R *E. coli* was co-resistant to both trimethoprim-sulfamethoxazole and quinolones (42% in 2004 to 49.1% in 2011, p=0.009), further limiting the available oral therapeutic options.

Introduction

Extended-spectrum cephalosporins (ESCs), such as those of third-generation (3GC, e.g. ceftriaxone, cefotaxime, ceftazidime) and fourth-generation (4GC, e.g. cefepime), are frequently used antibiotics for the treatment of severe infections, because of their ample spectrum, strong bactericidal activity, and low toxicity. However, during the past three decades, an increasing number of ESC-resistant (ESC-R) Gram-negative pathogens have been reported worldwide [1].

Several mechanisms such as production of extended-spectrum beta-lactamases (ESBLs), chromosomal (cAmpCs) or plasmid-mediated AmpCs (pAmpCs) or carbapenemases may lead to phenotypic resistance to ESCs. However, since their first description in 1983, ESBLs have been recognised as the most prevalent mechanism responsible for resistance to ESCs in *Enterobacteriaceae*. While ESBLs during the 1990s were mainly described in *Klebsiella pneumoniae* isolates causing nosocomial outbreaks, ESBL-producing *E. coli* causing community-acquired infections (especially urinary tract infections (UTIs)) nowadays also represent a serious challenge for the therapeutic armamentarium [2]. According to the Infectious Diseases Society of America (IDSA), ESBL-producing *Klebsiella* spp. and *E. coli* belong to the six most important multidrug-resistant (MDR) pathogens for which new therapies are urgently needed [3].

The prevalence of ESC-R *Enterobacteriaceae* varies worldwide. In 2009, 39% of *E.coli* isolated from intensive care patients in the Asian/Pacific area were ESBL producers, while rates were lower in Latin America (25%), Europe (16.3%) and North America (8.7%) [4]. As described by the European Antimicrobial Resistance Surveillance Network (EARS-Net), the prevalence rate of ESC-R *Enterobacteriaceae* causing invasive infections increased significantly from 2007 to 2010 in half of the reporting countries, but to different levels. For instance, while the rates in 2010 were below 5% in Scandinavia and Iceland, rates above 10% were found in 10 European countries (Bulgaria, Cyprus, Czech Republic, Greece, Hungary, Italy, Latvia, Malta, Romania and Spain) [5]. However, most surveillance programmes have taken into consideration only isolates responsible for invasive infections in hospitalised patients [6], and only a few studies at national and local level have described rates of ESBL producers in community-acquired UTIs or bloodstream infections (BSIs) [7-10]. As a result, data regarding the temporal

trends of antibiotic resistance in the community are still needed.

In this study, we describe in detail the temporal trends of ESC-R *E. coli* and *K. pneumoniae* isolates in hospital and community settings in Switzerland during an eight-year epidemiological study performed using the data of the Swiss Antibiotic Resistance Surveillance database ANRESIS [11].

Methods

Data collection

Antibiotic resistance data for *E. coli* and *K. pneumoniae* isolates were analysed using the ANRESIS database [11]. The ANRESIS programme collects all routine antibiotic resistance data from currently 22 clinical microbiology laboratories located in Switzerland. The ANRESIS laboratories are homogeneously distributed across the country. They include university laboratories, representing isolates mainly from tertiary-care hospitals, as well as cantonal and private laboratories, representing data from smaller hospitals and outpatient clinics. They send antimicrobial susceptibility test results (AST) of all routinely performed analyses, including isolates from none-sterile sites.

From 2004 to 2010, all participating laboratories interpreted their ASTs according to the Clinical Laboratory Standards Institute (CLSI) criteria in use at that time [12]. During 2011, five of the 11 laboratories included in this study changed their breakpoints according to the European Committee of Antimicrobial Susceptibility Testing (EUCAST) [13]. All institutions participated in at least one quality control programme from the United Kingdom National External Quality Assessment Service (UK NEQAS), and/or the National External Quality Program of the Institute of Medical Microbiology, Zurich [14]. AST results from each laboratory were sent on a regular basis, weekly or monthly, to the central database located at our institution (Institute for Infectious Diseases of the University of Bern).

For the present analysis, we used only data from the 11 laboratories sending data during the whole study period. These laboratories were representative for Switzerland. Moreover, hospitals performing fewer than 200 microbiological samples per year were excluded. Only clinical samples were analysed. When there were multiple isolates with an identical resistance pattern from the same patient and calendar year, only the first was included into the analysis. According to the hospital statistics of Switzerland for the year 2007 [16] and the statistics of Swiss physicians 2009 [17], the restricted data used for this analysis represent 30% of acute-care hospital beds in Switzerland and 11.2% of all Swiss family physicians. The number of BSIs was extrapolated using the 30% coverage of acute-care hospitals in this study.

Interpretation of the results

Resistant isolates were defined as those that were resistant or had intermediate susceptibility against the antibiotic tested. *E. coli* and *K. pneumoniae* isolates resistant to at least one 3GC and/or 4GC antibiotic were defined as ESC-R. The selection of 3GC and/or 4GC antibiotics tested differed between laboratories. If one antibiotic of an antibiotic class (e.g. quinolones or carbapenems) was resistant, the antibiotic class was classified as resistant. Results were stratified according to geographical region, in- versus outpatients (where outpatient was defined as a person attending a medical practice or outpatient clinic), age and sex of the patient, and whether the isolate was from UTI or BSI. For inpatients, nosocomial infection data (i.e. sample(s) positive for ESC-R isolates at least three days after hospitalisation) were analysed separately.

To examine seasonal trends, the period from April to September was defined as 'summer season', whereas that from October to March was defined as 'winter season'. To compare prevalence rates of ESC-R *E. coli* and confirmed ESBL-positive *E. coli*, we used data from our own institution for the years 2009 and 2010. In this case, detection of ESBL producers was performed by double-disk synergy test (i.e. ceftriaxone, ceftazidime, cefpodoxime discs combined with an amoxicillin-clavulanate disc, distance centre-to-centre 20 mm).

Statistical analysis

To calculate 95% confidence intervals (CIs) of proportions, we used the modified Wald method [18]. Proportions were compared using two-tailed chi-square test or Fisher's exact test using Epi info Version 3.4.3 (Centers for Disease Control and Prevention, Atlanta, United States). We analysed the time trends with linear regression using GraphPad Prism Version 5.04.

