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REVIEW

# Resistance surveillance studies: a multifaceted problem—the fluoroquinolone example

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**Abstract**
*Introduction* This review summarizes data on the fluoroquinolone resistance epidemiology published in the previous 5 years.
*Materials and methods* The data reviewed are stratified according to the different prescription patterns by either primary- or tertiary-care givers and by indication. Global surveillance studies demonstrate that fluoroquinolone-resistance rates increased in the past several years in almost all bacterial species except *Staphylococcus pneumoniae* and *Haemophilus influenzae* causing community-acquired respiratory tract infections (CARTIs), as well as *Enterobacteriaceae* causing community-acquired urinary tract infections. Geographically and quantitatively varying fluoroquinolone resistance rates were recorded among Gram-positive and Gram-negative pathogens causing healthcare-associated respiratory tract infections. One- to two-thirds of *Enterobacteriaceae* producing extended-spectrum $\beta$-lactamases (ESBLs) were fluoroquinolone resistant too, thus, limiting the fluoroquinolone use in the treatment of community- as well as healthcare-acquired urinary tract and intra-abdominal infections. The remaining ESBL-producing or plasmid-mediated quinolone resistance mechanisms harboring *Enterobacteriaceae* were low-level quinolone resistant. Furthermore, 10–30 % of *H. influenzae* and *S. pneumoniae* causing CARTIs harbored first-step quinolone resistance determining region (QRDR) mutations. These mutants pass susceptibility testing unnoticed and are primed to acquire high-level fluoroquinolone resistance rapidly, thus, putting the patient at risk. The continued increase in fluoroquinolone resistance affects patient management and necessitates changes in some current guidelines for the treatment of intra-abdominal infections or even precludes the use of fluoroquinolones in certain indications like gonorrhea and pelvic inflammatory diseases in those geographic areas in which fluoroquinolone resistance rates and/or ESBL production is high. Fluoroquinolone resistance has been selected among the commensal flora colonizing the gut, nose, oropharynx, and skin, so that horizontal gene transfer between the commensal flora and the offending pathogen as well as inter- and intraspecies recombinations contribute to the emergence and spread of fluoroquinolone resistance among pathogenic streptococci. Although interspecies recombinations are not yet the major cause for the emergence of fluoroquinolone resistance, its existence indicates that a large reservoir of fluoroquinolone resistance exists. Thus, a scenario resembling that of a worldwide spread of $\beta$-lactam resistance in pneumococci is conceivable. However, many resistance surveillance studies suffer from inaccuracies like the sampling of a selected patient population, restricted geographical sampling, and undefined requirements of the user, so that the results are biased. The number of national centers is most often limited with one to two participating laboratories, so that such studies are point prevalence but not surveillance studies. Selected samples are analyzed predominantly as either hospitalized patients or patients at risk or those in whom therapy failed are sampled; however, fluoroquinolones are most frequently prescribed by the general practitioner. Selected sampling results in a significant over-estimation of fluoroquinolone resistance in outpatients. Furthermore, the requirements of the users are often not met; the prescribing physician, the microbiologist, the infection control specialist, public health and

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regulatory authorities, and the pharmaceutical industry have diverse interests, which, however, are not addressed by different designs of a surveillance study. Tools should be developed to provide customer-specific datasets.
*Conclusion* Consequently, most surveillance studies suffer from well recognized but uncorrected biases or inaccuracies. Nevertheless, they provide important information that allows the identification of trends in pathogen incidence and antimicrobial resistance.

**Keywords** Fluoroquinolones · Resistance epidemiology · Global pool of primed bacteria · Inter- and intra-species recombinations · Biased surveillance studies

## Introduction

Fluoroquinolones have become established for the treatment of infections in outpatients and hospitalized patients. Despite millions of prescriptions in the first two decades of their use, the emergence of quinolone resistance during treatment was uncommon except in *Staphylococcus aureus*, particularly in methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa*. Resistance to fluoroquinolones emerged rapidly in these two species, predominantly due to clonal spread among nursing home residents and immunocompromised patients [1]. However, since the mid-1990s, quinolone resistance started to increase in almost all Gram-positive and Gram-negative species. The continued increase in resistance rates is concerning [2–4]. Since the approval of norfloxacin in the US in 1986, ciprofloxacin in 1987, levofloxacin in 1996, and moxifloxacin in 1999, there have been numerous updates to the warning sections of the package inserts because of severe adverse reactions. Restrictions have been placed upon the use of fluoroquinolones too; for example, the use of oral formulations of norfloxacin has been restricted by the European Agency for the Evaluation of Medicinal Products (EMEA) on July 4, 2008, as there was "not enough clinical data to demonstrate efficacy of the oral treatment with norfloxacin-containing medicines in complicated pyelonephritis" [5]. But changing susceptibility patterns of the causative pathogens have not yet resulted in modifications of the approvals once granted. Therefore, the first aim of this review is to demonstrate that a continued increase in fluoroquinolone resistance rates affects patient management and necessitates a change in some current treatment guidelines [6, 7], or even precludes the use of fluoroquinolones in certain indications, as will be discussed later in this paper [8, 9].

Surveillance studies provide important information that allows for the identification of trends in pathogen incidence and antimicrobial resistance at local, regional, national, or global levels. The traditional approach has been, and still is, to monitor pathogen antimicrobial susceptibility. However, many surveillance studies suffer from well recognized, but uncorrected, biases or inaccuracies like restricted focus, selected patient population to be sampled, selected geographical (global, national, or local) sampling, undefined requirements of the users like interest of the microbiologists and infection control specialists in data on prevalence or incidence of resistance, etc. [10]. Thus, surveillance studies are essential in order to detect and monitor the development and spread of resistance; however, the diversity of techniques and study designs used yields diverse results.

In general, several longitudinal surveillance studies [10, 11] seem to indicate that fluoroquinolone resistance is continuously increasing in Gram-positive as well as Gram-negative bacterial species. However, there were some discrepancies in the datasets; ciprofloxacin resistance was increasing in Belgium based on the SENTRY data, whereas it was decreasing in Belgium based on the MYSTIC dataset [12]. Most surveillance studies are hospital based, so that the agents studied like carbapenems, aminoglycosides, and piperacillin/tazobactam are primarily administered as second-line therapy, whereas fluoroquinolones are not and are most frequently prescribed by general practitioners. Therefore, the second aim of this review is to stratify data according to the different prescription patterns of fluoroquinolones by either general practitioners or tertiary-care physicians, patient population, and bacterial species. As surveillance data only are reviewed, the emergence or selection of fluoroquinolone resistance in species like *Salmonella* spp., *Clostridium difficile*, etc., which are not routinely surveyed by the major surveillance initiatives, will not be discussed.

## Fluoroquinolone resistance epidemiology

### Urinary tract infections

#### *Fluoroquinolone-resistance in uropathogens*

As reviewed in detail recently [13], fluoroquinolone-resistant *Enterobacteriaceae* isolated from female outpatients and male inpatients with urinary tract infections (UTIs) were almost non-existent (<1 %) until the mid-1990s; resistance to ciprofloxacin increased slowly from 1.2 % in 1998 to 2.5 % in 2001 and >20 % in 2009, with a trend towards higher resistance rates among elderly patients and nursing home residents. Actually, fluoroquinolone resistance in uropathogens is highly variable and different, first in patients with community-acquired UTIs (CA-UTIs) as compared to patients with healthcare-acquired UTIs (HA-UTIs), and second in pathogens producing or not producing extended-spectrum $\beta$-lactamases (ESBLs). Fluoroquinolone

resistance ranges on the one hand from ≤10 % in ESBL-negative strains to >70 % in ESBL-positive strains isolated from patients with uncomplicated CA-UTI and even up to >90 % for strains from patients with complicated CA-UTIs. Likewise, ESBL production ranged from 2.6 to 100 % [13]. Fluoroquinolone resistance and ESBL production were closely linked [14]. Both fluoroquinolone resistance and ESBL production were highest in the Asia–Pacific region and moderate to low in Europe and North America. Although the clonality of the isolates has not always been examined, clonal spread has been reported frequently [15–24]. The percentages of isolates with simultaneous resistance to ciprofloxacin, trimethoprim–sulfamethoxazole, and gentamicin were found to be 4.6 % in the ESBL-negative group and 39.2 % in the ESBL-positive group ($p < 0.001$) [25–27]. Not surprisingly, infections with these organisms have been associated with higher rates of morbidity and mortality [28]. CA-UTIs in the elderly are frequently caused by ESBL producers (56.2 %) and almost 80 % of all isolates were fluoroquinolone resistant [29, 30].

