

## ORIGINAL ARTICLE

# EFFECTS OF FLUOROQUINOLONE RESTRICTION IN THE HOSPITAL ON THE DEVELOPMENT OF SENSITIVITY OF SELECTED BACTERIAL PATHOGENS

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### Summary

**Introduction:** Fluoroquinolones are a frequently prescribed class of antibiotics, which has been blacklisted in recent years because of a growing evidence of the connection with serious undesirable effects, infections *Clostridioides difficile*, and a connection with the occurrence of multiresistant strains.

**Methods:** In the University Hospital Hradec Kralove in the course of the years 2009-2019, several antibiotic stewardship restrictive and educational interventions were performed by the Antibiotic Centre aiming to decrease quinolone antibiotics administration. The data of the consumption of quinolone antibiotics were retrospectively evaluated and correlated with the development of sensitivity and occurrence of multiresistance of selected bacteria in the hospital.

**Results:** In the period under investigation, consumption of fluoroquinolone antibiotics significantly decreased ( $p < 0.001$ ) in 10 years by 71.8% to 26.7 DDD/1000 patient day. Sensitivity of *Escherichia coli* and *Pseudomonas aeruginosa* to fluoroquinolones in the period under investigation increased by 4.8% (respectively by 15%); on the other hand, sensitivity of *Staphylococcus aureus* decreased by 4.2% to 85.5% share of sensitive strains. The incidence of the multiresistant isolates *Pseudomonas aeruginosa* decreased by 8.1%, but the occurrence of ESBL-producing *Klebsiella pneumoniae* was increased in the period under investigation. The occurrence of methicillin-resistant *Staphylococcus aureus* did not show a stable trend and finally it was moderately increased by 2.9%.

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**Conclusion:** Implementation of programmes of antimicrobial stewardship for hospitalized patients resulted in a decrease and a rationalization of fluoroquinolone administration. The reduction of their consumption in our hospital resulted in a statistically insignificant increase in the sensitivity of *Escherichia coli* and *Pseudomonas aeruginosa*, but not *Staphylococcus aureus*.

*Key words:* antibiotic consumption; antimicrobial stewardship; bacterial pathogen; fluoroquinolone; sensitivity

## Abbreviations

ABS antimicrobial stewardship  
ATC anatomic-therapeutic-chemical drug classification  
CFU colony forming unit  
DDD defined daily dose  
ESBL extended spectrum beta lactamase  
EUCAST The European Committee on Antimicrobial Susceptibility Testing  
FDA Food and Drug Administration  
MSSA methicillin sensitive *Staphylococcus aureus*  
MRSA methicillin resistant *Staphylococcus aureus*  
PD patient day

## Introduction

Fluoroquinolone antibiotics have been used for more than 30 years. They are highly effective with many advantages of their pharmacokinetics and pharmacodynamics: a wide spectrum of effect, high biological availability after oral administration, large distribution volume, very good penetration into the tissues (Grayson *et al.* 2010). Their effect aims both against gram-negative and some gram-positive bacteria. Though in infections they are not the drugs of first choice, they are well tolerated by patients, very popular with physicians, and widely employed throughout the world (Morales *et al.* 2018, Vaughn *et al.* 2019).

Their increased consumption has also made clear their disadvantages and risks: increased resistance of bacteria to fluoroquinolones as well confirmation of their contribution to the development and selection of multiresistant strains in hospitals and community (Pitiriga *et al.* 2017, Urbanek *et al.* 2005). The serious consequences of fluoroquinolone therapy have also included the danger of development of infections caused by *Clostridioides difficile* (Gaynes *et al.* 2004, Sarma *et al.* 2015 I, Dingle *et al.* 2017). Other serious undesirable effects in patients were first drawn attention to by the American psychiatrist Jay Cohen, and FDA in the year 2015 recommended their manufacturers to include these fluoroquinolone-associated disability (FAD) into drug information sheets. In the year 2016, it recommended to limit the use of fluoroquinolones due to potentially permanent undesirable effects on the tendons, muscles, nerves, and the central nervous system. In 2018, The European Medicines Agency terminated their reassessment and recommended to limit their use (EMA 2018).

In order to minimize all side undesirable effects of their use and because of their often useless administration, fluoroquinolones have become a target for interventions of antimicrobial stewardship programmes (ABS). They aim to limit the use of fluoroquinolones to the minimum, i.e. only to infections in which the benefit exceeds the risks of their use. The theoretical resultant effect of fluoroquinolone restriction should be decreased occurrence of infections caused by *Clostridioides difficile*, increased sensitivity of bacterial strains to fluoroquinolones, decreased occurrence of multiresistant strains, and decreased occurrence of undesirable effects.

The present paper aimed to confirm the sensitivity of the selected bacterial pathogens *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus aureus* (*S. aureus*) to fluoroquinolones (represented by ciprofloxacin) and to confirm decreased occurrence of multiresistant strains *P. aeruginosa* and methicillin-resistant

*S. aureus* (MRSA) and the strains *Klebsiella pneumoniae* (*K. pneumoniae*) producing the extended-spectrum beta-lactamase (ESBL) isolated from the clinical materials of the patients of the University Hospital Hradec Kralove in the years 2009-2019 in dependence on a decrease in total consumption of fluoroquinolones in the hospital.