Results

The overall study included 160,010 *E. coli* and 21,290 *K. pneumoniae* isolates. ESBL confirmation was done for 225 ESC-R *E. coli* and 48 ESC-R K. pneumonia isolated during the years 2009 and 2010 at the University Hospital of Bern. Of these, 210 (93.3%) *E. coli* and 46 (95.8%) *K. pneumoniae* isolates were confirmed as ESBL producers by the double disc synergy test.

During the eight-year period, a total of 63,743 *E. coli* (39.8%) and 11,083 (52.1%) *K. pneumoniae* were isolated from hospitalised patients from 34 different hospitals, and 96,267 *E. coli* (60.2%) and 10,207 *K. pneumoniae* (47.9%) isolates were collected from outpatients. Of the outpatient samples, 45,395 (47.2%) of *E. coli* isolates and 4,746 (46.5%) of *K. pneumoniae* isolates were collected in outpatient clinics, the rest were collected by general physicians.

Escherichia coli

Between 2004 and 2011, the prevalence of ESC-R *E. coli* increased significantly from 1.0% to 5.8% ($p<0.001$).

Table

Number and proportion of *Escherichia coli* and *Klebsiella pneumoniae* isolates with extended-spectrum cephalosporin resistance, Switzerland, 2004 and 2011

	Escherichia coli			*Klebsiella pneumoniae*		
	2004	2011	P[a]	2004	2011	P[a]
	n/all (%)	n/all (%)		n/all (%)	n/all (%)	
Switzerland all	157/15,469 (1.0)	1,425/24,631 (5.8)	<0.001	23/2,070 (1.1)	153/3,490 (4.4)	0.002
In- outpatient	P[b]=0.027			P[b]=0.189		
Inpatients	81/7,012 (1.2)	582/8,846 (6.6)	<0.001	16/1,163 (1.4)	87/1,659 (5.2)	0.007
Outpatients	76/8,457 (0.9)	843/15,785 (5.3)	<0.001	7/907 (0.8)	66/1,831 (3.6)	<0.001
Hospital size	P[b]=0.457			P[b]=0.733		
<200 beds (n=4)	28/2,827 (1.0)	251/3,883 (6.5)	<0.001	5/389 (1.3)	30/657 (4.6)	0.030
200–500 beds (n=12)	27/2,730 (1.0)	202/3,310(6.1)	<0.001	6/464 (1.3)	37/645 (5.7)	0.020
>500 beds (n=18)	26/1,455 (1.8)	129/1,653 (7.8)	<0.001	5/310 (1.6)	20/357 (5.6)	0.005
Departments	P[b]=0.546			P[b]=0.451		
Intensive care unit	5/398 (1.3)	35/500 /7.0)	<0.001	1/134 (0.8)	10/190 (5.3)	0.261
Others	76/6,614 (1.2)	547/8,346 (6.6)	<0.001	15/1,029 (1.5)	77/1,469 (5.2)	0.006
Outpatients	P[b]=0.399			P[b]=0.117		
Outpatient clinics	33/3,743 (0.9)	360/7,255 (5.0)	<0.001	3/417 (0.7)	35/824 (4.3)	0.002
General physicians	43/4,714 (0.9)	483/8,530 (5.7)	<0.001	4/490 (0.8)	31/1,007 (3.1)	0.001
Regions[c]	P[b]=0.037			P[b]=0.417		
Eastern Switzerland	94/9,161 (1.0)	896/14,402 (6.2)	<0.001	18/1,364 (1.3)	89/2,237 (4.0)	0.004
South-western Switzerland	63/6,308 (1.0)	529/10,229 (5.2)	<0.001	5/706 (0.7)	64/1,253 (5.1)	0.007
Sample[d]	P[b]=0.942			p[b]=0.869		
Blood	12/795 (1.5)	68/1,095 (6.2)	<0.001	2/145 (1.4)	8/226 (3.5)	0.047
Urine	119/12,815 (0.9)	1,112/20,815 (5.3)	<0.001	10/1,386 (0.7)	104/2,523 (4.1)	<0.001
Respiratory	3/373 (0.8)	57/547 (10.4)	<0.001	2/307 (0.7)	18/449 (4.0)	0.33
Wounds	18/1,293 (1.4)	156/1,167 (13.4)	<0.001	6/355 (1.7)	22/308 (7.1)	0.09
Age group (years)	P[b]<0.001			P[b]=0.432		
<2	9/860 (1.0)	27/857 (3.2)	0.018	3/122 (2.5)	6/120 (5.0)	0.737
2–15	12/1,204 (1.0)	68/1,300 (5.2)	<0.001	2/62 (3.2)	4/75 (5.3)	0.660
15–45	26/4,054 (0.6)	223/5,909 (3.8)	<0.001	2/311 (0.6)	20/452 (4.4)	0.016
45–65	30/3,070 (1.0)	313/4,983 (6.3)	<0.001	6/453 (1.3)	68/1,454 (4.7)	0.017
>65	80/6,281 (1.3)	794/11,582 (6.9)	<0.001	10/1,122 (0.9)	55/1,389 (4.0)	0.002
Sex[e]	P[b]<0.001			P[b]=0.138		
Female	111/11,738 (1.0)	958/18,825 (5.1)	<0.001	14/1,305 (1.1)	75/2,238 (3.4)	0.010
Male	46/3,725 (1.2)	467/5,800 (8.1)	<0.001	9/764 (1.2)	78/1,252 (6.2)	<0.001

[a] Significance level indicating the probability that the slope of the linear regression using data of all years between 2004 and 2011 equals 0.

[b] Significance level indicating the probability that the slopes in the subgroups are equal by chance.

