

Review Article

Global Fluoroquinolone Resistance Epidemiology and Implications for Clinical Use

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This paper on the fluoroquinolone resistance epidemiology stratifies the data according to the different prescription patterns by either primary or tertiary caregivers and by indication. Global surveillance studies demonstrate that fluoroquinolone resistance rates increased in the past years in almost all bacterial species except *S. pneumoniae* and *H. influenzae*, causing community-acquired respiratory tract infections. However, 10 to 30% of these isolates harbored first-step mutations conferring low level fluoroquinolone resistance. Fluoroquinolone resistance increased in Enterobacteriaceae causing community acquired or healthcare associated urinary tract infections and intraabdominal infections, exceeding 50% in some parts of the world, particularly in Asia. One to two-thirds of Enterobacteriaceae producing extended spectrum β -lactamases were fluoroquinolone resistant too. Furthermore, fluoroquinolones select for methicillin resistance in *Staphylococci*. *Neisseria gonorrhoeae* acquired fluoroquinolone resistance rapidly; actual resistance rates are highly variable and can be as high as almost 100%, particularly in Asia, whereas resistance rates in Europe and North America range from <10% in rural areas to >30% in established sexual networks. In general, the continued increase in fluoroquinolone resistance affects patient management and necessitates changes in some guidelines, for example, treatment of urinary tract, intra-abdominal, skin and skin structure infections, and traveller's diarrhea, or even precludes the use in indications like sexually transmitted diseases and enteric fever.

1. Introduction

Nalidixic acid—a byproduct of chloroquine synthesis—was marketed during the 1960s for oral treatment of urinary tract infections and is still available by prescription. Several quinolones were invented since then, including flumequine bearing a fluorine atom at position C-6, which was active against nalidixic acid resistant *Enterobacteriaceae*. However, development of newer fluoroquinolones did not progress significantly till it was demonstrated that substitutions at the C-6 and C-7 positions improved antibacterial activity and pharmacological properties [1]. Since then, fluoroquinolones have become established for treatment of urinary, respiratory, gastrointestinal, urogenital, intra-abdominal, and skin/skin structure infections in outpatients and hospitalised 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* and

P. aeruginosa. Resistance to fluoroquinolones emerged rapidly in these two species, predominantly due to clonal spread among nursing home residents and immunocompromised patients [2]. However, since the mid 1990s quinolone resistance started to increase in almost all Gram-positive and Gram-negative species and minimal concentrations (MICs) inhibiting 90% of the strains studied varied species specifically over a broad range from ≤ 0.015 up to ≥ 128 mg/L [3–5] thus indicating that resistant subpopulations were frequent already two decades ago but passed almost unnoticed. Recent surveillance studies demonstrate that resistance rates continue to increase thus affecting patient management and necessitating a change in some current treatment guidelines [6, 7], or even precluding the use of fluoroquinolones in certain indications as will be discussed below [8, 9].

This paper summarizes data from local, national, international, and global surveillance studies of antimicrobial resistance combining the complementary approaches of

routine surveillance (the active investigation of results generated in the course of routine clinical care) and targeted surveys (one-time or periodic study protocols to address specific scientific or public policy needs not adequately addressed by routine diagnostic test results). Data generated in the course of global, longitudinal surveillance studies are complemented with national and regional data. Only those studies using standardized test methods and defined susceptibility-/resistance-criteria according to national—or preferably CLSI—(formerly NCCLS) breakpoint definitions were selected. Many articles quoted in this paper originate from the author's files; others were chosen from searches on Pubmed. Articles summarized in recent reviews were excluded from this synopsis.