## Material and methods

In the years 2009-2019 in the University Hospital Hradec Kralove (a tertiary university hospital with 1375 beds), several ABS interventions were carried out (see Table 1) aiming to decrease fluoroquinolone administration. The data of fluoroquinolone consumption in the years 2009-2019 were retrospectively evaluated from the programme Pharmax Sophis and recalculated to the defined daily dose according to WHO 2019, see Table 2 (WHO 2019), and recalculated to 1000 patient day (1000 PD).

**Table 1.** Overview of antimicrobial stewardship interventions to limit the use of fluoroquinolones.

Year	Antimicrobial stewardship interventions
2009	Use of all fluoroquinolones without restriction
2010	Inclusion of parenteral fluoroquinolones in <b>bound antibiotics</b> (dispensing in the pharmacy bound for approval by a consultant of the Antibiotic Centre) Personal participation of antibiotic consultants in the work of 4 hospital departments
2011	<b>Guidelines for antibiotic prophylaxis of surgical site infection</b> , minimizing the use of fluoroquinolones Introduction of <b>annual audits</b> of antibiotic therapy and prophylaxis <b>with feedback</b> with workplace management
2012	Addition of oral forms of levofloxacin and moxifloxacin to bound antibiotics Personal participation of antibiotic consultants in the work of 6 hospital departments
2014	Directive of the hospital with a restriction of the approval of the <b>dispensing of bound antibiotics to 3-5 days</b> Personal participation of antibiotic consultants in the work of 9 hospital departments
2015	Inclusion of norfloxacin in bound antibiotics <b>Strict restriction of the recommendation</b> and approval of fluoroquinolones by consultants of the Antibiotic Centre (elimination of fluoroquinolones from empirical therapy of respiratory and urinary tract infections) Personal participation of antibiotic consultants in the work of 10 hospital departments
2016	<b>Guidelines for antibiotic prophylaxis in non-surgical departments</b> minimizing the use of fluoroquinolones Personal participation of antibiotic consultants in the work of 11 hospital departments
2017	<b>All forms of all fluoroquinolones</b> included in <b>bound antibiotics</b> Personal participation of antibiotic consultants in the work of 13 hospital departments
2018	<b>Guidelines for empirical antibiotic treatment</b> minimizing the use of fluoroquinolones

**Table 2.** Overview of the defined daily doses used by fluoroquinolones used (according to WHO)

ATC classification	Antibiotic	DDD oral	DDD parenteral
J01MA01	ofloxacin	0.4 g	0.4 g
J01MA02	ciprofloxacin	1 g	0.8 g
J01MA03	pefloxacin	0.8 g	0.8 g
J01MA06	norfloxacin	0.8 g	
J01MA12	levofloxacin	0.5 g	0.5 g
J01MA14	moxifloxacin	0.4 g	0.4 g

For the evaluation of sensitivity to fluoroquinolones, the strains isolated from the materials of the patients of the University Hospital Hradec Kralove in the years 2009-2019 were selected; the average number of included

strains in the individual years is presented in Table 3. Evaluation of sensitivity was based on the retrospective analysis of the data obtained from the electronic database of the Laboratory Information System OpenLims (Stapro CZ) of the Department of Clinical Microbiology of the University Hospital Hradec Kralove. The obtained data were processed in MS Office Excell, and the elaboration included the susceptibility data of the first strain from one patient from one body system (respiratory tract, urinary tract, blood, and others). Only the materials were selected in which the isolated bacteria can be the cause of infection: cerebrospinal fluid, blood culture, bronchoalveolar lavage fluid, bronchial aspirate, tracheal aspirate in a quantity  $\geq 10^4$  CFU/mL, sputum in a quantity  $\geq 10^5$  CFU/mL, urine  $\geq 10^5$  CFU/mL, pus. The strains from colonized sites (swabs from the oral cavity, materials from the upper respiratory tract, skin, chronic wounds, decubitus, and rectum) were excluded. The second category included only the strains from positive blood cultures, namely always the data from one patient (the average number of included strains is shown in Table 3). Determination of sensitivity and resistance of strains was performed and interpreted according to EUCAST. ESBL production was determined using the double disc synergy test. Multiresistant *P. aeruginosa* was defined as the strain which exerts resistance to at least one antibiotic of three from four groups (fluoroquinolones, piperacillin and cephalosporins, aminoglycosides, carbapenems).

Parameters of interest were analysed using the linear regression method. Data were analysed using Microsoft Excel 2016 (Microsoft, USA) and MedCalc 9.5.2.0 (MedCalc, Belgium). P-values  $<0.05$  were considered statistically significant and all tests were 2-sided.