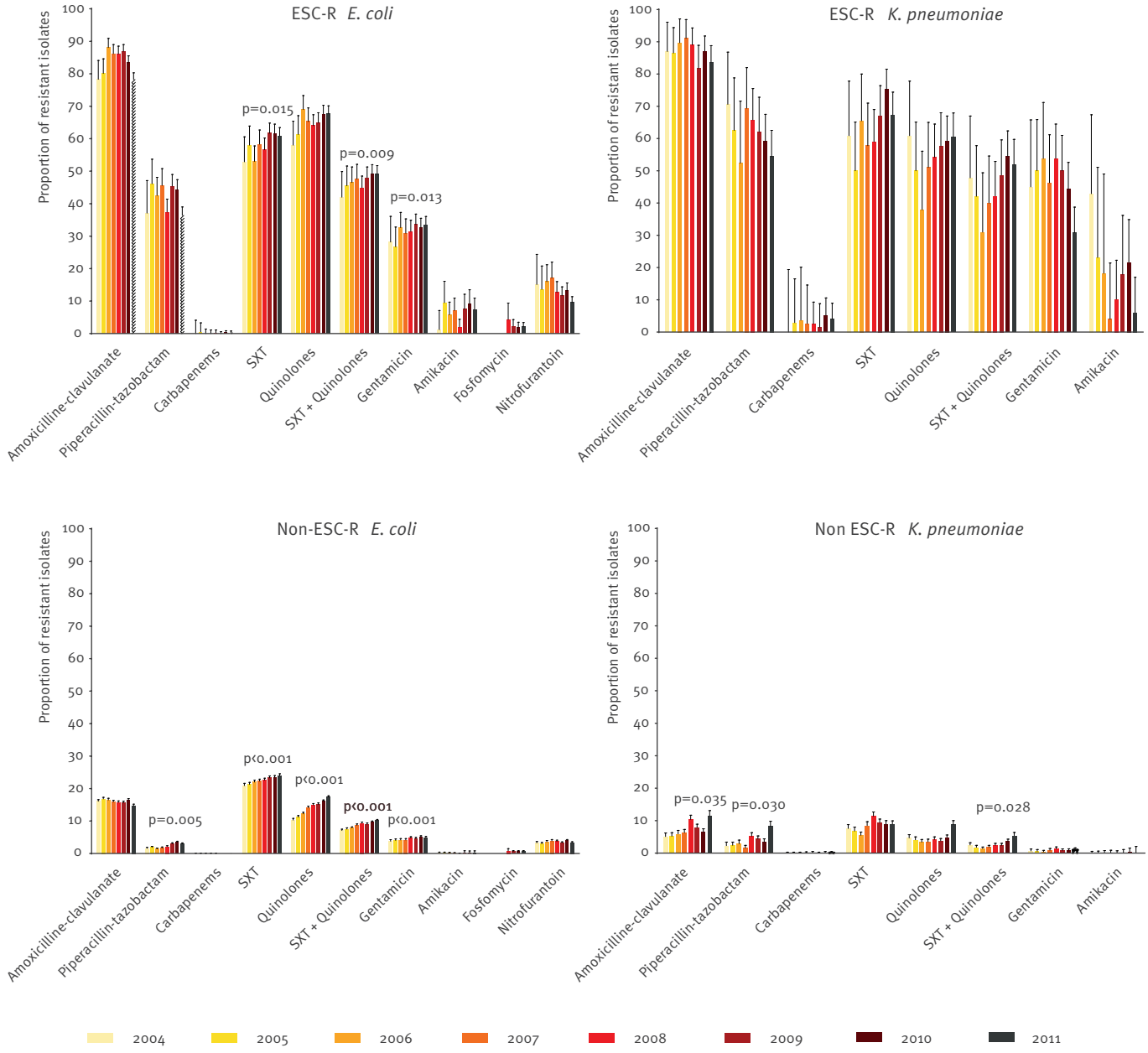
[c] South-western Switzerland includes the cantons Geneva, Vaud, Neuchâtel, Jura, Fribourg, Valais and Ticino; eastern Switzerland includes all other cantons.

[d] Other sample locations are not shown, therefore figures do no sum up to the total number.

[e] Sex was not specified for six *E. coli* isolates.

Figure 1

Co-resistance rates for ESC-R and non-ESC-R *Escherichia coli* and *Klebsiella pneumoniae* isolates, Switzerland, 2004–11