In general, fluoroquinolone resistance was lower in CA-UTI isolates than in HA-UTI isolates (reviewed in [13]). Two comprehensive monitoring programs in CA-UTI patients confirmed that fluoroquinolone resistance is lower in patients with community- compared to healthcare-acquired UTIs [31–34]; ciprofloxacin resistance in CA-UTI pathogens collected in Europe and Brazil from 1999 to 2006 ranged from 0 to >10 % and was, on average, as low as 1.1 %; the mean fluoroquinolone resistance increased to 3.9 % during the period 2007–2008 [34], still ranging in Europe from 1.7 % up to 12 % [35–37]. In the US, fluoroquinolone resistance in CA-UTI isolates increased from 3 % in 2000 to 17.1 % in 2010 [38]. ESBL production was not specified in these studies. On the other hand, the fluoroquinolone resistance of uropathogens isolated from patients admitted to tertiary-care hospitals ranged from 6.3 to 62 % in Gram-negative strains and 20 and 100 % of the methicillin-susceptible *S. aureus* (MSSA) and MRSA, respectively, as well as 59 % of the enterococci isolated from patients with complicated HA-UTI [13, 39–42]. Even higher rates of fluoroquinolone resistance were found in patients with HA-UTIs admitted to the emergency department [43] and in nursing home residents [26, 29, 30]. A retrospective analysis of 42,033 *Escherichia coli* urine isolates from an 11-year period (1999–2009) in a single Dublin teaching hospital revealed that ciprofloxacin resistance was highest in patients with nosocomial UTIs, approached 20 % in HA-UTI patients from the emergency department, and was lowest in isolates from patients with CA-UTIs [42]. A retrospective chart review (08/2008–03/2009) in a tertiary-care hospital in Chicago revealed that levofloxacin resistance amounted to 38 % in HA-UTIs versus 10 % in CA-UTIs [44].

### *Association between fluoroquinolone-resistance and the production of extended spectrum β-lactamases*

Although the production of ESBLs was not analyzed in the surveillance studies in the mid-1990s, it is conceivable that the increase in both fluoroquinolone resistance and ESBL production are closely associated [36]. ESBLs gained prominence and started to spread among uropathogens in North America at the time when these surveillance studies have been performed.

Since the early 1990s, *E. coli* isolates that produce CTX-M-type ESBLs have emerged as a serious cause of UTIs in the community [36, 45]. Risk factors for the acquisition of ESBL-producing *E. coli* in non-hospitalized patients with uncomplicated urinary tract infections (uUTIs) were diabetes mellitus [odds ratio (OR) = 5.5], previous fluoroquinolone use (OR = 7.6), previous hospital admission (OR = 18.2), and older age in male patients (OR = 1.03) [29, 46]. ESBL production was detected in 8.1 % of all isolates, with CTX-M-15 being the most common; about 30 % of strains belonged to the two predominant clonal groups O25:H4-ST131 and O15:K52:H1 [46–48]. Point source dissemination of ESBL producers is frequent in patients with uUTIs. The intercontinental pandemic spread of the ciprofloxacin-resistant *E. coli* O25:H4:ST131 clonal group producing CTX-M-15 has been described worldwide in hospital and community settings and contributes to 30–60 % to all fluoroquinolone-resistant *E. coli* [49–55]. Foreign travel to high-risk areas, such as the Indian subcontinent, plays a partial role in the spread of this clone across different continents [56]. This pandemic *E. coli* clone ST131 was isolated from humans as well as from companion animals. Thus, companion animals are reservoirs for human infections [57]. Furthermore, the isolation of a multidrug-resistant *E. coli* strain of sequence type ST131 from an 8-month-old girl with severe septic arthritis and contagious osteomyelitis and her healthy mother demonstrates that within-household transmission contributes to the dissemination of the ST131 clonal group as well [58].

### *Risk factors for the emergence of fluoroquinolone-resistance*

The impact of the prescribing of ciprofloxacin on the emergence of fluoroquinolone resistance in uropathogens is well documented and has been confirmed recently; an increase in prescriptions was paralleled by an increase in fluoroquinolone resistance [43, 59–65]. However, there are significant differences across species [66]. Additional factors favoring the selection of resistant uropathogens are poor adherence to treatment guidelines [67, 68], inappropriate prescriptions [69], and the dispensing of

antibacterials without prescription [70]. Irrational prescribing habits of fluoroquinolones in particular for UTIs and respiratory tract infections (RTIs) foster resistance development [71–76].

Another aspect is worth mentioning and relevant for prescribing policies, hygiene strategies, and resistance statistics. A study on the evolution of quinolone resistance in Barcelona, Spain, from 1992 to 1997 revealed that the prevalence of fluoroquinolone resistance in the feces of healthy people was unexpectedly high, being 24 % in adults and 16 % in children, although it was not used in the pediatric population [77, 78]. The carriage rate was higher than the fluoroquinolone resistance rates among patients with healthcare- and community-acquired infections. Increasing fluoroquinolone resistance rates in commensal *E. coli* in children were found in North as well as South America, and Africa and Asia as well [79–85]. The fecal carriage of CTX-M-producing *E. coli* was frequently found in families as well, indicating person-to-person transmission of this clone [86]. The emergence of fluoroquinolone resistance in children in the 1990s was not due to fluoroquinolone therapy given to children, as its use in pediatric populations was approved for the post-exposure treatment of inhalational anthrax in August 2000 and for the treatment of complicated urinary tract infections (cUTIs) in March 2004. The transmission of resistant isolates between adults and children in families, daycare, or school settings may be the likely cause of person-to-person transmission, which increased the numbers of resistant isolates independently from the selection of resistant strains in diseased patients; this phenomenon may bias resistance statistics. Analogous findings are reported next for RTI pathogens. Furthermore, these findings indicate that the treatment of fluoroquinolone-naïve patients, i.e., those who should not have been treated in previous years because of their age, may, nevertheless, carry primed bacteria which may develop high-level fluoroquinolone resistance quite rapidly during treatment.

### *Conclusion*

These data demonstrate that most of the uropathogens causing uUTIs in outpatients are still susceptible to fluoroquinolones. In the US and Europe, resistance rates in CA-UTI are 6–10 times lower than in HA-UTI. Although fluoroquinolone resistance is still low in CA-UTI pathogens, fluoroquinolones should be used with caution in the treatment of CA-UTIs because of the continuously rising trend in fluoroquinolone resistance. Furthermore, it has to be considered that previous fluoroquinolone use exerts an MRSA-selective potential and exhibits negative epidemiological effects, resulting in the selection of multi-resistant pathogens. Fluoroquinolones should be "reserved for important uses other than acute cystitis" [87] and are recommended as the first-line therapy in patients with uncomplicated pyelonephritis [37, 88, 89]. Considerable regional differences in drug susceptibility patterns exist, with significantly increased rates of fluoroquinolone-resistant and/or ESBL-producing uropathogens in the Asia–Pacific region and India. Because of the very close correlation between ESBL production and fluoroquinolone resistance in uropathogenic *Enterobacteriaceae*, fluoroquinolone susceptibility is still high in those geographic regions in which ESBL-producing, Gram-negative, community-acquired uropathogens are infrequent. Pathogens causing HA-UTIs or cUTIs in nursing home patients are less susceptible to fluoroquinolones. Thus, empiric therapy of UTIs should be guided by reports on both ESBL-producing and fluoroquinolone-resistant organisms.