**Table 3.** Average number of strains per year included in sensitivity assessment in the period 2009-2019

Average number of strains per year	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>K. pneumoniae</i>
Total clinical material isolates	2269	757	1066	1015
Blood culture isolates	118	40	78	66

## Results

The total consumption of fluoroquinolones in the University Hospital Hradec Kralove significantly decreased (determination coefficient  $R^2$  0.9420,  $p < 0.001$ ) within 10 years because of the interventions of the Antibiotic Centre by 71.8% to 26.7 DDD/1000 PD (see Table 4, Fig. 1). The data of the development of sensitivity of selected strains to fluoroquinolones and the occurrence of multiresistant strains in individual years of the period under investigation are presented in Table 4 and Fig. 1 and 2. Sensitivity of *E. coli* and *P. aeruginosa* in the period under investigation increased by 4.8% (respectively by 15%); on the other hand, the sensitivity of *S. aureus* decreased by 4.2% to 85.5% share of sensitive strains. The share of multiresistant strains (MRSA as well as *K. pneumoniae* ESBL+) in the period under investigation increased, only the share of the isolates of *P. aeruginosa* multiresistant decreased by 8.1%.

The data of the development of sensitivity of selected strains to fluoroquinolones and the occurrence of multiresistant strains isolated from positive blood cultures in the period under investigation are presented in Table 5 and Fig. 3 and 4. The share of the isolates from blood cultures sensitive to fluoroquinolones in the period under investigation increased in the strains *E. coli* (by 6.6%) and *P. aeruginosa* (by 15.4%); in *S. aureus* it was decreased by 1.2%. The share of resistant strains decreased only in *P. aeruginosa* multiresistant, the occurrence of other multiresistant strains under examination at the end of the period under investigation was higher (Fig. 4).

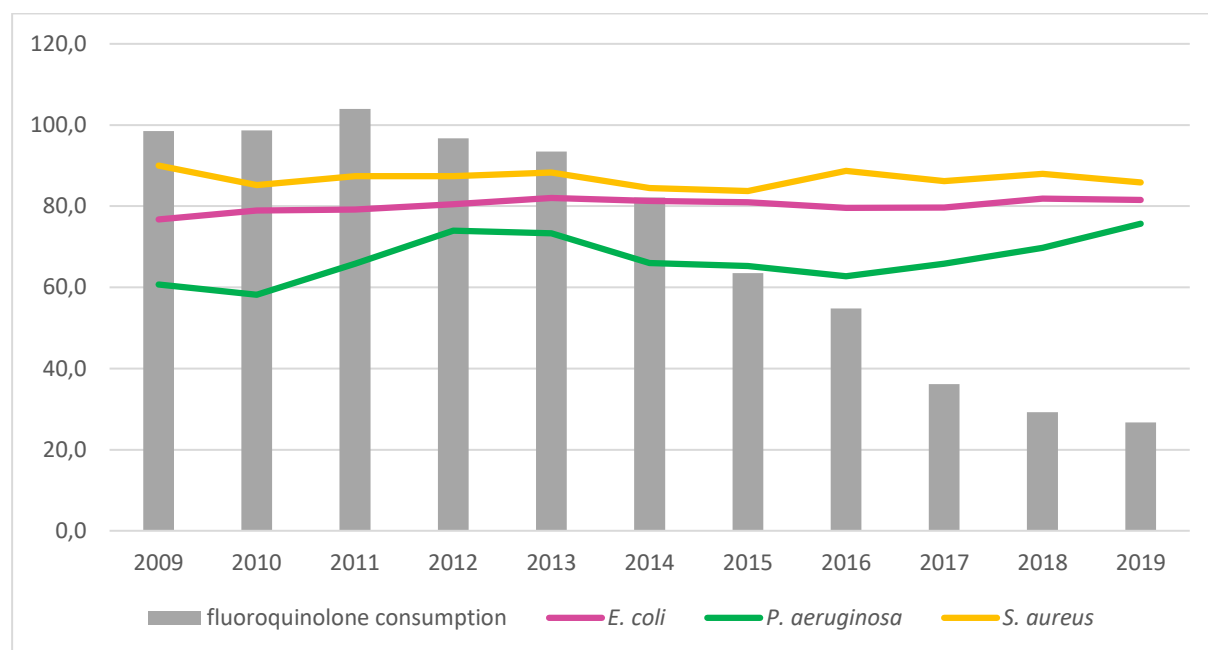
## Discussion

A combination of restrictive and educational interventions managed within 10 years to significantly decrease the consumption of fluoroquinolones from 98.5 DDD/1000 PD by 71.8%. The consumption for 2019 was 26.7 DDD/1000 PD. Various ABS strategies were able to decrease fluoroquinolones administration by 20-70% in various time periods (Borde et al. 2015, Wong-Beringer et al. 2005) in dependence on the applied measures, length of duration as well as the set aims. The present authors' study made use of both components of ABS interventions: restriction and recommendation.