Large global surveillance studies comprising centers in Asia, Asia/Pacific region, Japan, North, Central, and South America, and the EU have the strength that large numbers of pathogens are sampled and that standardized methods of data collection, susceptibility testing and data interpretation are used. Therefore, surveillance programmes like *SENTRY* (a global, longitudinal study on the susceptibility of pathogens causing blood-stream infections, community- and hospital acquired RTIs, skin and soft tissues, and UTIs, sponsored by Bristol Meyers Squibb, recently switched to a study on the susceptibility of Gram-positive pathogens to daptomycin and comparators), *MYSTIC* (meropenem yearly susceptibility test information collection, a global, longitudinal surveillance study designed to evaluate the prevalence and in-vitro antimicrobial susceptibility of isolates from intensive care units, neutropenia units, cystic fibrosis units, or non-specialist centres where meropenem is used, sponsored by Astra Zeneca), *SMART* (study monitoring antimicrobial resistance trends, a study on the susceptibility of intra-abdominal aerobic and anaerobic clinical isolates, sponsored by Merck), *PROTEKT* (prospective resistant organism tracking and epidemiology for the ketolide telithromycin, sponsored by Aventis Pharmaceuticals), *GLOBAL* (global landscape on the bacterial activity of levofloxacin) and the “*Alexander Project*” (an international study that began in 1992 and involved initially 6, later 27 countries, sponsored by GlaxoSmith Kline), data from major European programmes (e.g., European Antimicrobial Resistance Surveillance System (*EARSS*); *ECO. SENS* (*E. coli* sensitivity)) and national programmes (e.g., *NAUTICA* (North American Urinary Tract Infection Collaborative Alliance; the National Nosocomial Infections Surveillance System (*NNIS*)/National Healthcare Safety Network (*NHSN*) established by the Centers for Disease Control and Prevention in the US) are used as one major source of information. The second source of information constitute national or regional studies meeting the above mentioned criteria. The scope and design as well as the strengths and weaknesses of surveillance studies have been critically reviewed previously [10–12].

2. Mode of Action and Mechanisms of Resistance

2.1. Interaction with Bacterial Type II Topoisomerases. Fluoroquinolones are the only class of antimicrobial agents

in clinical use that are direct inhibitors of bacterial DNA synthesis. Fluoroquinolones inhibit two bacterial enzymes, DNA gyrase and topoisomerase IV, which have essential and distinct roles in DNA replication. The quinolones bind to the complex of each of these enzymes with DNA; the resulting topoisomerase-quinolone-DNA ternary complex subsequently leads to the generation of double-stranded breaks in DNA and blocks progress of the DNA replication enzyme complex. Ultimately, this action results in damage to bacterial DNA and bacterial cell death [13–16].

Resistance to quinolones occurs by mutation in chromosomal genes that encode the subunits of DNA-gyrase and topoisomerase IV (altered target mechanism), and that regulate the expression of cytoplasmic membrane efflux pumps or proteins that constitute outer membrane diffusion channels (altered permeation mechanism). Several excellent and comprehensive reviews have been published summarizing the current knowledge about the mode of action and resistance mechanisms of fluoroquinolones; the reader is kindly referred to these publications for further reading (e.g., [16–21]). Furthermore, reduced target expression has been described as another mechanism leading to low level quinolone resistance [22].

2.2. SOS Response and Autoinduction of Fluoroquinolone Resistance. Repair mechanisms are activated as a consequence of inhibition of bacterial type II topoisomerases. Any DNA-damage triggers the production of various repair proteins by activating an SOS gene network [23–27]. The SOS system is composed of more than 40 genes and is controlled by regulatory proteins RecA and LexA. RecA provides a signal for induction of SOS response, while LexA functions as a repressor; binding the gene repressor LexA unmasks its autoproteolytic activity, so that the 40 SOS genes are no longer repressed. The LexA binding site is located in the sequence upstream from *qnrB* (but not *qnrA* or *qnrS*), so that *qnrB* is regulated by the SOS-system, too, in response to DNA damage [28]. In addition, it has been shown recently that the SOS response promotes *qnrB* expression [29]. The peptide QnrB protects bacterial DNA-topoisomerases from quinolone inhibition and provides low-level quinolone resistance (see below Section 2.3. “plasmid mediated fluoroquinolone resistance”). The Qnr-determinants facilitate the emergence of high-level resistance. In *E. coli*, this latter effect depends on the increased mutation ability conferred by the nonessential polymerases Pol II, Pol IV, and Pol V on LexA-cleavage-mediated derepression of their respective genes (*polB*, *dinB*, and *umuDC*; 106). Thus, *qnrB*-mediated quinolone resistance and increased mutation ability are two events triggered by the same signal, namely, the SOS response. Quinolone resistance gene *qnrB* is upregulated by ciprofloxacin in a RecA/LexA-dependent manner, so that quinolone resistance development is an integral part of their mode of action in *qnrB* harboring bacteria. Ciprofloxacin resistant mutants could be elicited much more frequently in LexA positive wild-type strains than in LexA mutant strains [30, 31]. Vice versa, preventing LexA cleavage renders bacteria unable to evolve resistance to fluoroquinolones [30, 31]. Furthermore, SOS response induces persistence to