## Respiratory tract infections

### *Community acquired respiratory tract infections*

Although a number of significant pathogens like *Haemophilus influenzae*, *Moraxella catarrhalis*, and atypicals are associated with community-acquired respiratory tract infections (CARTIs) in all age groups, *Staphylococcus pneumoniae* is the most frequent one. High-level [minimum inhibitory concentration (MIC) $\geq$2 mg/L] penicillin resistance rates in pneumococci varied from 40 to 50 % in France, Spain, and Japan, 57 % in Hong Kong, and 71 % in South Korea and Taiwan, whereas no penicillin resistance was detected in Indonesia or the Netherlands [90, 91]. Interestingly, even in these "hot spots" of penicillin and/or macrolide and/or trimethoprim/sulfamethoxazole resistance like Asia or Spain, where fluoroquinolone use is high and low doses are administered frequently, rates of fluoroquinolone resistance remain low, ranging from 0.5 to 7 % (reviewed in detail in [13]) .

Surveillance studies in the US from 1987 to 2009 demonstrated low rates of resistance (0.1–1.3 %) to levofloxacin and to moxifloxacin (0.1 %), although ciprofloxacin has been used in the US since 1987 and has, thus, exerted a selective pressure on *S. pneumoniae*. Three major surveillance programs demonstrated that >96 % of the pneumococci were moxifloxacin and levofloxacin susceptible [13]. In 1.2 % of the isolates, a first-step mutation was detected and 6.7 % exhibited an efflux phenotype, despite high fluoroquinolone usage [92].

However, a trend for rising levofloxacin resistance from <0.5 to >3 % was noted in some regions of North America. High fluoroquinolone resistance rates (>10 %) were recorded in patients who acquired pneumococcal infections in nursing homes or hospitals, as well as in adults $\geq$65 years of age (reviewed in detail in [13]).

Occasionally, fluoroquinolone resistance resulted in clinical failures in patients with pneumococcal pneumonia having been previously treated empirically with oral fluoroquinolones. In total, there were 20 ciprofloxacin and levofloxacin treatment failures reported from 1995 to January 2005 and were reviewed by Fuller and Low [93]. A pre-therapy isolate was available in five cases only, with MICs ranging from 1 to 16 mg/L; MICs for the during-therapy isolates ranged from 4 to >32 mg/L [93]. Thus, the question cannot be answered as to whether resistance may have developed during therapy, resulting in clinical failure. This question was recently addressed by Orr et al. [94], who investigated in a tertiary referral hospital in England the incidence and epidemiology of levofloxacin-resistant pneumococci among 865 patients. In six patients, a shift towards reduced levofloxacin susceptibility or resistance was recorded. Five patients had acquired a new distinct strain and one patient only harbored the same clone [94]. A limitation of this study is that all isolates of *S. pneumoniae* from any body site were eligible for inclusion in the study, irrespective of whether the patient has been treated with a fluoroquinolone or not. Furthermore, hospital guidelines recommend to treat severe community-acquired pneumonia (CAP) with levofloxacin plus intravenous benzylpenicillin [94]. High-level levofloxacin resistance (MIC >8 mg/L) developed under levofloxacin treatment in eight out of 164 patients with chronic obstructive pulmonary disease (COPD) whose pre-therapy isolates were susceptible [95] and one fatal outcome was described [96]. A *P. aeruginosa* infection was treated successfully with oral ciprofloxacin in another COPD patient in whom a ciprofloxacin-resistant but moxifloxacin-susceptible (MIC 0.125 mg/L) *S. pneumoniae* strain with a *parC* mutation was isolated subsequently [97].

The prevalence of first-step fluoroquinolone-resistant *S. pneumoniae* mutants is increasing [98–100]. Although the subtle changes in the MICs of third-generation fluoroquinolones for primed bacteria remained within the susceptible range in most CARTI isolates, many isolates contained a single *gyrA* or *parC* mutation, which prime the bacteria to acquire additional mutations within the quinolone resistance determining region (QRDR), conferring high-grade fluoroquinolone resistance [101, 102]. Approximately up to 30 % of clinical pneumococcal isolates contain mutations in the *gyrA* and/or *parC* loci [102–107]. Many pneumococcal isolates with first-step fluoroquinolone resistance pass unnoticed in routine susceptibility testing because of the high resistance breakpoints [108, 109].

Previously, the resistant breakpoints for ciprofloxacin and levofloxacin were ≥4 and ≥8 mg/L, respectively. Actually, the resistant breakpoints of ciprofloxacin and levofloxacin for *S. pneumoniae* defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are both ≥2 mg/L. The EUCAST provides two comments in this context: first, wild-type *S. pneumoniae* are not considered to be susceptible to ciprofloxacin, and second, the breakpoints for levofloxacin relate to high-dose therapy. However, high levofloxacin doses, i.e., 750 mg once daily or 500 mg twice daily, are rarely administered, so that an extrapolation from the categorization "susceptible" due to in vitro breakpoint-based susceptibility testing to advice on therapy for the patient is limited. Two case reports describing levofloxacin treatment failures confirm the limited predictability of routine in vitro susceptibility testing. The pre-therapy pathogens isolated from two elderly patients suffering from pneumococcal pneumonia were characterized as levofloxacin susceptible; the isolates had MICs of 1 and 2 mg/L and harbored pre-existing point mutations in *parC* and *gyrA*, respectively. Therapy with 500 mg levofloxacin i.v. failed in both cases. The post-therapy isolates had acquired additional mutations in *gyrA* and *parC*, respectively, resulting in MICs of ≥16 mg/L [110, 111]. Both patients had, apart from advanced age, additional risk factors like COPD and others. These clinical examples confirm that first-step mutants of *S. pneumoniae* are phenotypically considered to be susceptible and are primed to acquire additional QRDR mutations conferring high-grade fluoroquinolone resistance, resulting in clinical failure. As most first-step mutants pass routine susceptibility testing unnoticed, they are not effectively detected in surveillance studies. Consequently, the routine susceptibility testing of suspicious cases should at least be modified, e.g., by using a second fluoroquinolone like ciprofloxacin as an indicator for the acquisition of a first mutation [99, 109]. Furthermore, it should be considered to use a more potent anti-pneumococcal fluoroquinolone than levofloxacin, e.g., a C-8-methoxyquinolone, which exerts more pronounced anti-pneumococcal activities than levofloxacin [4].

Recently, fluoroquinolone-resistant streptococci were isolated from children. Ciprofloxacin resistance rates in the US increased significantly between 1997 and 2006 from 0 to 4.5 % in children aged 0–15 years [112]. Fluoroquinolone-resistant streptococci were also isolated from children in Spain [113]. Ciprofloxacin-resistant *S. pneumoniae* was detected in 28 % of children aged 6–60 months living in rural Vietnam, about half of whom were treated previously with antibacterial agents except fluoroquinolones [114]. These findings could be due to the transmission of fluoroquinolone-resistant strains within daycare centers or the household from adults to children.

The emergence of levofloxacin-resistant *S. pneumoniae* strains was noted in South Africa, where fluoroquinolones are used to treat multidrug-resistant tuberculosis. A survey of 21,521 invasive pneumococcal isolates identified between 2000 and 2006 in South Africa detected levofloxacin

resistance (MIC ≥4 μg/mL) in only 12 cases (<0.1 %) [115]. All were HIV-infected children, nine were on therapy for tuberculosis, and 10 isolates (83 %) were serotype 19F, suggesting clonal spread. Furthermore, levofloxacin-resistant pneumococci were detected in >50 % of asymptomatic carriers (irrespective of prior exposure to fluoroquinolones). These data suggest that the use of fluoroquinolones to treat multidrug-resistant tuberculosis is a risk factor for the endemic and clonal spread of fluoroquinolone-resistant pneumococci. Furthermore, horizontal gene transfer may have transformed low-level into high-level levofloxacin-resistant strains [116].