**Table 4.** Development of total fluoroquinolone consumption in the hospital in the period 2009-2019 [DDD/1000 PD] and development of sensitivity of selected strains to fluoroquinolones [%] and the occurrence of multiresistant strains isolated from all clinical materials [%]

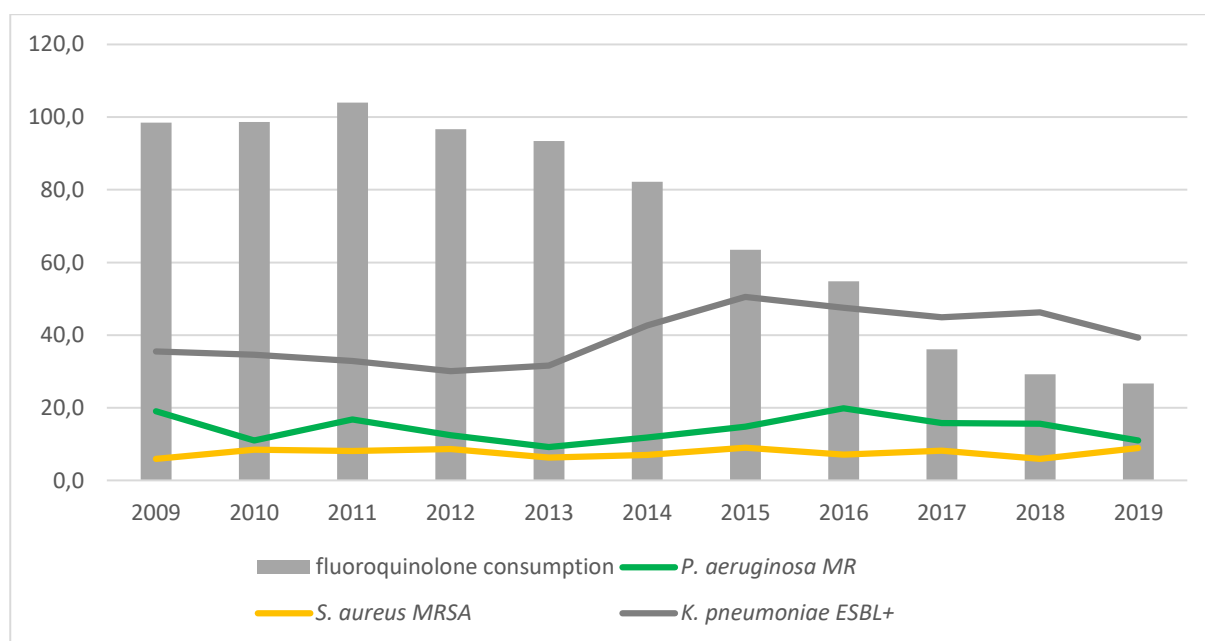
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Δ	T	p
<b>Consumption</b>	98.5	98.7	104.0	96.7	93.5	82.2	63.5	54.8	36.1	29.3	2.7	-71.8	↘	<0.001
<b>Sensitivity to fluoroquinolones [%]</b>														
<i>E. coli</i>	76.7	78.9	79.2	80.5	82.0	81.3	81.0	79.6	79.7	81.9	81.5	+4.8	↗	0.335
<i>P. aeruginosa</i>	60.7	58.2	65.8	74.0	73.3	66.0	65.3	62.7	65.8	69.7	75.7	+15.0	↗	0.545
<i>S. aureus</i>	90.0	85.2	87.4	87.4	88.3	84.5	83.7	88.7	86.2	88.0	85.8	-4.2	→	0.977
<b>Proportion of multiresistant strains [%]</b>														
<i>P. aeruginosa</i> MR	19.1	11.0	16.8	12.5	9.2	11.8	14.8	19.9	15.8	15.6	11.0	-8.1	↘	0.410
<i>S. aureus</i> MRSA	6.0	8.5	8.1	8.7	6.3	7.0	9.0	7.1	8.2	6.0	8.9	+2.9	→	0.824
<i>K. pneumoniae</i> ESBL+	35.5	34.6	32.9	30.1	31.6	42.7	50.5	47.5	44.9	46.3	39.3	+3.8	↗	0.026

Δ – change since 2009, T – trend, p – p-value

**Figure 1.** Development of total fluoroquinolone consumption in the hospital in the period 2009-2019 [DDD/1000 PD] and development of sensitivity of selected strains isolated from all clinical materials to fluoroquinolones [%]

The restriction measures of the present study can include a positive list of antibiotics, and a necessary electronic approval of the bound antibiotic for a specific patient prior to its supply from the hospital pharmacy, restriction of the maximal amount of the supplied bound antibiotic only for 3-5 days. Restrictive interventions exert a greater immediate effect for antibiotic prescription, even though after the termination of restriction they may possess a reverse effect. Parienti in University Hospital carried out a restriction in fluoroquinolones administration, within 1 year achieving a decrease to 5.2 DDD/1000 PD, after the termination of restriction in the following five years the consumption reached the values before restriction (56.6 DDD/1000 PD) and remained stable for another period of 5 years (Parienti *et al.* 2011). Restrictive measures require permanent attention and are time- and personnel-demanding. In the present authors' study all restrictive measures are implemented every day and the observance of the measures and their sustainable development requires much energy, time and patience from the party of ABS consultants as well as clinical physicians.

