7 Resistance in bacteria from human clinical isolates

7.1 *Escherichia coli*

Escherichia coli is the most frequent Gram-negative microorganism causing bacteremia and the most frequent pathogen in humans. It is a colonizer of the intestinal tract and as such the most frequent microorganism causing urinary tract infections. As urinary tract infections are (after respiratory tract infections) the second most frequent infectious disease in ambulatory care, increasing resistance trends directly affect the hospital as well as the ambulatory settings.

In 2021, resistance was still very low for fosfomycin and nitrofurantoin, the first-line antibiotics recommended for the therapy of cystitis (Table 7. a). However, resistance to fosfomycin increased slightly but significantly from 0.2% in 2012 to 1.5% in 2021 (Figure 7. b). Trimethoprim-sulfamethoxazole still remains a first-line option in lower urinary tract infections [https://ssi.guidelines.ch/]. Its resistance rate decreased significantly from 29% in 2012 to 25.4 % in 2021. Because *E. coli* is one of the most important pathogens in the outpatient setting as well, resistance rates of outpatient urinary samples are compared with invasive samples (Figure 7. a). These data not only demonstrate significantly lower resistance rates in urinary samples for trimethoprim-sulfamethoxazole (19.5% in 2021), but for most of the antibiotics tested. Since resistance testing is usually not performed for uncomplicated lower urinary tract infections, ANRESIS data still overestimate the resistance rates. In a recent study by A. Plate *et al.*, susceptibility rates to trimethoprim-sulfamethoxazole in uncomplicated lower urinary tract infections were 85.7% [1].

Fluoroquinolones should not be used as first-line treatment for lower urinary tract infections, in particular, to preserve their efficacy for invasive infections. Fluoroquinolone resistance has steadily increased from 10.3% in 2004 to 19.4% in 2015 but has since then slightly decreased to 16.6% in 2021. Although this observation could at least partly be explained by the integration of resistance data from newer, smaller laboratories within ANRESIS (which tend to have

Table 7. a: Resistance rates of invasive *Escherichia coli* isolates in humans in 2021.

***Escherichia coli* (invasive)**											**2021**
	West		**North–East**		**South**		**Total**			**Trend**	
Antimicrobial	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**95% CI**	**4y**	**10y**
Aminopenicillins	1,098	52.1	4,075	45.3	487	43.7	5,660	46.4	45.7–47.1	↓	↓
Amoxicillin-clavulanic acid	1,091	33.5	4,423	24.8	487	21.4	6,001	26.1	25.5–26.7	↑	↑
Piperacillin-tazobactam	1,247	9.1	4,261	6.6	487	3.3	5,995	6.9	6.6–7.2	↑	↑
Cephalosporin 2nd gen.	560	16.2	3,320	11.9	419	10.5	4,299	12.4	11.9–12.9	↓	↑
Cephalosporin 3rd/4th gen.	1,305	13.4	4,458	9.6	487	8.2	6,250	10.3	9.9–10.7	–	↑
Carbapenems[1]	1,217	0	4,330	0.1	487	0	6,034	0	0.0–0.0	–	–
Aminoglycosides	1,129	13.1	4,314	8.3	487	7.2	5,930	9.1	8.7–9.5	–	↑
Trimethoprim-sulfamethoxazole	1,303	28.5	4,095	25.1	487	19.9	5,885	25.4	24.8–26.0	↓	↓
Fluoroquinolones[2]	1,302	21	4,448	15.6	486	13.8	6,236	16.6	16.1–17.1	↓	↓
Nitrofurantoin	474	0.8	911	0.4	1	0	1,386	0.6	0.4–0.8	↓	↓
Fosfomycin	479	2.5	1,539	1.2	1	0	2,019	1.5	1.2–1.8	–	↑