Several factors may have contributed to the low resistance rates in *S. pneumoniae*: more potent "respiratory fluoroquinolones" like the C-8-methoxyquinolones moxifloxacin and gatifloxacin, or gemifloxacin may have replaced the previous fluoroquinolones in the treatment of CARTIs; treatment guidelines may have been adapted recommending the use of a second agent like benzylpenicillin in, e.g., the elderly or patients with other risk factors; information about patient history and previous antibiotic use is crucial for determining appropriate empirical therapy [117, 118]; the acquisition of some *parC* and *gyrA* mutations may impose a fitness cost to the first-step fluoroquinolone-resistant strains, although equivocal data have been generated [119–121].

*H. influenzae* is generally highly susceptible to fluoroquinolones; global surveillance studies demonstrated that susceptibility to fluoroquinolones remained at or near 100 %; resistant isolates have been recovered occasionally (reviewed in [13]). Clonal outbreaks of fluoroquinolone-resistant *H. influenzae* were observed in long-term care facilities [122–124] and in the elderly in Japan [125]. Because of the occurrence of fluoroquinolone-resistant strains, Hirakata et al. [126] screened a total of 400 *H. influenzae* strains isolated in 138 hospitals throughout Japan. The strains were consistently very susceptible to ciprofloxacin, with MICs ranging from ≤0.03 to 0.25 mg/L; the majority of strains was inhibited by ciprofloxacin concentrations ≤0.03 mg/L. Therefore, the authors examined the strains ($n = 37$ out of 400) with MICs 0.06 mg/L and higher for QRDR mutations. From these, one ciprofloxacin-resistant isolate (MIC 16 mg/L) and 31 ciprofloxacin-susceptible isolates (MICs 0.06–0.5 mg/L) had amino acid changes in their QRDRs. Moreover, 9.8 % of the 363 highly ciprofloxacin-susceptible isolates (MICs ≤0.03 mg/L) had mutations in their QRDRs, particularly in the case of β-lactamase-positive amoxicillin–clavulanate-resistant isolates [126]. Primed strains could be isolated from kindergarten children in Hong-Kong [127] and caused treatment failures in the elderly [128].

These data clearly demonstrate that—in analogy to *S. pneumoniae*—many fluoroquinolone-susceptible *H. influenzae* have acquired QRDR mutations; these strains pass routine susceptibility testing unnoticed, but are primed to mutate further. Routine susceptibility testing of suspicious cases should at least be modified, e.g., by using nalidixic acid as an indicator for the acquisition of a first mutation [129].

*M. catarrhalis* remains fluoroquinolone susceptible to almost 100 %, although resistant strains have been detected in a very few single cases (reviewed in detail in [13]); a fluoroquinolone resistance rate of 15.9 % has been reported from India [130]. Two treatment failures with clonally unrelated resistant strains have been reported in patients at risk [131].

### *Healthcare acquired respiratory tract infections*

Nosocomial pneumonia is further differentiated into healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). Bacterial pathogens most frequently associated with HCAP, HAP, and VAP are MSSA and MRSA, *P. aeruginosa*, *H. influenzae*, *K. pneumoniae*, *E. coli*, and, occasionally, (2–5 %) *S. pneumoniae* and *Acinetobacter* spp. Resistance surveillance studies differentiating the origin of isolates tested according to pneumonia categories are almost non-existent; resistance rates are quoted in very general terms, even in some of the guidelines quoted above. Therefore, the information compiled below summarizes the susceptibility data for invasive pneumococci or pathogens isolated from sputa obtained preferably from intensive care unit (ICU) patients.

Fluoroquinolone resistance in *S. pneumoniae* isolated from patients with invasive as well as non-invasive diseases in eight European countries and Latin America ranged from 0 % in Austria, Switzerland, and Belgium to 0.9 % in Germany and 1.2–1.3 % in Italy and Portugal [132]. From the bacteremic pneumococci isolated from 1999 to 2007 in the UK and Ireland, 14.3 % were resistant to ciprofloxacin [133]. In Canada, all bacteremic isolates were ciprofloxacin susceptible [134, 135]. Rates of levofloxacin resistance in invasive *S. pneumoniae* collected by the Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance (ABCS) program remained stable throughout the years at about 0.3–0.43 % [136–138]. This finding contradicts reports of an expansion of fluoroquinolone-resistant seven-valent pneumococcal conjugate vaccine serotypes [113, 139–141]; others have hypothesized that a decrease in fluoroquinolone resistance among invasive pneumococci may be due to the reduction of absolute numbers of isolates within the vaccine serotypes [142]. Nevertheless, the potential for the clonal expansion and dissemination of fluoroquinolone-resistant strains obtained from the ABCS program has been

demonstrated [140]. A random sample of ABCS isolates collected between 1998 and 2003 revealed that 16.2 % of first-step mutants were recovered from nursing home patients and 6.4 % from non-nursing home patients [143].

Pathogens isolated from ICU patients showed variable fluoroquinolone resistance [144]. Pneumococci collected in the USA, Canada, France, Germany, and Italy from January 2000 to December 2002 were highly susceptible in all geographic regions. All *H. influenzae* blood isolates were ciprofloxacin susceptible as well [134]. In MSSA and MRSA, fluoroquinolone resistance varied from 4.8 % in Canada to 8 % in Germany, and from 90.6 % in France to 9.6 % in Germany, respectively. In *E. coli*, fluoroquinolone resistance ranged from 6.5 % in France to 12.7 % in Italy; resistance in *K. pneumoniae* ranged from 7.2 % in Canada to 9.9 % in Italy; resistance in *P. aeruginosa* ranged from 22.9 % in Germany to 76.7 % in Italy [144]. Ciprofloxacin resistance among MSSA and MRSA blood and respiratory isolates collected in 2008 amounted to 8–11 % and 81.6–95.6 %, respectively [135]. Ciprofloxacin resistance rates in *E. coli*, *P. aeruginosa*, and *K. pneumoniae* isolated from blood or the respiratory tract were 21.6 or 31.7 %, 16 or 18.4 %, and 4.3 or 4.5 %, respectively. Eight percent of these *E. coli* isolates were ESBL producers [135]. In ten Asian countries, ciprofloxacin resistance rates in *P. aeruginosa*, *E. coli*, and *K. pneumoniae* isolated from HAP and VAP patients ranged from 4 to 44 %, 26 to 80 %, and 13 to 68 %, respectively [145]. Similar rates were reported for Gram-negative species isolated from Indian VAP patients [146].

Fluoroquinolones have, in the past, shown good activity against *A. baumannii* [147]; however, over the past decade, there has been a constant rise in fluoroquinolone and multidrug resistance [148, 149]. Fluoroquinolone resistance in *Acinetobacter* spp. isolated from HAP and VAP patients in ten Asian countries varied from 23.2 to 92 % [145]. Fluoroquinolone resistance in *Acinetobacter* spp. isolates from North American and European ICU patients with/without nosocomial RTIs ranged from 25.9 % in Canada to 76.7 % in Italy [144]. Fluoroquinolone resistance in *A. baumannii* isolates sampled from sputa and tracheal aspirates of ICU patients in a tertiary-care hospital in Ankara amounted to 86 % [150].