fluoroquinolones [32]. These results support the notion that fluoroquinolones are not only mere selectors of resistant variants but that bacteria themselves play an active role in the mutation of their own genomes. Quinolone resistance is not only acquired via target site mutations, but also via the SOS system by derepression of genes whose products increase mutation rates. In general, interference with bacterial stress response may reduce the emergence of resistance [33]. Furthermore, it was shown recently that ciprofloxacin stimulated SOS independent recombination of divergent DNA sequences in *E. coli*. Thus, fluoroquinolones increase genetic variation via a second, SOS independent mechanism [34]. This mechanism, too, may favour acquisition, evolution, and spread of resistance determinants.

Not only DNA damaging agents like quinolones trigger the SOS response. Beta-lactams interfering with penicillin binding protein 3 [35, 36], zidovudine or trimethoprim [37], and rifampin [30] activate the SOS gene network as well. These data demonstrate that induction of SOS response by any of these drug classes facilitates persistence and evolution of resistance in general. Thus, it may be speculated that these agents, too, may affect quinolone activity and/or resistance development via the SOS promoted expression of *qnrB*. Furthermore, the SOS system contributes to the spread of antibiotic resistance by promoting horizontal dissemination of antibiotic-resistance genes [38] or mutations.

2.3. Plasmid Mediated Fluoroquinolone Resistance. The genetic information for target site or efflux resistance mechanisms is commonly chromosomally encoded. However, the emergence of plasmid-mediated and thus transferable fluoroquinolone resistance has also been reported; several mechanisms are known: 1. Qnr, 2. Aminoglycoside acetyltransferase AAC(6')-Ib-cr, 3. OqxAB, QepA [39–44].

The emergence of plasmid-mediated quinolone resistance was first found in strains of *Klebsiella pneumoniae* in one region of the United States in 1998 [45] and shown to be due to a member of the pentapeptide repeat (PPR) family of proteins Qnr (later named QnrA). In the following years, several distantly related plasmid mediated Qnr determinants were described in Enterobacteriaceae (QnrB, QnrC, QnrD, QnrS) [46, 47]. They have been identified worldwide and are almost always associated with the production of expanded spectrum β -lactamases [48–50]. Qnr-like peptides (sharing an amino-acid identity with QnrA of 16 to 22%) have been found in the Gram-positive bacteria *Mycobacterium tuberculosis*, *M. smegmatis*, and *M. avium* [51], *E. faecalis* [52], and in *E. faecium*, *Listeria monocytogenes*, *C. perfringens*, *C. difficile* [53]. Recently, a new chromosomally encoded quinolone resistance gene of the PPR family has been identified in *Stenotrophomonas maltophilia* and has thus been named Smqnr [54]; a *maqnr* gene has been found in *Serratia marcescens* [55].

Qnr interacts with DNA-gyrase and topoisomerase IV to prevent quinolone inhibition [39, 56]. Qnr protein causes nalidixic acid resistance and reduced susceptibility to or low-level fluoroquinolone resistance [56]. *Qnr*-genes have been found in ciprofloxacin-susceptible isolates as well as quinolone resistant isolates, suggesting that their

presence promotes higher level resistance due to chromosomal mutation, as has been shown in the laboratory. Therefore, the presence of *qnr* genes in clinically relevant species of both, Gram-positive and Gram-negative bacteria may foster quinolone resistance development. Furthermore, *qnrA* and *qnrB* genes are usually integrated into integrons which harbor other antibiotic resistance genes such as β -lactamases or aminoglycoside inactivating enzymes. Although *qnrS*-genes are not harbored by integrons, they are associated with transposons containing TEM-1 type β -lactamases [57]. Consequently, the association of genes encoding for quinolone resistance and resistance to other drug classes like β -lactams and aminoglycosides favour the selection and dissemination of fluoroquinolone resistant strains by chemically unrelated drug classes, and vice versa, of β -lactam or aminoglycoside-resistant strains by fluoroquinolones (the close correlation between extended spectrum β -lactamases (ESBL) production and quinolone resistance is discussed in the chapters on fluoroquinolone resistance).