[1] Carbapenems: imipenem, meropenem

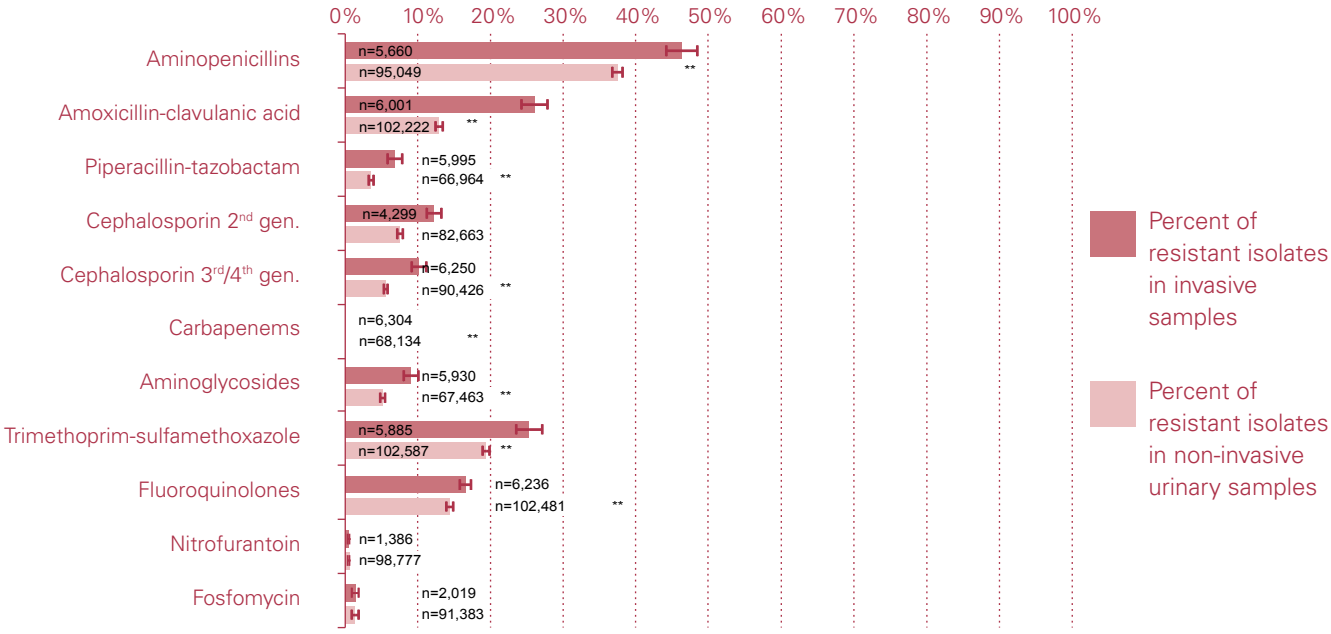
[2] Fluoroquinolones: ciprofloxacin, norfloxacin, ofloxacin

West (GE, NE, VD, JU, FR), South (TI), North–East (other cantons) according to linguistic regions. 95% confidence intervals (CI) were calculated by the Wilson score method, calculations of trends were performed by logistic regression. Trends were modeled with logistic regressions. Arrows represent a significant effect ($p < 0.05$) of the year on the corresponding outcome (increase, decrease).

lower resistance rates), this trend seems to be real, as in EU/EEA states a similar slight, but significant decrease from 26.4% in 2016 to 23.8% in 2020 has been observed [2].

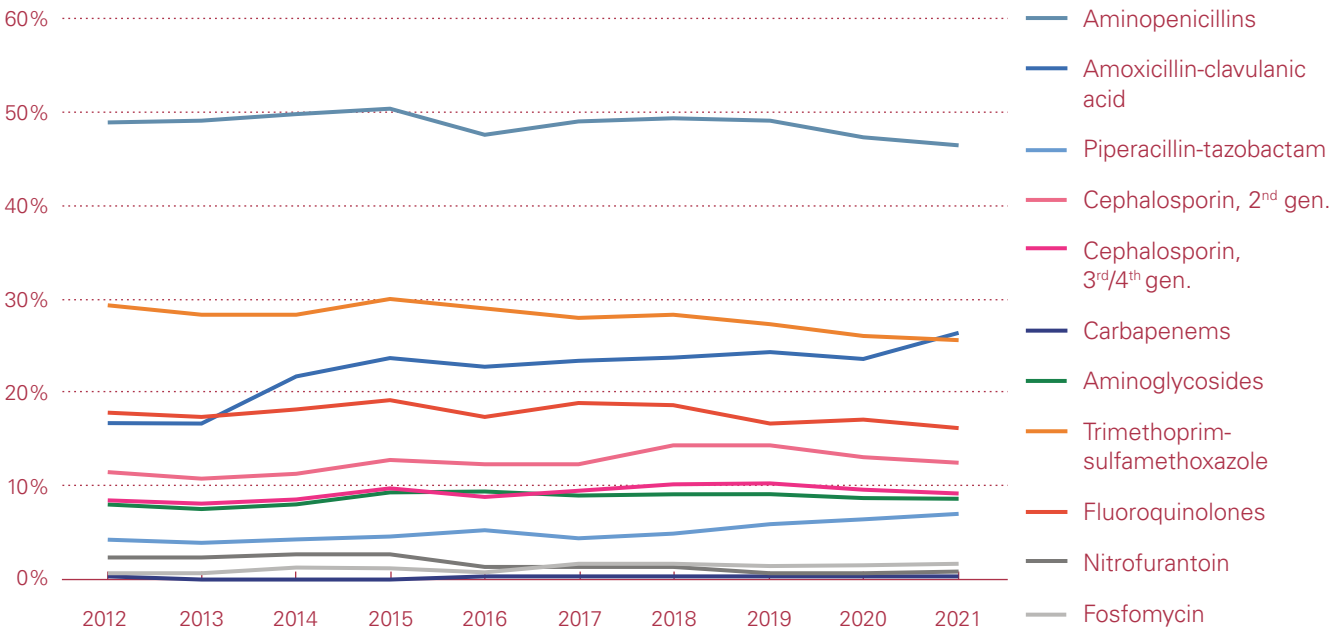
As for quinolones, resistance rates to third-/fourth-generation cephalosporins have steadily increased from 0.9% in 2004 to 11% in 2018, and have stabilized since then (10.3% in 2021). A slight but significant decrease from 15.7% to 14.9% was observed between 2016 and 2020 in EU/EEA states [2]. However, large differences between countries located in Europe and nearby geographical areas were observed, i. e., only 10 out of 40 countries (including Switzerland) reported resistance rates for third-/fourth-generation cephalosporins below 10% in 2020, whereas rates above 50% were observed in 5 eastern countries (Belarus, North Macedonia, Russian Federation, Turkey, Ukraine) [2].