### *Conclusion*

Three major pathogens causing CARTI are fluoroquinolone susceptible to almost 100 %. However, first-step mutants have been detected frequently not only in treated patients, but also in healthy individuals and even children. Such isolates are primed to mutate to high-level fluoroquinolone resistance during subsequent fluoroquinolone treatment. Pneumococci and haemophili isolated from HCAP, HAP, and VAP patients are almost all fluoroquinolone susceptible. MSSA and, in particular, MRSA are frequently fluoroquinolone resistant. *Enterobacteriaceae* and non-fermenters are variably fluoroquinolone resistant, so that the regional resistance pattern has to be considered prior to the use of a fluoroquinolone in the treatment of nosocomial pneumonias.

## Skin and skin structure infections

Acute bacterial skin and skin structure infections (ABSSSIs) are typically monomicrobial and caused by *S. aureus* and *S. pyogenes*, which are also the most common pathogens in complicated skin and skin structure infections (cSSSIs), which are frequently polymicrobial. The most common Gram-negative organisms in cSSSIs include *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and *E. cloacae*. The most common anaerobes isolated are typically *Prevotella*, *Bacteroides*, and *Peptostreptococcus* species.

Although *S. pyogenes* was and still is highly susceptible to fluoroquinolones, low incidences ($\leq$8 %) of ciprofloxacin resistance have been found in the US, Canada, and Europe. Fluoroquinolone resistance in Japan is almost non-existent [151–157]. It is important to note that, in Belgium, approximately 55 % of the fluoroquinolone-resistant *S. pyogenes* isolates were recovered from children aged <16 years [158]. Although fluoroquinolones are contraindicated in children, ciprofloxacin is often used off-label for select life-threatening conditions. Furthermore, older and, thus, cheap second-generation fluoroquinolones are used topically for the treatment of otitis media with otorrhea through tympanostomy tubes in pediatric patients [158].

In the early days of fluoroquinolone development and clinical use, the fluoroquinolones were regarded as potential alternatives to MRSA therapy with a $\beta$-lactam, vancomycin or imipenem [1, 159, 160]. Unfortunately, staphylococci acquire resistance to antibacterials rapidly, as they are genetically highly variable [161]. The determinant for methicillin resistance (SCC*mec*) contains additional genes for antibiotic resistance elements encoding for aminoglycoside, tetracycline, and macrolide–lincosamide–streptogramin resistance [162, 163]. Furthermore, HA-MRSA tended to develop fluoroquinolone resistance [164, 165] and increased pathogenicity [166, 167]. Thus, almost any antibacterial drug class has a methicillin resistance selective potential [168–171], so that strains of HA-MRSA are almost always multidrug resistant. Therefore, fluoroquinolone resistance developed rapidly in the early days of fluoroquinolone therapy in HA-MRSA. In addition, fluoroquinolone-resistant HA-MRSA were spread horizontally as were HA-MRSA as such, so that, nowadays, neither the second- nor third-generation fluoroquinolones represent alternatives for the treatment of HA-MRSA infections [4, 172, 173].

In recent years, the emergence of CA-MRSA has complicated the treatment of even ABSSSI [174]. In contrast to multidrug resistance usually seen in HA-MRSA strains, antibiotic resistance in CA-MRSA was most often limited to macrolides [163, 174–178], so that it has previously been proposed that some third-generation fluoroquinolones could be useful in the treatment of CA-MRSA, since the causative pathogens were usually susceptible to even ciprofloxacin [179–184]. But, recently, mupirocin, tetracycline, clindamycin, and moxifloxacin (and, thus, to any commercially available fluoroquinolone) resistance development has been reported [185, 186]. The clone USA300 became the predominant strain type in the USA and has spread to Europe, South America, and Australia [185, 187, 188]. The lineage USA100 is frequent as well [189]. Fluoroquinolone resistance in isolates recovered from a phase IV study in patients with cSSSI in the USA and Europe from 2004 to 2007 was high; 100 % of USA100 isolates and 42.6 % of USA300 isolates were resistant to gatifloxacin [189]. cSSSI pathogens collected in USA and Europe in 2009 were variably susceptible to fluoroquinolones: levofloxacin resistance in the USA/Europe amounted to 70.3/84.1 % in MRSA, 11.1/5.4 % in MSSA, 54.2/52.3 % in coagulase-negative staphylococci, 0.9/0.0 % in $\beta$-hemolytic streptococci, 13.6/1.1 % in viridans streptococci, 37/29.2 % in *E. faecalis*, 24.7/21.8 % in *E. coli*, 11/13.3 % in *Klebsiella* spp., and 20.8/8.0 % in *P. mirabilis* [190]. These resistance rates are within the same range as those reported in the late 1990s and 2001–2004 for Gram-negative and Gram-positive aerobic pathogens isolated in North America, Latin America, and Europe from skin and soft tissues [191–194], thus, indicating that resistance rates did not change substantially over time.

Overall, 24–27 % of anaerobic bacteria isolated in the late 1990s from skin and soft tissue infections and moderate to severe diabetic foot infections were fluoroquinolone resistant [190, 191, 195]. All *Peptostreptococcus* species isolated from hospitalized patients with diabetic foot wound infection were susceptible to levofloxacin and moxifloxacin; moderate resistance (5–7 %) was found in isolates of *B. fragilis*, *B. ovatus*, and *Prevotella* species [196, 197]. Moxifloxacin resistance was highest (43 %) in the *B. fragilis* group [277]. As levofloxacin is less active against anaerobes, resistance rates were correspondingly higher. Of all infection sites, decubitus ulcer isolates had the highest resistance rates [198].

### *Conclusion*

Fluoroquinolone resistance rates among pathogens causing skin and soft tissue infections is low in MSSA and streptococci, moderate in Gram-negative aerobes as well as Gram-positive anaerobes, and high in CA-MRSA, HA-MRSA, and Gram-negative anaerobes. This heterogenous susceptibility pattern may limit the use of fluoroquinolones in the treatment of ABSSSIs and cSSSIs. In principle, a third-generation fluoroquinolone is well suited for the treatment of polymicrobial SSSIs because of its broad antibacterial spectrum.

## Intra-abdominal infections

Intra-abdominal infections (IAIs) are commonly due to mixed aerobic and anaerobic populations, so that a clinically effective regimen has to cover both the aerobic *Enterobacteriaceae* and enterococci, as well the anaerobic bacteria. Several surveillance studies have demonstrated that there is, since two decades, a global trend towards decreasing susceptibilities of anaerobes to antibacterial agents in general. Although the rates of resistances show clinically important variations between continents, countries, and counties, all drug classes except metronidazole lose activity against anaerobes. As reviewed in detail recently [13], fluoroquinolone resistance in both aerobes and anaerobes causing IAIs is high in the Asian–Pacific region, the USA, and Europe; 9 to >50 % of the Europe and US *B. fragilis* group isolates were moxifloxacin resistant. In analogy to UTI isolates, fluoroquinolone resistance in *Enterobacteriaceae* causing IAIs is closely linked to ESBL production [13].

The situation in Asia is concerning, as resistance rates surpass 60 % of the isolates being resistant to ampicillin–sulbactam or a quinolone and producing ESBLs [13]. In Europe, ESBL production ranged from 0 to 30 %. From these, 70–78 % and 50–70 % of the community- or hospital-acquired *Enterobacteriaceae*, respectively, were ciprofloxacin resistant. Consequently, fluoroquinolone susceptibility in IAI pathogens is still high in all those geographic regions in which ESBL-producing Gram-negative bacilli are infrequent. Furthermore, fluoroquinolone resistance was much lower in strains isolated from patients with community-acquired IAIs than in those from hospital-acquired infections.

### *Conclusion*

Fluoroquinolone resistance is high amongst aerobic and anaerobic intra-abdominal pathogens. Therefore, the Infectious Diseases Society of America (IDSA) and the Surgical Infection Society published a guideline in late 2009 recommending that antibacterials to be used in the empiric treatment of even community-acquired IAIs including mild to moderate infections should be active against both aerobic and anaerobic pathogens [199]. Consequently, the use of quinolones should be restricted unless resistance rates are <10 % [7, 282].