The highest and more permanent effect is achieved by a combination of education, recommendations and restrictive measures, the ideal aim is a change in the behaviour of clinical physicians towards rational use of antibiotics without necessary restrictions (Claeys *et al.* 2018, Davey *et al.* 2017). Claeys also draws attention to the fact that a simple restrictive policy may result in the effect of a compressed ball – restriction of one group of antibiotics results in the overuse of other groups (Claeys *et al.* 2018). To avoid this effect we decided to implement also interventions of educative character. These measures in our study included the formulation of local guidelines of antibiotic therapy and prophylaxis, personal involvement of ABS consultants in the work of the clinic, audits with feedbacks, and seminars at individual clinics. In our opinion, the implementation of these interventions was the main reason for reducing the consumption of all antibiotics, not just fluoroquinolones, in our hospital. In our opinion, this was initially mainly due to the reduction of unnecessary antibiotic administration and the shortening of the duration of antibiotic administration according to the our guidelines.

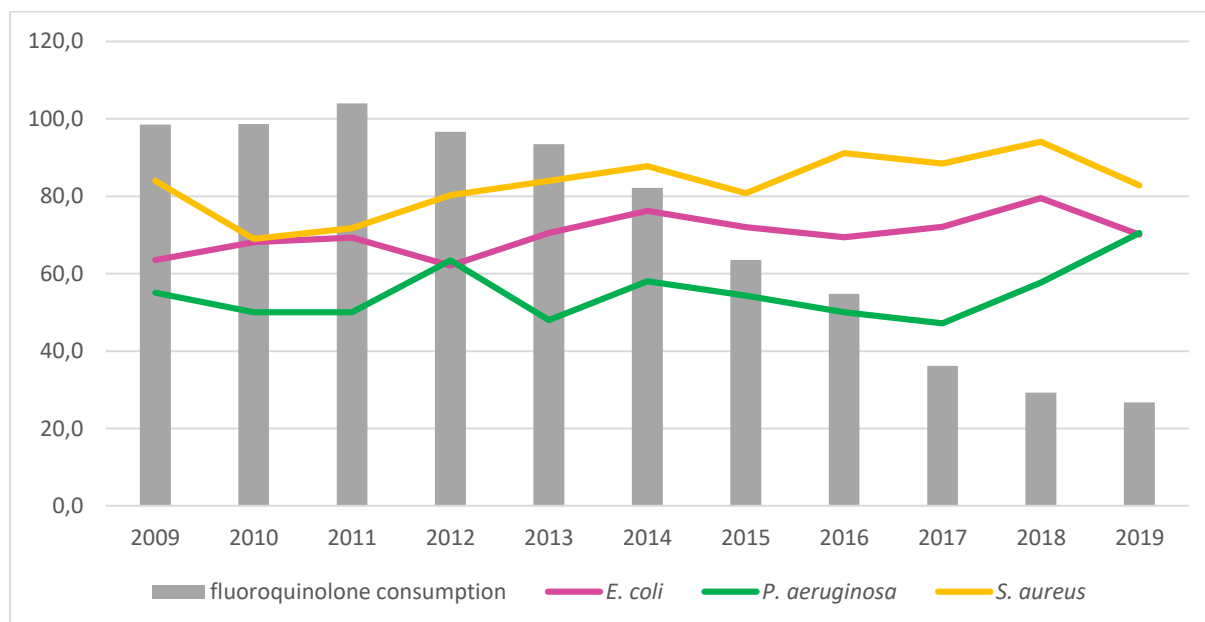


**Figure 2.** Development of total fluoroquinolone consumption in the hospital in the period 2009-2019 [DDD/1000 PD] and the occurrence of multiresistant strains isolated from all clinical materials [%]

**Table 5.** Development of total fluoroquinolone consumption in the hospital in the period 2009-2019 [DDD/1000 PD] and development of sensitivity of selected strains to fluoroquinolones [%] and the occurrence of multiresistant strains isolated from blood cultures [%]

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Δ	T	p
<b>Sensitivity to fluoroquinolones [%]</b>														
<i>E. coli</i>	63.5	68.1	69.3	62.1	70.5	76.2	72.0	69.4	72.1	79.5	70.1	+6.1	↗	0.128
<i>P. aeruginosa</i>	55.1	50.0	50.0	63.4	48.0	58.0	54.3	50.0	47.2	57.7	70.5	+15.4	↗	0.373
<i>S. aureus</i>	84.0	69.0	71.8	80.3	84.0	87.8	80.8	91.1	88.4	94.1	82.8	-1.2	↗	0.028
<b>Proportion of multiresistant strains [%]</b>														
<i>P. aeruginosa</i> MR	22.4	27.3	31.6	24.4	20.0	18.0	30.4	31.6	30.0	26.9	11.4	-11.0	↗	0.675
<i>S. aureus</i> MRSA	9.1	18.2	15.8	14.1	14.1	8.3	15.6	7.8	9.7	2.4	12.8	+4.0	↘	0.044
<i>K. pneumoniae</i> ESBL+	38.0	40.0	37.7	41.3	52.2	43.8	54.0	54.9	49.1	46.2	44.9	+6.9	↗	0.213