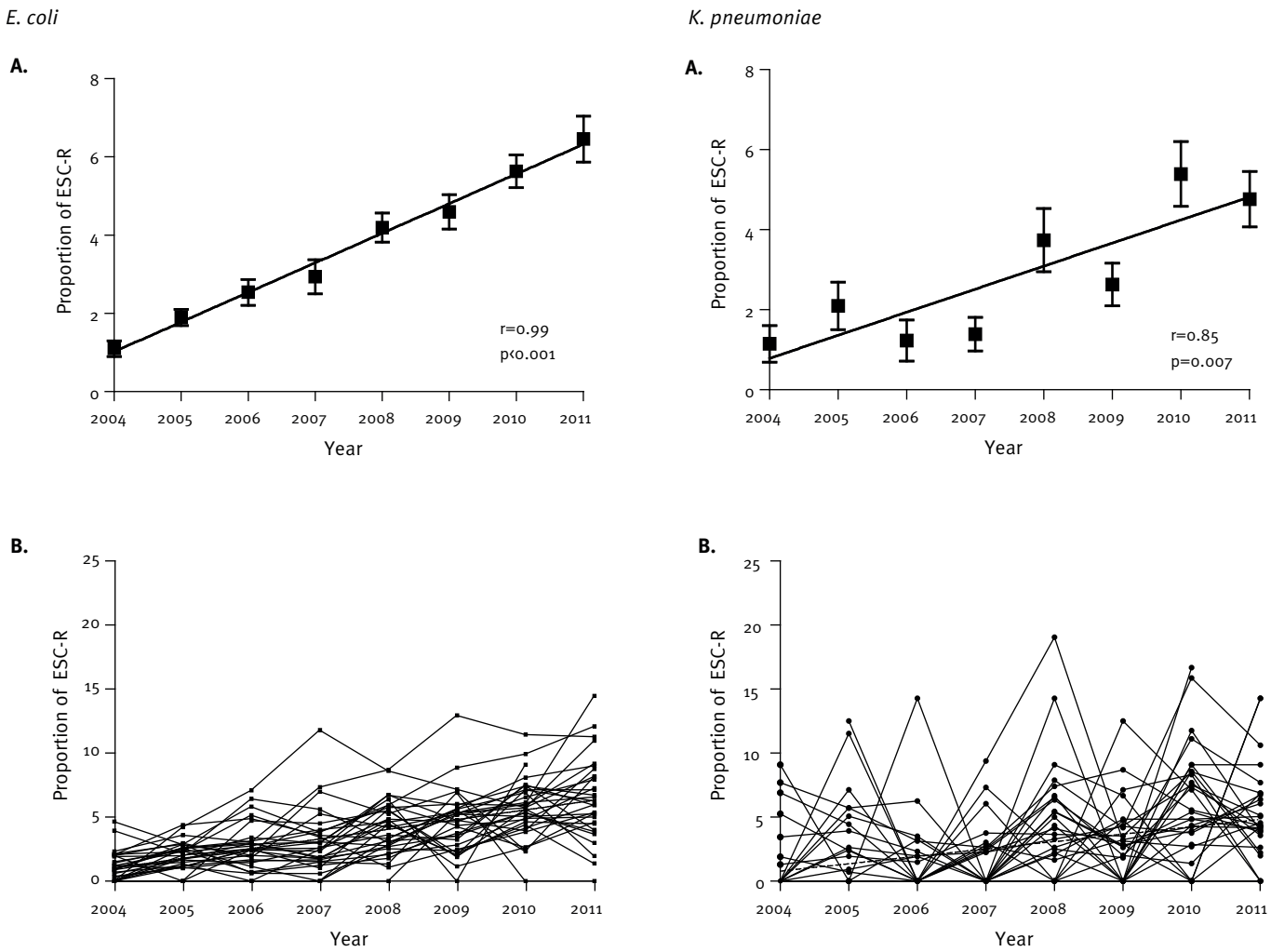


ESC-R: extended-spectrum cephalosporins-resistant; SXT: trimethoprim-sulfamethoxazole.

Resistance rates and 95% confidence intervals for different antibiotics for ESC-R and non-ESC-R *E. coli* and *K. pneumoniae* for the years 2004 to 2011. Fosfomycin and nitrofurantoin were not tested against *K. pneumoniae* isolates. Because of low numbers data are not shown for fosfomycin for the years 2004 to 2007. P values are given for significant trends only (p<0.05).

Figure 2

Increase in ESC-R rates in *Escherichia coli* and *Klebsiella pneumoniae* in 34 hospitals in Switzerland, 2004–11



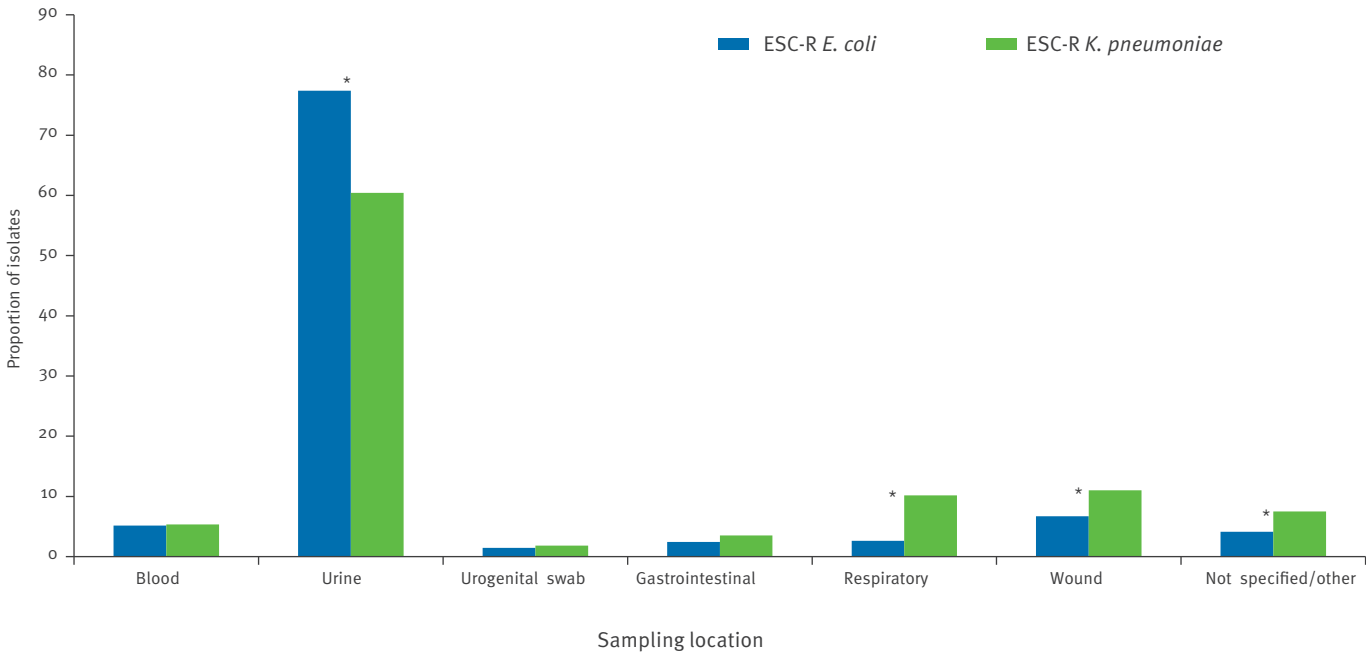
ESC-R: extended-spectrum cephalosporins-resistant; p: significance for correlation; r: Pearson's correlation index.

A. Means and standard error of the means of ESC-R prevalence rates in 34 Swiss hospitals from 2004 to 2011. The linear regression showed significant increase over time for *E. coli* and *K. pneumonia* ($p<0.001$ for both), correlation was linear for *E. coli* ($p<0.001$) and *K. pneumoniae* ($p=0.007$).

B. Rates of ESC-R isolates for individual hospitals. While the increase of ESC-R rates was steady and comparable in all hospitals for *E. coli*, we observed high variability between different years and hospitals for *K. pneumoniae*.

Figure 3

Distribution of ESC-R *Escherichia coli* and *Klebsiella pneumoniae* isolates, by sampling location, Switzerland, 2004-2011



ESC-R: extended-spectrum cephalosporins-resistant.

* p<0.001.

ESC-R *E. coli* as well as ESC-R *K. pneumoniae* were isolated mostly from urinary samples. ESC-R *K. pneumoniae* were isolated 2.2 times more frequently from respiratory or wound samples than ESC-R *E. coli* (p<0.001).