## Sexually transmitted diseases

Infections caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most frequent ones among reportable bacterial sexually transmitted diseases (STDs) gonorrhea, syphilis, and chancroid.

Pelvic inflammatory disease (PID) is a common and serious complication of some STDs. Two-thirds of cases are considered to be due to sexually transmitted infections caused by *N. gonorrhoeae* and *C. trachomatis*. Other pathogens such as *Mycoplasma genitalium* and, rarely, bacterial vaginosis pathogens may cause PID too. Therefore, the management of PID must take into account in particular the three major pathogens *N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium*.

### *Neisseria gonorrhoeae*

Initially, *Neisseria* spp. was extremely susceptible to fluoroquinolones with ciprofloxacin MICs $\leq$0.008 mg/L. However, low-level resistance (0.06–0.5 mg/L) was reported shortly after its launch, followed soon after by high-level resistance (MICs of ciprofloxacin >1.0 mg/L) associated with treatment failures. High-level fluoroquinolone resistance is more likely to emerge in areas with a high prevalence of low-level resistance and is spread intercontinentally or within and between cities by travelers. Both low- and high-level fluoroquinolone resistance has been reported from all parts of the world (reviewed in [13, 200]), ranging in Asia from 40 to 100 % and from 15 to 30 % in Europe and North America. Consequently, quinolones are no longer recommended as the first-line therapy for *N. gonorrhoeae* infections [201–203].

Typically, several different strain types can be identified, but only a few of these were considered to be outbreak types and comprised 66 % of all the isolates [204]. Furthermore, importation (often repeated importation) of one or a few clone(s) and ultimate introduction into established sexual networks have caused the emergence and spread of resistant gonococci rather than de novo emergence as a result of selection by quinolone use or misuse [205].

### *Chlamydia trachomatis*

High-level resistance to ofloxacin, sparfloxacin, and ciprofloxacin occurred in *C. trachomatis* upon serial exposure to subinhibitory quinolone concentrations, whereas spontaneous mutation frequencies resulting in moxifloxacin resistance were very low or even non-existent. Nevertheless, fluoroquinolone-resistant strains of *C. trachomatis* have been isolated occasionally. However, no mutations could be detected in these clinical isolates. Fluoroquinolone resistance elicited in vitro in *C. trachomatis* serovar $L_2$ was due to a single nucleotide point mutation in *gyrA*, while no mutations were found in the *gyrB*, *parC*, or *parE* genes (reviewed in [13]).

### *Mycoplasma genitalium*

Surveillance studies for antimicrobial resistance in general and fluoroquinolone resistance in particular are non-existent, as the culturing of this species from clinical specimens is extremely difficult. Acquired resistance to fluoroquinolones has been described in single cases. QRDR mutations have been described rarely (reviewed in [13]).

### *Conclusion*

The resistance of *N. gonorrhoeae* to antimicrobials continues to increase worldwide, although considerable geographical variations in resistance exist. Therefore, fluoroquinolones are no longer recommended as the first-line therapy for *N. gonorrhoeae* infections [201–203]. However, local quinolone treatment options based on local surveillance data may be reasonable, due to the geographical variations in resistance. All regimens used to treat PID should cover both *N. gonorrhoeae* and *C. trachomatis*, so that the use of fluoroquinolones in this indication is limited as well [206]. In case parenteral $\beta$-lactam therapy is not feasible, oral use of fluoroquinolones with or without metronidazole is recommended, provided treatment is based on the results of antimicrobial susceptibility testing [206].

## Effect of fluoroquinolones on commensals and colonizers

The impact of fluoroquinolone administration on the fecal and oropharyngeal flora has been summarized comprehensively [207–211]. Fluoroquinolones affect quantitatively (total numbers of aerobic and anaerobic species) and qualitatively (selection of resistance) the resident flora. Such studies are routinely performed in healthy and young volunteers who may not have been treated with antibacterials since quite a while prior to the administration of the study drug.

Studies in patients are scarce, although it could be anticipated that fluoroquinolone resistance would emerge in pharyngeal streptococci, thus, generating a scenario resembling that of a worldwide spread of $\beta$-lactam resistance in pneumococci [212]. In particular, the selection of fluoroquinolone-resistant viridans group streptococci in neutropenic patients during therapy or prophylaxis with second-generation fluoroquinolones with weak anti-pneumococcal activity is of concern [213–216]. Gatifloxacin and also moxifloxacin (most of the patients received

concomitantly penicillin) selected for resistance [217]. On average, fluoroquinolone resistance in viridans streptococci emerged after 8 days of exposure to either fluoroquinolone. The hypothesis that fluoroquinolones with weak antipneumococcal activity may select for fluoroquinolone resistance among viridans streptococci has been studied recently [218]. Six different 14-day dosages of oral ciprofloxacin were administered to 48 healthy volunteers. Individual pharmacokinetic and pharmacodynamic parameters combining antibiotic exposure in plasma, saliva, and feces, and MICs of ciprofloxacin for viridans group streptococci in the pharyngeal flora were estimated. Their links with the emergence of resistance to levofloxacin 7, 14, or 42 days after ciprofloxacin initiation were investigated. Resistance emerged in the pharyngeal flora in 33 % of the subjects, mainly when local concentrations of ciprofloxacin were less than the MIC. Probabilities of the emergence of resistance were not significantly different across the different antibiotic dosages. This analysis confirms that resistant commensals are selected frequently during ciprofloxacin therapy and is not preventable by dosage optimization. Analogous results were obtained for *E. coli* isolated from the feces of the volunteers [218].

Having established the important role of commensal flora as a natural reservoir of bacterial resistance to fluoroquinolones, investigators analyzed prospectively the colonization with fluoroquinolone-resistant bacteria in the three main commensal floras from 555 hospitalized patients at admission, targeting *E. coli* in the fecal flora, coagulase-negative staphylococci in the nasal flora, and α-hemolytic streptococci in the pharyngeal flora [219]. Fluoroquinolone resistance carriage rates were 8.0 % in *E. coli*, 30.3 % in coagulase-negative staphylococci, and 27.2 % in streptococci; 56 % of the patients carried resistance in at least one flora, but only 0.9 % carried resistance simultaneously in all floras, which is no more than random. Risk factors associated with the carriage of fluoroquinolone-resistant strains differed between fecal *E. coli* (i.e., colonization by multidrug-resistant bacteria) and nasal coagulase-negative staphylococci (i.e., age, healthcare facility residents, and previous antibiotic treatment with a fluoroquinolone), while no risk factors were identified for pharyngeal streptococci [219].

Horizontal gene transfer between viridans streptococci and pneumococci has been proven [220–225]. Such events could contribute significantly to the spread of resistance in infectious foci with high population density [226]. However, the contribution of horizontal gene transfer and interas well as intraspecies recombination to the emergence of fluoroquinolone resistance in *S. pneumoniae* seems to be minimal [221, 222]. However, penicillin resistance emerged about 50 years after the commercialization of penicillin G.

Furthermore, gene transfers between *S. pyogenes* and group C/G streptococci has been demonstrated [223, 227–229], so that the acquisition of fluoroquinolone resistance by *S. pyogenes* may put the patient at risk. Group A streptococci frequently colonize the throats of asymptomatic persons. Pharyngeal carriage rates vary geographically, seasonally, and with the age of the patient [230]. Carriage of *N. meningitidis* in the nasopharynx has been known for a long while; 18 % of the population are carriers [231]. Household members and other close contacts of persons with meningococcal disease have a higher risk for carriage and, therefore, invasive disease. These persons should receive an antibiotic prophylaxis; previously, ciprofloxacin has been considered as an effective single-dose oral prophylactic agent. However, isolates of *N. meningitidis* with decreased fluoroquinolone susceptibility or even resistance are becoming globally more frequent [232–247], so that contact persons should no longer be prophylaxed with a fluoroquinolone [233]. Nalidixic acid should serve as a surrogate marker in order to detect fluoroquinolone-resistant *N. meningitidis* [248]. Similarities in the mechanisms of fluoroquinolone resistance in *N. gonorrhoeae* and *N. meningitidis* have prompted concerns that resistance prevalences will be similar in both species in due course [244].