Δ – change since 2009, T – trend, p – p-value



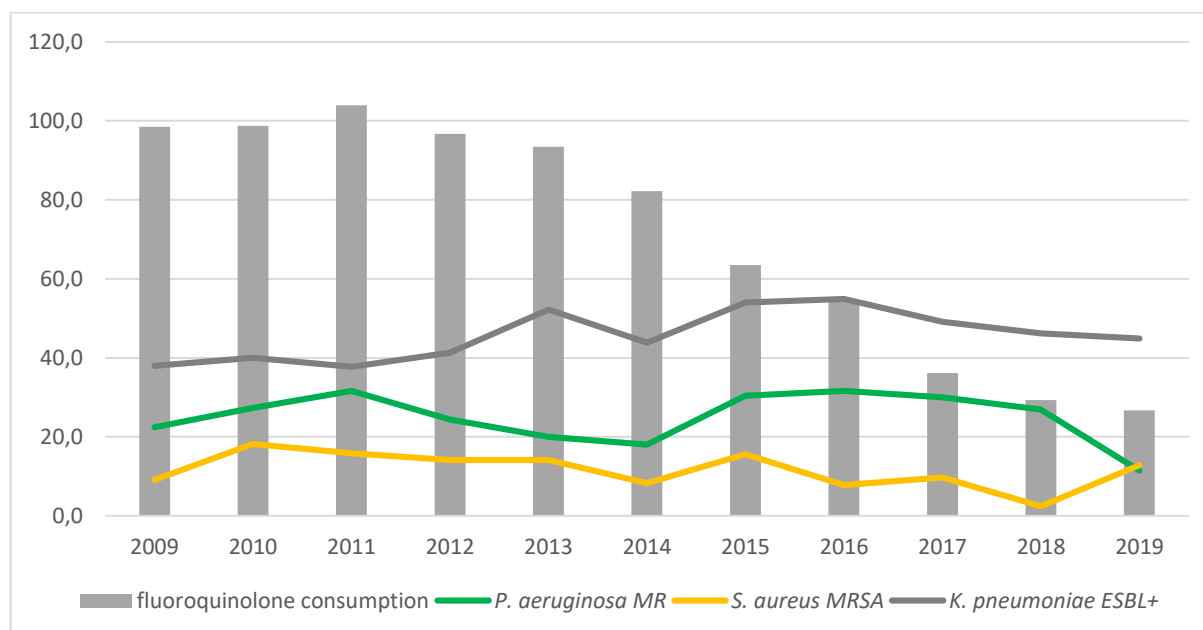
**Figure 3.** Development of total fluoroquinolone consumption in the hospital in the period 2009-2019 [DDD/1000 PD] and development of sensitivity of selected strains isolated from blood cultures to fluoroquinolones [%]

In the course of the period under investigation, the present study observed increased sensitivity to ciprofloxacin in *E. coli* by 4.8% (by 6.1% in the strains from positive blood cultures), in *P. aeruginosa* even by 15% (60.7-75.7%), respectively by 15.4% in the strains from blood cultures. None of these increases was, nevertheless, statistically significant. In the study of Hecker, investigating the syndrome impact of specific measures on fluoroquinolones consumption, sensitivity to fluoroquinolones was significantly increased in *P. aeruginosa* 75-84%, but not in *E. coli* (84-85%) or *K. pneumoniae* (Hecker *et al.* 2019). Increased sensitivity to *P. aeruginosa* has been confirmed also by other studies – during a ten-year period an increase by 16% (Lafaurie *et al.* 2012), by 18.4% in 6 months (Aubert *et al.* 2005), and also by others (O'Brien *et al.* 2015, Wu *et al.* 2011). Sarma studied the effect of decreased fluoroquinolones consumption on the trend of resistance of enterobacteria isolated from urine and blood cultures. During a three year period they arrived at the conclusion that decreased fluoroquinolones consumption <20 DDD/1000PD in the hospital sufficiently decreases the selection pressure for resistant bacteria, increases the sensitivity of *E. coli* (including the strains producing ESBL) as well as of enterobacteria isolated from urine (Sarma *et al.* 2015 II).

Increased sensitivity to fluoroquinolones after a decrease in the selection pressure is probably due to the principal mechanism of resistance to fluoroquinolones, which is chromosomal mutation in the genes coding DNA-gyrase, which is closely connected with exposure to fluoroquinolones (Chatzopoulou *et al.* 2020). But the result of interventions depends also on whether the microorganisms are resistant only to fluoroquinolones or also to other antibiotics, e.g. due to the presence of the genes of multiple resistance (Morosini *et al.* 2005). At the same time, it is not possible to replace one fluoroquinolone by another. Reduction of administration of ciprofloxacin in exchange for ofloxacin did not increase the sensitivity of strains to fluoroquinolones. There was an improvement only in the case of a decrease in total consumption of all fluoroquinolone antibiotics (Peterson *et al.* 1998).