This time trend was linear and without seasonality (data not shown). This increase in rates of ESC-R isolates was observed in all patient groups analysed and was significantly more pronounced in inpatients (p=0.027), in eastern Switzerland (p=0.037), in male patients (p<0.001), and those older than 45 years (p<0.001) (Table). There was no difference between patients under 15 and those 15–45 years of age, or between the age groups 45–65 years and over 65 years, although there was a trend for lower resistance in children younger than two years compared with those 2–15 years-old (p=0.055). We noted a significant increase of ESC-R isolates (from 0.6% in 2004 to 3.5% in 2011; p<0.001) in female patients aged between 15 and 45 years. In inpatients, we did not record differences between those with a nosocomial infection and those without (p=0.15).

The absolute number of BSIs due to ESC-R *E. coli* increased from 12 in 2004 to 68 in 2011. Extrapolated to the overall Swiss population with 7.95 million inhabitants at the end of 2011 [19], we would expect that BSIs due to ESC-R *E. coli* increased from 40 (0.5/100,000 inhabitants) to 227 (2.9/100,000 inhabitants) episodes per year.

The co-resistance rates to other antibiotic classes are shown in Figure 1. Rates were significantly higher for ESC-R than non-ESC-R *E. coli* isolates. Co-resistance did not differ between in- and outpatients (data not shown). For the non-ESC-R *E. coli* isolates, rates increased significantly over time for sulfamethoxazole-trimethoprim (SXT; 20.9% in 2004 versus 24.0% in 2011, p<0.001), quinolones (10.3% in 2004 versus 17.4% in 2011, p<0.001), the combined resistance to SXT and quinolones (7.1% in 2004 versus 10.1% in 2011, p<0.001), piperacillin-tazobactam (1.6% in 2004 v versus. 3.0% in 2011, p=0.005), and gentamicin (3.8% in 2004 versus 4.9% in 2011, p<0.001). For the ESC-R *E. coli*, we observed an increase in co-resistance to gentamicin (28.2% in 2004 versus. 33.6% in 2011, p=0.013), SXT (52.9% in 2004 versus. 60.1% in 2011, p=0.015), and combined resistance to SXT and quinolones (42.0% in 2004 versus 49.1% in 2011, p=0.009), and a non-significant increasing resistance rate for quinolones alone (58.0% in 2004 versus 67.8% in 2010, p=0.06).

Klebsiella pneumoniae

Overall, from 2004 to 2011 ESC-R *K. pneumoniae* isolates increased significantly from 1.1% to 4.4% (p=0.002). The increase was comparable in all patient subgroups (Table) and significant and linear in inpatients (Table, Figure 2A). However, in contrast to ESC-R *E. coli*, the Pearson's correlation index was lower due to higher variability between different years in single hospitals (Figure 2B). Furthermore, ESC-R *K. pneumoniae* isolates were more frequently isolated from other sites than blood or urine than ESC-R *E. coli* (34.3% *K. pneumoniae* versus 17.4% *E. coli*, p<0.001). In particular, about two thirds of these non-blood, non-urine ESC-R *K. pneumoniae* were isolated from wounds or respiratory samples (Figure 3).

As shown in Figure 1, co-resistance in ESC-R *K. pneumoniae* exceeded 50% for all antibiotic classes tested except for aminoglycosides (gentamicin 30.8% and amikacin 6.0%) and carbapenems (4.1%) in 2011. These resistance rates were significantly higher in ESC-R than in non-ESC-R *K. pneumoniae* isolates. While there was no significant trend in co-resistance in ESC-R *K. pneumoniae*, we observed a significant increase in resistance in non-ESC-R *K. pneumoniae* for amoxicillin-clavulanate (5.1% in 2004 versus 11.5% in 2011, p=0.035), piperacillin-tazobactam (2.3% in 2004 versus 8.3% in 2011, p=0.030), and for double resistance to SXT and quinolones (2.5% in 2004 versus 5.3% in 2011, p=0.028).

Discussion

Increasing rates of ESC-R *Enterobacteriaceae* have been described worldwide, however most data rely on BSIs in inpatients [2,6,20]. Data on prevalence of ESC-R isolates among outpatients are rare and restricted to single years (e.g. France, 2006 [7]; Italy, 2003 [8]; Spain, 2006 [9]; Turkey, 2007 [10]). Only one of these studies compared rates of ESC-R *Enterobacteriaceae* among in- and outpatients [8], and data regarding temporal trends among outpatients are missing. Here, we present the temporal trends of ESC-R *E. coli* and *K. pneumoniae* among outpatients and compare the epidemiology of in- and outpatients from 2004 to 2011.

E. coli

According to EARSS data, rates of ESC-R *E. coli* isolated from BSIs increased from 2.7% in 2003 to 8.2% in 2009 [21]. Although such prevalence was lower in our population (1.5% in 2004 and 6.2% in 2011), the increasing trend was comparable with the above European data. We calculated an annual incidence of 2.9/100,000 cases of BSI due to ESC-R *E. coli* in 2011, which is in the same range as the average of 2.6/100,000 cases described in the 31 countries participating in EARSS in 2007 [21]. The societal and economic burden of infections due to ESC-R *E. coli* is remarkable. Taking into consideration the morbidity and mortality data available in the literature, we would estimate 58 additional deaths and 1,131 additional hospital days attributable to BSI due to ESC-R *E. coli* in 2011 in Switzerland [22]. Extrapolating to other clinical manifestations, such as lower respiratory tract infections, skin and soft tissue infections and UTIs, we would expect 838 infections leading to 131 deaths and 9,233 additional days of hospitalisation [23] in Switzerland during the year 2011.

Rates of ESC-R *E. coli* increased steadily in all patient subgroups analysed, but especially in patients older than 45 years, in male patients and inpatients. This observation probably reflects the higher prevalence of established risk factors for infections due to ESBL producers in these sub-populations, such as older age, diabetes mellitus, prostate disease, previous antibiotic use, indwelling catheters, recurrent UTIs, recent hospital admission and residence in long-term care facility [24-30].