Fluoroquinolone-resistant *S. pyogenes* strains have been isolated worldwide in children and adults [151–157, 249–255]. Furthermore, interspecies recombinations between *S. pyogenes* and group C/G streptococci colonizing the skin have been demonstrated [226, 228]; group C/G streptococci may have acquired fluoroquinolone resistance from the environment. Although marketing authorizations for the treatment of infections caused by *S. pyogenes* (except SSSIs) have not been granted, fluoroquinolones may, in principle, offer a therapeutic alternative in penicillin-allergic cases. However, the emergence of fluoroquinolone-resistant *S. pyogenes* strains limits the use of quinolones in such cases.

In general, QRDR-mediated fluoroquinolone resistance was found to be stable in clinical isolates and laboratory-derived mutants of Gram-positive cocci and Gram-negative bacteria [246, 256–259], so that fluoroquinolone resistance is irreversible and affects the long-term use of these agents.

## *Conclusion*

Fluoroquinolone resistance has been selected among the commensal flora colonizing the gut, nose, oropharynx, and skin, so that horizontal gene transfer between the commensal flora and the offending pathogen, as well as inter- and intraspecies recombinations, contribute to the emergence and spread of fluoroquinolone resistance among pathogenic streptococci. Although interspecies recombinations are not yet the major cause for the emergence of fluoroquinolone resistance, its existence indicates that a

large reservoir of fluoroquinolone resistance exists. Thus, a scenario resembling that of a worldwide spread of $\beta$-lactam resistance in pneumococci is conceivable.

## Discussion

Fluoroquinolone resistance rates increased in the past several years in almost all bacterial species. Furthermore, high numbers of first-step QRDR mutants or otherwise primed bacteria were recorded, which pass susceptibility testing unnoticed but may put the patient at risk. The continued increase in fluoroquinolone resistance affects patient management and necessitates changes in some current guidelines for the treatment of UTIs [5, 37, 87–89] or typhoid fever [6], and even precludes the use of fluoroquinolones in certain indications like complicated IAIs [7] and gonorrhea and PID [201–203]. Two extremes have caused the CDC to advise physicians not to treat patients with *N. gonorrhoeae* infections and not to prophylax close contacts of *N. meningitidis* cases. On the one hand, fluoroquinolone resistance in *N. gonorrhoeae* approaches 100 % in many regions, and on the other hand, fluoroquinolone resistance in *N. meningitidis* is certainly rare, but meningococcal disease causes substantial morbidity and mortality; those who survive suffer from long-term sequelae. Therefore, the advice of the CDC to no longer use fluoroquinolones in these two indications is more than justified, despite the two extremes of fluoroquinolone resistance rates in these two species. However, once granted, marketing authorizations are still valid, although the CDC advised and the infectious diseases societies strongly recommended not to use fluoroquinolones in the above mentioned indications.

Because of the highly variable fluoroquinolone resistance rates, the following questions have to be raised:

1. At which threshold of resistance should an agent no longer be used empirically?
2. Does local variability allow a generalizing nationwide recommendation to refrain from using a given drug in specific drug/bug associations?
3. Is the key denominator for result interpretation the clinical source of the isolate and patient condition or just the bacterial species as such?
4. Are datasets biased, as isolates from hospitalized and/or difficult to treat patients may be over-represented?
5. Who is the user of the data?

### 1. Resistance treatment threshold

Recently published guidelines suggest different threshold levels for different infectious diseases. The IDSA and the Surgical Infection Society published a guideline in late 2009 recommending that the use of quinolones in the empiric treatment of community-acquired IAIs including mild to moderate infections should be restricted unless resistance rates are lower than 10 % [7]. The IDSA and American Thoracic Society released guidelines suggesting a 25 % rate of high-level macrolide resistance as a threshold at which macrolides should no longer be used as empirical therapy for the treatment of CAP [260]. This definition has been debated controversially [261–263]. Other guidelines on the use of antibacterial agents in patients with CA-UTI suggest thresholds of 10, 20, or 30 % [87, 264–266]. The previous EMEA note for guidance states that all species for which the prevalence of resistance has reached 10 % or more should be categorized as "species for which acquired resistance may be a problem" [267].

These examples demonstrate that the question remains unanswered regarding at which resistance rates should a given drug no longer be used as empirical therapy. The problem is that, on the one hand, thresholds are defined by expert consensus, but, on the other hand, such threshold levels are not linked to clinical outcomes or patient populations. By linking the prevalence of macrolide resistance to patient outcome, it was demonstrated that the previously defined threshold was inadequate and underestimated the risk of failure [262]. It was shown that low-level macrolide resistance contributes significantly to treatment failures and deaths [261–263], so that the threshold should be modified. The same may hold true for fluoroquinolones as well. Breakpoint-defined fluoroquinolone resistance rates in *S. pneumoniae* and *H. influenzae* are low; however, it has been demonstrated that approximately 30 % of the isolates have already acquired first-step QRDR mutations [98–109, 126]. Such isolates pass routine susceptibility tests unnoticed and are categorized as susceptible; however, they are primed to mutate rapidly to high-level fluoroquinolone resistance, so that inadequate therapy with a second-generation fluoroquinolone may fail as demonstrated clinically [110, 111, 128]. Therefore, routine susceptibility testing of suspicious cases should be modified by using a second-generation fluoroquinolone or nalidixic acid as an indicator for the acquisition of a first-step mutation in *S. pneumoniae* or *H. influenzae*. The most recent IDSA and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis make another problem evident. Concern was raised that an association exists between fluoroquinolone use and increased rates of MRSA [265]. Therefore, fluoroquinolones should "be reserved as an alternative only when other UTI agents cannot be used". As discussed in the section titled "Sexually transmitted diseases", almost any antibacterial drug

class including fluoroquinolones has a methicillin resistance selective potential [168–171]. But not all fluoroquinolones are alike. Ciprofloxacin and levofloxacin are good selectors, and moxifloxacin is a poor selector of methicillin resistance [164, 165]. Poor hygiene is another factor contributing to the selection and spread of MRSA. The implementation of a hand hygiene program combined with restricted fluoroquinolone use resulted in a ten-fold greater reduction of MRSA infections as compared to just restricted fluoroquinolone use [268]. Another association between fluoroquinolone resistance and $\beta$-lactam resistance exists in particular among UTI and IAI isolates, as summarized in the sections titled "Urinary tract infections" and "Intra-abdominal infections". Plasmid-coded ESBL production is often linked to the co-synthesis of pentapeptide repeat (Qnr) proteins [269]. These proteins reduce susceptibility to quinolones by protecting the complex of DNA and DNA gyrase or topoisomerase IV enzymes from the inhibitory effect of quinolones. Again, most of such isolates co-expressing ESBLs and Qnr proteins are fluoroquinolone susceptible and pass routine susceptibility testing unnoticed. Of concern, ESBL production and reduced fluoroquinolone susceptibility are associated with additional resistance elements and emerge and expand simultaneously with increasing ubiquity [269]. Thus, two pools of primed bacteria exist which are prone to acquiring additional mutations under fluoroquinolone treatment, i.e., low-level resistant first-step QRDR mutants and isolates harboring plasmid-encoded fluoroquinolone resistance. In addition, fluoroquinolones exhibit an MRSA-selective potential, so that a considerable potential for adverse ecological effects exists. The so called "collateral damage" from the use of fluoroquinolones may put patients at risk [270]. Therefore, definitions of resistance thresholds should not only consider resistance statistics, but, in addition, the implications for patient outcome, the collateral damage, the risks of clinical failure that are associated with low-level resistance, and the development and costs of future resistance should be taken into account.