It is difficult to demonstrate a causal relationship between consumption of antibiotics and infections connected with healthcare caused by multiresistant gram-negative rods. Several studies have pointed out a moderate decrease in ESBL-producing strains in connection with the policy of fluoroquinolones restriction (Sarma *et al.* 2015 II, Aldayb *et al.* 2012). These papers rather aimed at *E. coli* and urinary infections. In the present study, the authors examined the occurrence of the ESBL-producing *K. pneumoniae* strains. In the course of the period under examination, not only there occurred no decrease in ESBL, but, on the other hand, an increasing trend lasted till the year 2015,





**Figure 4.** Development of total fluoroquinolone consumption in the hospital in the period 2009-2019 [DDD/1000 PD] and the occurrence of multiresistant strains isolated from blood cultures to fluoroquinolones [%]

which negatively correlated with a decrease in fluoroquinolones consumption ( $p=0.026$ ). Then a plateau to a moderate decrease in the share of ESBL-positive strains from all strains as well as blood cultures is formed. Probably there exist a large number of variables: practice of infection controls, a complex of interventions and changes in prescriptions of antibiotics of different risk profiles, occurrence of strains in the population of the given region. Dancer found that ciprofloxacin administration was connected with a new gain of colonization of ESBL-producing strains and after fluoroquinolones restriction the extent of new colonization of ESBL in the hospital ward was decreased (Dancer *et al.* 2013). Also, Nseir paid attention to this problem: he examined immunocompetent adults at the Intensive Care Unit and found a significantly higher share of new colonization by ESBL-producing enterobacteria in patients treated with fluoroquinolones (40% vs. 20%). However, this did not hold true for new colonisations by multiresistant *P. aeruginosa* or *Acinetobacter baumannii* (Nseir *et al.* 2005). In the present study, the share of multiresistant *P. aeruginosa* in the period under investigation decreased by 8.1%, but this decrease was not statistically significant. It is difficult to interpret the effect of decreased fluoroquinolones administration in multiresistant strains, because the results of annual surveys of occurrence of multiresistant pathogens can be influenced by imports of strains from other hospitals, outbreaks of multiresistant strains at some wards and the measures of infection control related to them (isolation of the patient, recommendation of contact and nursing, increased cleaning of the surroundings).

The effect of decreased fluoroquinolones consumption on the sensitivity of gram-positive bacteria is not studied so often. The majority of studies are aimed at MRSA. The present study examined the sensitivity of all strains of *S. aureus* regardless the sensitivity to methicillin and in the course of the period under investigation no positive correlation was found; sensitivity to ciprofloxacin did not show a clear trend and at the end it was decreased by 4.2%. A significant increase in sensitivity was found in the strains from blood cultures ( $p=0.032$ ), even though in the final year sensitivity was finally decreased by 1.2% as against the year 2009. The share of MRSA did not show a stable trend and finally was moderately increased by 2.9%. The occurrence of MRSA in blood cultures showed a decreasing trend ( $p=0.044$ ), but in the final year there was an increase by 4% as against the year 2009. These findings are not in harmony with other studies: Lafaurie investigated the occurrence of MRSA in the course of 10 years, when in the period under investigation fluoroquinolones consumption decreased from 148.2 to 29.1 DDD/1000 PD. At the end of the period, the share of MRSA decreased from 27 to 21% (Lafaurie *et al.* 2012). Fluoroquinolones probably increase the adherence of MRSA to the tissue because of increased expression of fibronectin-binding proteins as well as eradication of protective microflora in the course of therapy (Parienti *et al.* 2011). The inconclusive effect of decreased fluoroquinolones



consumption in the present study may be due to a low occurrence of MRSA (in the period under investigation it ranged between 6-9%) and a higher share of community strains in staphylococcal infections. The results of testing of the strains from blood cultures can be influenced by a small number of strains (mean 78/year). Weber and his team examined the groups of patients with the finding of *S. aureus* (MSSA as well as MRSA) obtained in the hospital surroundings. They found that exposure to fluoroquinolones is a significant risk factor connected with MRSA colonisation (Weber *et al.* 2003). In another study, in the course of restriction the occurrence of MRSA was decreased ( $p < 0.05$ ) and in the course of increased consumption in other years the occurrence of MRSA was significantly increased ( $p < 0.02$ ). Though the paper suggested a possible additive effect of fluoroquinolones restrictions with regard to other hygienic measures for a decrease in the occurrence of MRSA (Parienti *et al.* 2011), Cochrane's review of 2017 did not find clear evidence that restriction of any antibiotics exerts effect on MRSA control (Davey *et al.* 2017).

A positive effect of restriction of fluoroquinolones administration is described in the occurrence of infections caused by *Clostridioides difficile*. The first reports appeared in the year 2004 (Gaynes *et al.* 2004). Then the same theory was confirmed by several other papers (Sarma *et al.* 2015 I, Dingle *et al.* 2017). A suitable antimicrobial stewardship is considered to be the basis of controls of occurrence of these infections because of a lower selection of *Clostridioides difficile* resistant to fluoroquinolones (Dingle *et al.* 2017).