Qnr genes were also found on the chromosome of an environmental water bacterium, *Shewanella algae*. Other *qnr* homologs have been found in the genome sequences of several *Vibrio* spp. and *Photobacterium profundum* suggesting that water-borne *Vibrionaceae* may have been the source of and may constitute a reservoir for the *qnr* genes [58–60]. Recently it was demonstrated in vitro that the plasmid borne *Shewanella algae qnr* gene could be transferred to Enterobacteriaceae [58].

Another plasmid-encoded quinolone resistance determinant was identified, a variant of the *aac(6')Ib* gene encoding an aminoglycoside acetyltransferase. The bifunctional aminoglycoside and fluoroquinolone active variant AAC(6')-Ib-cr catalyzes acetylation of both drug classes [61]. The variant enzyme has acquired the ability to acetylate ciprofloxacin and norfloxacin and reduces ciprofloxacin's activity fourfold [62, 63]. Moxifloxacin and levofloxacin are not acetylated due to the absence of a piperazinyl substituent at position C-7. Interestingly, the first ciprofloxacin resistant clinical isolate (*S. marcescens*) was isolated from a patient treated in the pre-quinolone era with a β -lactam and an aminoglycoside; the pre- and post therapy MICs of ciprofloxacin were 0.06 and 4 mg/L, respectively. This strain produced an aminoglycoside acetyltransferase and showed changes in the outer-membrane composition [64]. AAC(6')-Ib-cr may be more widespread than Qnr-determinants. Both, Qnr- and AAC(6')-Ib-cr-production are associated with the ESBL production, thus, representing a second mechanism of co-selection of drug-resistance due to exposure to chemically unrelated agents.

Most recently, a third type of plasmid-mediated quinolone resistance has been identified: the quinolone efflux pumps OqxAB and Qep, [42–44, 65, 66]. The OqxAB- and QepA-proteins confer resistance to hydrophilic fluoroquinolones like norfloxacin, ciprofloxacin, and enrofloxacin, causing a 32- to 64-fold increase in MICs [65–68]. QepA extrudes in addition to quinolones a narrow range of agents such as erythromycin, ethidium bromide, and acriflavine; OqxAB exports a wider range of agents like ethidium bromide, tetracyclines, chloramphenicol, trimethoprim,

olaquinox, and the disinfectants like triclosan [57, 68, 69]. The problem is that the *qepA* gene and an aminoglycoside ribosome methyltransferase are part of a transposable element [66], so that there is a potential of selection of QepA determinants by aminoglycosides and vice versa aminoglycoside resistance by quinolones; the same holds true for *aac(6')Ib* gene mediated resistances. Extrusion of chemically unrelated agents by efflux-pumps represents a third mechanism of cross-resistance. In conclusion, fluoroquinolone resistance can emerge even in the absence of exposure to this drug class as several coselection mechanisms favour the emergence of quinolone resistance.

Additional, unknown mechanisms of quinolone resistance must exist as known chromosomally- and plasmid-mediated resistance mechanisms plus the presence of the multidrug efflux pump AcrAB were detected in just 50–70% of high-level quinolone resistant *E. coli* clinical isolates with MICs up to 1,500-fold higher than expected [70].

2.4. Additional Resistance Mechanisms. Any antibacterial agent interacting with an intracellular target must traverse the bacterial cell-wall and cytoplasmic membrane to reach the target. Once taken up, most antibacterials are actively effluxed. Therefore, fluoroquinolones, too, are affected by permeation barriers and efflux pumps, either in association with target modifications or on their own.