## 2. Resistance surveillance: a global or de facto regional approach?

A major drawback of many surveillance studies is that the number of national centers participating is often limited. For example, 198 laboratories from 22 European countries participated in the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS) study, 2002 to 2009; the numbers of laboratories per country ranged from one to 33, with the consequence that the mean numbers of *E. coli* and *S. aureus* isolates reported yearly per country ranged from 96 to 1,973 and from 56 to 1,290, respectively [271]. Consequently, the size as well as the patient characteristics (i.e., age, co-morbidities, hospitalized vs. outpatient, etc.) of the catchment population is highly variable. Many studies on the resistance epidemiology describe changes in resistance trends in one hospital or even one ward only. The epidemiology of resistance varies locally, regionally, nationally, and internationally, so that strains may have been included originating from pockets with unusual resistance patterns. Resistance clusters exist prohibiting the use of an affected agent in such areas; vice versa, the drug can be used in low-risk areas or conditions [272]. Overall resistance rates aggregating drug/bug data have little relevance and are often misleading. Consequently, most surveillance studies reporting resistance rates for a given drug/bug association are basically point prevalence studies representing a local *resistance frequency* but do not provide information about the *resistance epidemiology*, *prevalence*, or *incidence*.

## 3. Key denominator for results interpretation

The choice of sampling methods and organisms as well as the selection of the host population to be sampled has a fundamental impact on the outcome of surveillance studies. For example, 53.8, 9, and 3.3 % of *P. aeruginosa* isolated from patients with cystic fibrosis, moderate to severe diabetic foot ulcers, and keratitis, respectively, were resistant to ciprofloxacin [273–276]. Furthermore, chronically infected patients will be sampled repeatedly. As these patients receive long-term therapy, the causative pathogen will likely have acquired resistance; in addition, hospitalization or residence in a nursing home favors the acquisition and selection of fluoroquinolone-resistant populations [1, 26, 29, 30]. Such isolates have a significant impact on the susceptibility pattern of strain collections studied and, consequently, on resistance statistics, as resistant subpopulations or clones will be over-represented [1, 9].

In hospital-based studies, isolates predominate which have been sampled from hospitalized patients and a small percentage originates from outpatient treatment. This is problematic in so far as the patient population within and between hospitals is diverse (e.g., age, risk factors, tertiary- or primary-care hospital, etc.), so that significant differences in drug susceptibilities were recorded across different hospital departments, between different hospitals, and between in- and outpatients, respectively [277]. Hospital-wide reports can mask differences large enough to affect the appropriate choice of an adequate antibacterial. Therefore, arguments reviewed previously [4] or published recently [278–283] confirm that there is a systematic bias in surveillance based on routinely collected data, leading to an overestimation of true resistance rates.

Therefore, it is crucial to define the patient population to be sampled and to stratify data collection and interpretation

according to infection site and disease status in order not to compromise the denominator material. It is essential not to collect in very general terms species-specific laboratory-based surveillance data, but, instead, to use infection-based information stratified according to the severity of disease, patient population, and risk profile [284]. Otherwise, initial therapy may be inadequate, either putting the patient at risk [285] or fostering resistance development because of an indiscriminate use of antibacterials [286].

4. Biased datasets

Fluoroquinolones are most frequently prescribed by general practitioners to outpatients. However, outpatients are sampled only when initial therapy has failed and in whom resistant subpopulations will likely have been selected [279]. In 57 % of all contacts, and even 100 % of the patients who consulted the general practitioner for the first time, an antibacterial was issued for RTIs; an antibiogram was ordered in none of the cases [280]. Similar, but varying by physicians' speciality, data were reported for the diagnosis and management of UTIs. Urine culture reports were misleading in many cases, as cultured patients differed from the majority of patients treated empirically; cultured patients had higher rates of comorbidities, severity of illness, and previous antibacterial therapies than the majority of patients treated empirically [287]. The leading reasons given for not ordering a culture were that it was too costly (76 %) and that species specification and susceptibility testing rarely affect treatment (74 %) [288]. Resistance in pathogens causing uUTIs was rarer than that predicted from susceptibility testing [289]. The Dutch guidelines for the diagnosis and treatment of severe gastroenteritis by general practitioners state that stool samples should be obtained, but this advice was followed in 22 % only [290]. Additional studies supporting the notion that routine samples are biased have been reviewed by the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) and its subgroups [291]. Among the studies reviewed by Hayward et al. [292], seven have shown significant differences in resistance levels between routine samples and those taken selectively; one study could not find a correlation between antibiotic use and resistance, and another study could not demonstrate a relationship between the urine submission rate and resistance after controlling for prescription and other variables. However, these two latter studies do not falsify the theory of sampling bias in unselected versus selected samples. A longitudinal community-based study among outpatients between September 2003 and September 2004 revealed, on the one hand, that the prevalence of fluoroquinolone-resistant *E. coli* cultured from *unselected* samples remained unchanged (7.7 %) prior to, during, and after fluoroquinolone treatment [293]. On the other hand, a German surveillance study revealed that fluoroquinolone resistance among outpatients from whom samples were *selectively* withdrawn was almost twice as high as in unselected samples (14.4 %) in 2001 and this increased to 29.2 % in 2007 [294–296]. Thus, there is a systematic sampling bias in surveillance data based on routinely collected specimens sampled by general practitioners. Selective testing in difficult to treat patients or a situation of treatment failure does not reflect the resistance epidemiology in the majority of outpatients to be treated effectively and successfully with the appropriate regimen by the general practitioner. Furthermore, ignoring intercenter variation and differences in the numbers of samples collected per center leads to erroneous conclusions about resistance frequencies [297]. These examples demonstrate that drug susceptibilities should be reported unit-specifically and disease-specifically rather than in species-specific cumulative figures as actually done by the pharmaceutical industry upon request by the regulatory authorities.

5. Who is the addressee?

The data generated from surveillance studies are used by microbiologists, prescribing physicians, infection control specialists, in diagnostic and reference laboratories, by public health authorities, regulatory authorities, industry and academia, and by politicians. These users have different interests in the data. The microbiologist needs data on the prevalence and the infection control specialist needs data on the incidence of resistance. The prescribing physician needs local data and authorities need national or even continental data. Industry is interested in broad-range surveillance data on the phenotype of resistance and academia in organism-specific information on the genotype of resistance.

The actual procedure meets the requirements of both the pharmaceutical industry and the regulatory authorities. The pharmaceutical industry needs the data for regulatory purposes and marketing, and the regulatory authorities need the data for risk assessment. The EMEA requests a regular update of surveillance data to be reported in the periodic safety update report; resistance development is considered to be an adverse event putting the patient at risk. However, while incidences of any other adverse event are reported to the EMEA, the results of resistance surveillance studies are reported without any correlation to neither the total nor disease-specific number of patients treated.

In contrast, the expectations of the treating physicians are not always met. They often misinterpret susceptibility testing, so that an inadequate antibacterial is prescribed [298, 299]. In one institution, only one in five of all

susceptibility tests contributed to an adequate treatment and only 8.5 % led to a change in therapy [300]. General practitioners reported that 83 % of susceptibility reports were seen as beneficial and 28 % led to a change of therapy [300].

The interests are diverse, but the datasets are most frequently monotonous. Tools should be developed to provide customer-specific datasets. Actually, the requirements of the users are often not met, so they exploit the data incongruously. In conclusion, surveillance studies are of utmost importance in order to detect and monitor the emergence and longitudinal development of resistance. However, for the results to be of value, the samples collected, the data generated, and the information published and distributed must be unbiased. Several factors discussed above lead to obvious but uncorrected biases. Consequently, many studies are misinterpreted.

**Conflict of interest** The author declares that he has no conflict of interest.

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