The hospital is not an isolated ecological surroundings, it is influenced by the community, movement of patients within health facilities of a smaller or larger territories. For the evaluation of the effect of restriction of antibiotics, the important factor is whether the microorganism under investigation occurred in ecological surroundings where the reduction of antibiotics was carried out. Many previous studies evaluated strains from the same ecological areas (e.g. hospital wards), in which the reducing interventions took place (Lafaurie *et al.* 2012, Aubert *et al.* 2005). The present study included strains mainly from hospitalized patients (from all wards), but a portion of strains (primarily *E. coli* and *S. aureus*), was of a community origin. A similar relationship of strains was also found in the study by Hecker, where a 30% share of *E. coli* was obtained from hospitalized patients (Hecker *et al.* 2019). The strains from a community are not influenced by decreased consumptions of antibiotics in the hospital and their share may thus distort the results of the study.

The present study is also limited by the use of the complex data of resistance with the inclusion of strains from all materials, where the strains are the probable causative agent of infection. This method may be different from other studies, which examined only urine isolates or strains from blood cultures (Sarma *et al.* 2015 II), and materials from the digestive tracts of patients at the intensive care units (Nseir *et al.* 2005). The present study used the % of sensitive or multiresistant strains. Studies can also differ in the employed method of the determinant of consumption; in the year 2019 WHO changed the value of DDD of parenteral ciprofloxacin (0.5 g to 0.8 g). As for a long time our hospital uses the same dosage of fluoroquinolones in order to observe the continuity of the method, the values of DDD 2019 were used for the evaluation of fluoroquinolones consumption.

Decreased fluoroquinolones consumption should finally result in decreased occurrence of undesirable effects, which are viewed at present as a great medical and social problem. Molecular activities of fluoroquinolone in cells remain unexplained in many respects for the time being; the effect on mammal topoisomerases II occurring in mitochondria has been confirmed (Hangas *et al.* 2018). Fluoroquinolones are also an effective chelator of iron, which produces epigenetic changes finally resulting in a disorder in collagen maturation. This effect can explain nephrotoxicity, tendinopathies as well as effects on the vascular wall (Badal *et al.* 2015). The majority (>85%) of fluoroquinolones-related tendinopathies appears within one month after the beginning of therapy (Khalig *et al.* 2003), a higher risk occurs in patients >60 years with simultaneous administration of corticoids (Alves *et al.* 2019). Nephrotoxicity is also well documented (Badal *et al.* 2015). The forms of long-term affections are problematic (fatigue, problems with concentration, neuropathy, anxiety, depression, insomnia, fits of panic, depersonalization, suicidal thoughts), beginning days after the commencement of fluoroquinolones administration and outlasting even months after termination of administration. Effective therapy of these chronic conditions turned out to be complicated (Kaur *et al.* 2016, Michalak *et al.* 2017). No study of the effect of fluoroquinolones restriction on decreased unwanted effects has been published for the time being.

There are thus numerous reasons why fluoroquinolones administration should be limited. In any case, according to our opinion it is advisable to exclude the use of norfloxacin, to markedly limit or exclude all fluoroquinolones

administration in empiric and targeted treatment of mild and unimportant respiratory and urinary infections, if other antibiotics can be administered. In the indication of interstitial pneumonia and other chlamydious or mycoplasmatic infections, tetracyclines or macrolides should be preferred. All of these recommendations were included into our local guidelines.

Fluoroquinolones, in spite of their disadvantages, still remain important antibiotics for the treatment of serious infections: complicated urinary infections, acute bacterial prostatitis, tuberculosis, complicated infections of bones and joints, serious gastrointestinal and intra-abdominal infections, otitis externa caused by *P. aeruginosa* (Shea *et al.* 2015). Aiming at a rational decrease in fluoroquinolones consumption, we recommend in accordance with other authors a “smart restriction” at the beginning, aiming only at definition and shortening of the therapy of urinary infections, therapy of community pneumonia, and also the patients at the highest risk (mainly geriatric ones), and the wards which have problems with the control of occurrence of infections caused by *Clostridioides difficile* (Chatzopoulou *et al.* 2020, Pitiriga *et al.* 2017). The essentials of the programme of optimal use of fluoroquinolones include: limitation of their use in infections with little therapeutic contribution, administration of sufficiently high doses, limitation of uselessly long administration, minimization in prophylactic administration.

## Conclusion

With regard to their high-risk profile, fluoroquinolones are now considered as reserved antibiotics, which should be used in precisely defined infections. Programmes of antimicrobial stewardship are an effective tool of rationalization of fluoroquinolones administration, and a decrease in the consumption of fluoroquinolones results in an increase in the sensitivity of enterobacteria to fluoroquinolones and a decrease in the occurrence of some multiresistant strains.

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## Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

## Adherence to ethical standards

This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

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