Rates of ESC-R *E. coli* also increased significantly over time in lower risk populations, such as young women and outpatients. This correlates well with European studies demonstrating increasing faecal carriage rates of ESBL-producing *E. coli* in the outpatient setting [31-34]. In Switzerland, a recent study detected ESBL-producing *E. coli* in 5.8% of routine stool samples from staff members of meat-processing companies [35], whereas as many as 15.2% of pigs and 17.1% of cattle at slaughter carried ESBL-producing *E. coli*, indicating that there is an established reservoir of these organisms in farm animals in Switzerland [36].

Co-resistance in ESC-R *E. coli* is frequent and at least in part due to the fact that genes coding for the resistance to different antibiotics are located on the same plasmids [6]. In our study, roughly half of ESC-R *E. coli* were resistant to both SXT and quinolones. Resistance rates to these antibiotics increased over time, whereas resistance to nitrofurantoin and fosfomycin did not increase between 2004 and 2011, indicating that both antibiotics are still a valuable alternative for non-complicated UTIs [37]. For invasive infections, carbapenems are still a valuable option, but it is feared that spread of carbapenemase producers (e.g. KPC and NDM producers) will increase the incidence of MDR bacteria [38].

K. pneumoniae

K. pneumoniae is the second most frequent cause of Gram-negative BSIs after *E. coli* and often affects patients with impaired immune system such as patients with diabetes, alcohol problems and hospitalised patients with indwelling devices [5]. In our population, BSIs due to *K. pneumoniae* in 2011 were eight times less frequent than those due to *E. coli*.

As for *E. coli*, prevalence rates of ESC-R *K. pneumoniae* are increasing worldwide. Between 2007 and 2010 rates of ESC-R *K. pneumoniae* increased significantly in nine of 28 countries participating in EARSS, leading to very different rates (from below 1% in northern countries to greater than 50% in some south-eastern countries) [6]. Restricting our analysis to blood cultures, we

observed an increase in ESC-R isolates from 1.4% in 2004 to 3.5% in 2011 (p=0.05), which is comparable to the northern countries of Europe [5].

As for *E. coli*, rates of ESC-R *K. pneumoniae* increased in all patient subgroups but, in contrast to *E. coli*, there were no differences by age or sex. Resistance to other antibiotic classes was even higher than in *E. coli*. Indeed, ESC-R K. pneumonia resistance rates in 2011 were above 50% for all antibiotics tested except aminoglycosides and carbapenems. Carbapenemase resistance in ESC-R *K. pneumoniae* increased from 0% to 4.1%, which was not significant (p=0.11). However, in view of the global epidemiology, this finding probably anticipates a worrisome expansion of these life-threatening pathogens [39].

In contrast to *E. coli*, infections with ESC-R *K. pneumoniae* are still mainly hospital-associated [40], with outbreaks more frequently reported for ESC-R K. pneumonia than for ESC-R *E. coli* [41,42]. This is supported by our analysis demonstrating that the increase of infections due to ESC-R *K. pneumoniae* was more pronounced in inpatients, which is mainly due to the accumulation of multiple small outbreaks in single hospitals (see Figure 2b). Several reasons for the higher frequency of outbreaks in *K. pneumoniae* have been postulated: (i) environmental contamination occurs significantly more often when the patient is carrying ESBL-producing *K. pneumoniae* compared with ESBL-producing *E. coli* [41]; (ii) *K. pneumoniae* has a higher ability to persist in the environment due to the formation of biofilms [43]; (iii) some antiseptics (e.g. chlorhexidine or hexamidine) are less effective against *K. pneumoniae* [44]. In addition, our data demonstrate that ESC-R *K. pneumoniae* were more frequently isolated from wounds or the respiratory tract, which may facilitate transmission, when standard hygiene precautions are not implemented.

Our study has several limitations. Because physicians frequently implement an empirical treatment for UTIs and provide a urine sample only if the infection does not improve, our analysis may overestimate the real incidence of ESC-R [45]. In addition, it is important to note that our study describes the epidemiology of ESC resistance, which includes ESBL, pAmpCs and cAmpCs. However, our data are consistent with those of the European Center for Disease Prevention and Control (ECDC), which also use ESC-R as a surrogate for ESBL production, demonstrating that 65 to 100% of ESC-R *E. coli* in Europe are ESBL producers [5]. We were not able to perform genetic analysis to confirm the presence of ESBL genes in our collection of isolates. Performing phenotypic ESBL confirmation tests in a subset of our samples, we speculate that about 93 to 96% of ESC-R isolates in Switzerland are true ESBL producers. However, the clinical impact of confirming ESBL production is debated, and newer guidelines even abstain from confirmatory tests and at least for clinical decisions completely rely on phenotypic resistance testing results [46,47].

In conclusion, we demonstrate a significant increase of ESC-R *E. coli* and *K. pneumoniae* isolates in the period from 2004 to 2011 in Switzerland. This increase is comparable to other European countries. Our data allowed us to demonstrate an increase in ESC-R in non-invasive and in outpatient samples and to estimate the burden of disease in Switzerland. National surveillance should be implemented and maintained to monitor the spread of life-threatening MDR pathogens and support physicians in the implementation of correct and efficacious antibiotic treatments in community and hospital settings.

Acknowledgements

For development and support of the ANRESIS database we obtained financial support from the Swiss National Science Foundation, the Swiss Federal Office of Public Health, the Swiss Conference of the Cantonal Ministers of Public Health and the University of Bern. We thank all ANRESIS laboratories for providing their resistance data. This manuscript is dedicated to Kathrin Mühlemann who was very engaged in building up ANRESIS, but unfortunately died before completion of this manuscript.

Conflict of interest

None declared.