As mentioned above, many Gram-positive and Gram-negative fluoroquinolone-resistant mutant strains do not show any mutation in the quinolones resistance determining region (QRDR). For example, 70% of *E. coli* mutants recovered from besifloxacin selection plates were characterized by the absence of classical QRDR mutations [71] and 61% high-level ciprofloxacin-resistant isolates of *E. coli* accumulated lower levels of ciprofloxacin than the wild type, in addition to the *gyrA* mutations found in all of them [72]. Furthermore, chemically unrelated substances like cyclohexane, salicylate, and tetracycline affected fluoroquinolone susceptibilities of *E. coli*, too; 21 of 57 high level fluoroquinolone-resistant clinical isolates of *E. coli* showed tolerance to cyclohexane, suggesting an elevated broad spectrum efflux activity [73]. Multiple antibiotic resistance (*mar*) genes cause an efflux of a variety of chemically unrelated compounds including different drug classes of antibacterials [74] and are affected by a variety of chemically unrelated substances. The *mar* genes regulate accumulation and thus intracellular concentrations of quinolones by altering the expression of porins and efflux pumps [72, 74]. Another efflux pump, AcrAB, extrudes quinolones out of the bacteria. The pump is partly controlled by the *mar* gene and appears to be the major mechanism of resistance for *mar* mutants [75]. Salicylate and tetracycline induce MarA production, a positive regulator of *acrAB* transcription, so that salicylate stimulates fluoroquinolone resistance selection. Resistance may be seen with *mar* expression alone or in combination with type II topoisomerase mutations [74]. The combination of AcrAB overexpression with topoisomerase mutations causes high level fluoroquinolone resistance; over 60% of high-level ciprofloxacin-resistant isolates had an increased production of AcrA [76–78].

Additional nontopoisomerase resistance mechanisms that are not under *mar* control can change quinolone resistance patterns. The *nfxB* gene codes for an altered outer cell membrane protein F, thereby decreasing quinolone entry into the cell [79]. In addition, *soxRS* gene products, which are involved in bacterial adaptation to superoxide stress, affect fluoroquinolone activity, too [73].

Various combinations of target enzyme alteration, diminished antibiotic accumulation, and efflux are often seen in fluoroquinolone-resistant *E. coli*, other Enterobacteriaceae and nonfermenters [72, 80]. Cross-resistance between fluoroquinolones and antibacterials of chemically unrelated drug classes is associated with the increased expression of efflux pumps because of their limited substrate specificity. For example, MexAB confers resistance to nonfluorinated and fluoroquinolones, tetracycline, and chloramphenicol, Mex CD confers resistance to fluoroquinolones, erythromycin, trimethoprim, and triclosan, Mex EF confers resistance to the latter plus chloramphenicol, imipenem, and triclosan, and Mex XY confers resistance to fluoroquinolones, erythromycin, and aminoglycosides. Several comprehensive reviews have summarized the impact of fluoroquinolone-extrusion and resistance [80–83]. Consequently, a fluoroquinolone resistant or even multidrug-resistant phenotype can easily be selected by an exposure to a broad range of chemically unrelated drug classes, thus, representing the fourth type of cross-resistance.

These examples illustrate the complexity of fluoroquinolone resistance mechanisms, selection by fluoroquinolones and coselection of resistance by chemically unrelated classes of antibacterials and antiseptics.

3. Fluoroquinolone Resistance Epidemiology

3.1. Urinary Tract Infections. The first quinolone used clinically, that is, nalidixic acid, was classified as an “urinary antiseptic;” previous nonfluorinated quinolones were almost exclusively used for treatment of lower urinary tract infections (UTIs). The fluorinated quinolones are characterized by more marked antibacterial activity against uropathogens, so that ciprofloxacin resistant *E. coli* strains isolated from female outpatients were almost nonexistent (<1%) till the mid-1990s; resistance to ciprofloxacin increased slowly from 1.2% in 1998 to 2.5% in 2001 [84]. The same holds true for uropathogenic *E. coli* isolated from male and inpatients, respectively, with a trend towards higher resistance rates among elderly patients [85, 86]. However, the NAUTICA (North American Urinary Tract Infection Collaborative Alliance) study revealed that ciprofloxacin resistance increased to 5.5% in 2004 [87]. Likewise, uropathogens studied between the years 1996 and 2009 in the province of British Columbia demonstrated an increase in fluoroquinolone resistance. The resistance rates in *E. coli* and *K. pneumoniae* increased from <2% in 1996 to ≥20% in 2009; the resistance rates of fluoroquinolones for *P. mirabilis* remained almost constant throughout the years at ≤2%. *Enterococci* demonstrated frequently resistance against fluoroquinolones although resistance rates decreased between 2002 and 2009 [88].