Figure 7. a: Comparison of resistance rates in invasive versus outpatient urinary samples in *Escherichia coli* isolates in humans for 2021.



n = number of isolates tested with error bars indicating 95% confidence intervals. Fisher Exact Tests were performed to assess for independence:
* = p-value <0.05; ** = p-value <0.01.

Figure 7. b: Resistance rates in invasive *Escherichia coli* isolates in humans between 2012 and 2021.



Significant increases in resistances to aminoglycosides from 7.9% to 9.1%, to amoxicillin-clavulanic acid from 16.6% to 26.1% and to piperacillin-tazobactam from 4.1% (and even 1% in 2004) to 6.9% were observed during the last ten years in Switzerland. For all antibiotics tested (except carbapenems), resistance rates were highest in the western part of Switzerland, and lowest in Ticino (Table 7 a.). Multiresistance was frequent. However, no clear trend for *E. coli* isolates resistant to two to five antibiotic groups was observed during the last ten years (Table 7. b, Figure 7. c).

Carbapenem-resistance in *E. coli* is still very rare (less than 0.1%) and comparable to the EU/EEA population weighted means (0.2% in 2020) [2]. While there was no significant trend in Switzerland, a slight but significant increase from 0.1% to 0.2% between 2016 and 2020 was observed in EU/EEA states, and increasing rates of carbapenemase-producing Enterobacterales (CPE) around the world are alarming. In order to survey these trends more accurately, knowledge regarding the genetic mechanisms is indispensable. The Federal Office of Public Health therefore introduced an obligation to report CPE in January 2016, and since 2019 all strains are collected by the National Reference Centre for Emerging Antibiotic Resistance in Fribourg (NARA, www.nara-antibiotic-resistance.ch). A detailed analysis of Swiss CPE data from 2013 to 2018 has been published in Eurosurveillance [3], and updated data are displayed regularly on the ANRESIS homepage.

In future, colistin, a rather toxic reserve antibiotic belonging to the polymyxin group, might become more important as a "last resort antibiotic" for the treatment of infections due to carbapenemase producers. Currently, colistin resistance is rare in Switzerland, but reports from China, describing a mobile plasmid encoding a colistin resistance gene (mcr types), are worrisome [4]. Some small surveys performed in Switzerland showed very rare spread of mcr producers among human isolates [5/6]. So far, colistin resistance is not systematically tested in Switzerland, although testing algorithms and adequate testing methods have been published by the NARA.

Table 7. b: Resistance combinations in invasive *E. coli* isolates in humans 2021. Only isolates tested against all five antibiotic groups (aminopenicillins, third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones) were considered (n = 5098/6226 [81.9%]).

Resistance patterns	Number of isolates	% of total
Fully susceptible	**2,550**	**49.6%**
Resistance to one antimicrobial group	**1,592**	**31.0%**
Fluroquinolones	144	2.8%
Third-generation cephalosporins	4	0.1%
Aminopenicillins	1,423	27.7%
Aminoglycoside	21	0.4%
Resistance to two antimicrobial groups	**528**	**10.3%**
Aminopenicillins + fluoroquinolones	235	4.6%
Aminopenicillins + third-generation cephalosporins	141	2.7%
Aminoglycoside + fluoroquinolones	15	0.3%
Aminopenicillins + aminoglycosides	137	2.7%
Resistance to three antimicrobial groups	**304**	**5.9%**
Aminopenicillins + third-generation cephalosporins + fluoroquinolones	215	4.2%
Aminopenicillins + third-generation cephalosporins + carbapenems	1	0.0%
Aminoglycoside + fluoroquinolon + third-generation cephalosporins	1	0.0%
Aminopenicillins + fluoroquinolones + aminoglycosides	87	1.7%
Aminopenicillins + third-generation cephalosporins + aminoglycosides	41	0.8%
Resistance to four antimicrobial groups	**123**	**2.4%**
Aminopenicillins + third-generation cephalosporins + aminoglycosides + fluoroquinolones	123	2.4%
Resistance to all five antimicrobial groups	**1**	**0.0%**
Aminopenicillins + third-generation cephalosporins + aminoglycosides + fluoroquinolones + carbapenems	1	0.0%

Figure 7. c: Multiresistance in invasive *E. coli* isolates in humans between 2012 and 2021 (for details refer to Table 7. b).