References

1. Reinert RR, Low DE, Rossi F, Zhang X, Wattal C, Dowzicky MJ. Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline. J Antimicrob Chemother. 2007;60(5):1018-29. http://dx.doi.org/10.1093/jac/dkm310 PMid:17855724
2. Pitout JD. Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. Drugs. 2010;70(3):313-33. http://dx.doi.org/10.2165/11533040-000000000-00000 PMid:20166768
3. Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clin Infect Dis. 2006;42(5):657-68. http://dx.doi.org/10.1086/499819 PMid:16447111
4. Bertrand X, Dowzicky MJ. Antimicrobial susceptibility among gram-negative isolates collected from intensive care units in North America, Europe, the Asia-Pacific Rim, Latin America, the Middle East, and Africa between 2004 and 2009 as part of the Tigecycline Evaluation and Surveillance Trial. Clin Ther. 2012;34(1):124-37. http://dx.doi.org/10.1016/j.clinthera.2011.11.023 PMid:22154196
5. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2010. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/1111_SUR_AMR_data.pdf.pdf
6. Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. Euro Surveill. 2008;13(47):pii=19044. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19044
7. Arpin C, Quentin C, Grobost F, Cambau E, Robert J, Dubois V, et al. Nationwide survey of extended-spectrum {beta}-lactamase-producing Enterobacteriaceae in the French community setting. J Antimicrob Chemother. 2009;63(6):1205-14. http://dx.doi.org/10.1093/jac/dkp108 PMid:19329798
8. Luzzaro F, Mezzatesta M, Mugnaioli C, Perilli M, Stefani S, Amicosante G, et al. Trends in production of extended-spectrum beta-lactamases among enterobacteria of medical interest: report of the second Italian nationwide survey. J Clin Microbiol. 2006;44(5):1659-64. http://dx.doi.org/10.1128/JCM.44.5.1659-1664.2006 PMid:16672390 PMCid:1479207
9. Andreu A, Planells I. Etiology of community-acquired lower urinary infections and antimicrobial resistance of Escherichia coli: a national surveillance study. Med Clin (Barc). 2008;130(13):481-6. Spanish. http://dx.doi.org/10.1157/13119488
10. Yilmaz N, Agus N, Yurtsever SG, Pullukcu H, Gulay Z, Coskuner A, et al. Prevalence and antimicrobial susceptibility of Escherichia coli in outpatient urinary isolates in Izmir, Turkey. Med Sci Monit. 2009;15(11):PI61-5. PMid:19865064
11. Anresis.ch. Swiss Centre for Antibiotic Resistance. Bern: Institut für Infektionskrankheiten Universität Bern. [Accessed: 22 Oct 2012]. Available from: http://www.anresis.ch/en/index.html
12. Clinical and Laboratory Standards Institute (CLSI). Wayne: CLSI. [Accessed: 22 Oct 2012]. Available from: http://www.clsi.org
13. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, valid from 2012-01-01. Växjö: EUCAST. [Accessed: 22 Oct 2012]. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_2.0_120221.pdf
14. Institut für medizinische Mikrobiologie. Externe Qualitätskontrolle. Zurich: University of Zurich. [Accessed: 22 Oct 2012]. German. Available from: http://www.imm.uzh.ch/services/qc.html
15. Kronenberg A, Mühlemann K. Temporal trends of Enterobacteriaceae with resistance to higher generation cephalosporins in Switzerland, 2004 to 2010. Poster at 21th ECCMID: 7–10 May 2011; Milano, Italy. Available from: http://www.eccmidabstracts.com/abstract.asp?id=91888
16. Bundesamt für Gesundheit (BAG), [Federal Office of Public Health]. Spitalstatistiken. [Hospital statistics]. Bern: BAG. [Accessed: 22 Oct 2012]. German. Available from: http://www.bag.admin.ch/hospital/index.html?lang=de
17. Verbindung der Schweizer Ärztinnen und Ärzte (FMH). [Swiss Medical Association]. Aerztestatistik [Doctors statisitcs]. Bern: FMH. [Accessed: 22 Oct 2012]. German. Available from: http://www.fmh.ch/themen/aerztedemographie/aerztestatistik.html
18. Agresti A, Coull BA. Approximate is better than "Exact" for interval estimation of binomial proportions. The American Statistician. 1998;52(2):119-26. http://dx.doi.org/10.1080/00031305.1998.10480550 http://dx.doi.org/10.2307/2685469
19. Bundesamt für Statistik (BFS). [Swiss Federal Statistical Office]. Bevölkerung. [Population]. Neuchâtel: BFS. [Accessed: 22 Oct 2012]. Available from: http://www.bfs.admin.ch/bfs/portal/de/index/themen/01.html
20. Oteo J, Perez-Vazquez M, Campos J. Extended-spectrum [beta]-lactamase producing Escherichia coli: changing epidemiology and clinical impact. Curr Opin Infect Dis. 2010:23(4):320-6. http://dx.doi.org/10.1097/QCO.0b013e3283398dc1 PMid:20614578
21. de Kraker ME, Davey PG, Grundmann H. Mortality and Hospital Stay Associated with Resistant Staphylococcus aureus and Escherichia coli Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe. PLoS Med. 2011;8(10):e1001104. http://dx.doi.org/10.1371/journal.pmed.1001104 PMid:22022233 PMCid:3191157
22. de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. J Antimicrob Chemother. 2011:66(2):398-407. http://dx.doi.org/10.1093/jac/dkq412 PMid:21106563
23. European Centre for Disease Prevention and Control (ECDC)/European Medicines Agency (EMA). The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. Joint technical report. Stockholm: ECDC; 2009. EMEA doc. ref. EMEA/576176/2009. Available from: http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf
24. Siedelman L, Kline S, Duval S. Risk factors for community- and health facility-acquired extended-spectrum beta-lactamase-producing bacterial infections in patients at the University of Minnesota Medical Center, Fairview. Am J Infect Control. 2012;40(9):849-53. http://dx.doi.org/10.1016/j.ajic.2011.10.019 PMid:22325481
25. Rodriguez-Bano J, Alcala JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Arch Intern Med. 2008;168(17):1897-902. http://dx.doi.org/10.1001/archinte.168.17.1897 PMid:18809817
26. Pitout JD, Hanson ND, Church DL, Laupland KB. Population-based laboratory surveillance for Escherichia coli-producing extended-spectrum beta-lactamases: importance of community isolates with blaCTX-M genes. Clin Infect Dis. 2004;38(12):1736-41. http://dx.doi.org/10.1086/421094 PMid:15227620
27. Colodner R, Rock W, Chazan B, Keller N, Guy N, Sakran W, et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. Eur J Clin Microbiol Infect Dis. 2004;23(3):163-7. http://dx.doi.org/10.1007/s10096-003-1084-2 PMid:14986159
28. Rodriguez-Bano J, Navarro MD, Romero L, Martinez-Martinez L, Muniain MA, Perea EJ, et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in nonhospitalized patients. J Clin Microbiol. 2004;42(3):1089-94. http://dx.doi.org/10.1128/JCM.42.3.1089-1094.2004 PMid:15004058 PMCid:356843
29. Ben-Ami R, Rodriguez-Bano J, Arslan H, Pitout JD, Quentin C,Calbo ES, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. Clin Infect Dis. 2009;49(5):682-90. http://dx.doi.org/10.1086/604713 PMid:19622043
30. Azap OK, Arslan H, Serefhanoglu K, Colakoglu S, Erdogan H, Timurkaynak F, et al. Risk factors for extended-spectrum beta-lactamase positivity in uropathogenic Escherichia coli isolated from community-acquired urinary tract infections. Clin Microbiol Infect. 2010;16(2):147-51 http://dx.doi.org/10.1111/j.1469-0691.2009.02941.x PMid:19689464
31. Valverde A, Coque TM, Sanchez-Moreno MP, Rollan A, Baquero F, Canton R. Dramatic increase in prevalence of fecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae during nonoutbreak situations in Spain. J Clin Microbiol. 2004;42(10):4769-75. http://dx.doi.org/10.1128/JCM.42.10.4769-4775.2004 PMid:15472339 PMCid:522353
32. Paniagua R, Valverde A, Coque TM, Baquero F, Canton R. Assessment of prevalence and changing epidemiology of extended-spectrum beta-lactamase-producing Enterobacteriaceae fecal carriers using a chromogenic medium. Diagn Microbiol Infect Dis. 2010;67(4):376-9. http://dx.doi.org/10.1016/j.diagmicrobio.2010.03.012 PMid:20638607

33. Stromdahl H, Tham J, Melander E, Walder M, Edquist PJ, Odenholt I. Prevalence of faecal ESBL carriage in the community and in a hospital setting in a county of Southern Sweden. Eur J Clin Microbiol Infect Dis. 2011 ;30(10):1159-62. http://dx.doi.org/10.1007/s10096-011-1202-5 PMid:21399889

34. Janvier F, Merens A, Delaune D, Soler C, Cavallo JD. Fecal carriage of third-generation cephalosporins-resistant Enterobacteriaceae in asymptomatic young adults: evolution between 1999 and 2009. Pathol Biol (Paris). 2011;59(2):97-101. http://dx.doi.org/10.1016/j.patbio.2010.07.012 PMid:20828938

35. Geser N, Stephan R, Korczak BM, Beutin L, Hachler H. Molecular Identification of Extended-Spectrum-beta-Lactamase Genes from Enterobacteriaceae Isolated from Healthy Human Carriers in Switzerland. Antimicrob Agents Chemother. 2012;56(3):1609-12. http://dx.doi.org/10.1128/AAC.05539-11 PMid:22155836 PMCid:3294945

36. Geser N, Stephan R, Kuhnert P, Zbinden R, Kaeppeli U, Cernela N, et al. Fecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in swine and cattle at slaughter in Switzerland. J Food Prot. 2011;74(3):446-9. http://dx.doi.org/10.4315/0362-028X.JFP-10-372 PMid:21375882

37. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103-20. http://dx.doi.org/10.1093/cid/ciq257 http://dx.doi.org/10.1093/cid/cir102 PMid:21292654

38. Poirel L, Schrenzel J, Cherkaoui A, Bernabeu S, Renzi G, Nordmann P. Molecular analysis of NDM-1-producing enterobacterial isolates from Geneva, Switzerland. J Antimicrob Chemother. 2011;66(8):1730-3. http://dx.doi.org/10.1093/jac/dkr174 PMid:21628303

39. Cantón R, Akóva M, Carmeli Y, Giske CG, Glupczynski Y, Gniadkowski M, et al. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect. 2012;18(5):413-31. http://dx.doi.org/10.1111/j.1469-0691.2012.03821.x PMid:22507109

40. Pitout, JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis. 2008;8(3):159-66. http://dx.doi.org/10.1016/S1473-3099(08)70041-0

41. Guet-Revillet H, Le Monnier A, Breton N, Descamps P, Lecuyer H, Alaabouche I, et al. Environmental contamination with extended-spectrum beta-lactamases: Is there any difference between Escherichia coli and Klebsiella spp? Am J Infect Control. 2012;40(9):845-8. http://dx.doi.org/10.1016/j.ajic.2011.10.007 PMid:22325483

42. Hilty M, Betsch B, Bögli-Stuber K, Heiniger N, Stadler M, Küffer M, et al. Transmission dynamics of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae in the tertiary care hospital and the household setting. Clin Infect Dis. 2012;55(7):967-75. http://dx.doi.org/10.1093/cid/cis581 PMid:22718774 PMCid:3436924

43. Jones K, Bradshaw SB. Biofilm formation by the enterobacteriaceae: a comparison between Salmonella enteritidis, Escherichia coli and a nitrogen-fixing strain of Klebsiella pneumoniae. J Appl Bacteriol. 1996;80(4):458-64. http://dx.doi.org/10.1111/j.1365-2672.1996.tb03243.x

44. Grare M, Dibama HM, Lafosse S, Ribon A, Mourer M, Regnouf-de-Vains JB, et al. Cationic compounds with activity against multidrug-resistant bacteria: interest of a new compound compared with two older antiseptics, hexamidine and chlorhexidine. Clin Microbiol Infect. 2010;16(5):432-8. http://dx.doi.org/10.1111/j.1469-0691.2009.02837.x PMid:19456831

45. Kronenberg A, Koenig S, Droz S, Muhlemann, K. Active surveillance of antibiotic resistance prevalence in urinary tract and skin infections in the outpatient setting. Clin Microbiol Infect. 2011;17(12):1845-51. http://dx.doi.org/10.1111/j.1469-0691.2011.03519.x PMid:21880098

46. Leclercq R, Canton R, Brown DF, Giske CG, Heisig P, Macgowan AP, et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect. 2013;19(2):141-60. http://dx.doi.org/10.1111/j.1469-0691.2011.03703.x PMid:22117544

47. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement. CLSI document M100-S20. Wayne: SLCI; 2010.