3.1.1. Community Acquired Urinary Tract Infections. Data summarized in Table 1 demonstrate that fluoroquinolone resistance ranges from 2.2% to 69% for strains isolated from patients with uncomplicated, community acquired UTI (CAUTI) and even up to 98% for strains from patients with complicated CAUTIs. Likewise, ESBL production ranged from 2.6% to 100%. Both, fluoroquinolone resistance and ESBL production were highest in the Asia-Pacific region and moderate to low in Europe and North America. The clonality of the isolates has rarely been examined, although high numbers of ESBL producers may indicate that a few clones may predominate amongst the isolates studied (see below, Section 3.1.3). Furthermore, data summarized in Table 1 indicate that on the one hand the *relative* numbers of ESBL producers per centre is high whereas on the other hand the *total* numbers of isolates is still quite small. For example, 100% of the ESBL positive strains were fluoroquinolone-resistant; but this corresponds to 11.8% of the total number of isolates studied [89]. The high relative figures of fluoroquinolone resistant ESBL-producers—which are often mentioned in the abstract instead of the total numbers—may mask the prevalence of fluoroquinolone resistance in uropathogens.

The risk for acquisition of CAUTIs caused by ESBL-positive *E. coli* and the distribution of the ESBL enzyme types was determined in a prospective cohort study [90]. A total of 510 patients with CAUTIs caused by Gram-negative bacteria were included in the study. ESBL producers were detected in 6.3% of uropathogenic *E. coli* isolated from uncomplicated UTIs and 17.4% of *E. coli* isolates from complicated UTIs ($P < 0.001$), most of which (90.2%) were found to harbour CTX-M-15. According to multivariate analysis, more than three urinary tract infection episodes in the preceding year (OR 3.8, $P < 0.001$), use of a β -lactam antibiotic in the preceding 3 months (OR 4.6, $P < 0.001$) and prostatic disease (OR 9.6, $P < 0.004$) were found to be associated with ESBL positivity. The percentages of isolates with simultaneous resistance to trimethoprim-sulphamethoxazole, ciprofloxacin, and gentamicin were found to be 4.6% in the ESBL negative group and 39.2% in the ESBL positive group ($P < 0.001$) [90].

Comprehensive reviews of the worldwide emergence of ESBL producing Enterobacteriaceae indicate that 1st their numbers increase continuously, 2nd ESBL production is diverse, scatters geographically, and originates from both, community associated—as well as healthcare associated infections [91–93], 3rd most of the community isolates are multi-resistant, [92, 94], 4th many isolates are often genetically related and clonal spread has been reported frequently [95–101], 5th the pandemic multiresistant, community associated clone ST 131 is highly prevalent and contributes to 30% to 60% to all fluoroquinolone resistant *E. coli* [93, 102].

Clearly, the continuously increasing prevalence of ESBL-producing Enterobacteriaceae isolated from out-patients is alarming. However, several studies indicate that the prevalence of ESBL-producing, fluoroquinolone-resistant CAUTI-pathogens may be low. The ECO. SENS (*E. coli* sensitivity) project is a Pan-European survey of the antimicrobial susceptibilities of pathogens from uncomplicated UTIs. Data

published in 2003 demonstrate that overall ciprofloxacin resistance in the 2,478 *E. coli* strains collected amounted to 2.3%, ranging from 0% in Austria and Sweden to 5.8% and 14.7% in Portugal and Spain, respectively. Ciprofloxacin-resistance rates in *P. mirabilis*, *Klebsiella* spp. and other Enterobacteriaceae were 2.1%, 1.0%, and 0.8%, respectively [103]. The ARESC (Antimicrobial Resistance Epidemiological Survey on Cystitis) study revealed that in uropathogens collected in nine European countries and Brazil from 2003 to 2006 ciprofloxacin resistance in *E. coli* was recorded in >10% of all the isolates in Brazil, Spain, Italy, and Russia; in the remaining European countries, ciprofloxacin resistance ranged from 1.4% in France to 6.7% in Poland [104–106]. As national parts of the ARESC study, 335 and 650 uropathogens, respectively, were isolated most recently from German and Spanish patients with uncomplicated cystitis; fluoroquinolone resistance amounted to 7.7% and 11.9%, respectively [107, 108], thus, indicating that fluoroquinolone resistance did not increase as compared to the previous study period. ESBL production was neither specified in the ECO. SENS nor the ARESC study.

3.1.2. Healthcare Associated Urinary Tract Infections. Fluoroquinolone resistance ranged from 6.3% to 62% in Gram-negative strains and 20% and 100% of the methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), respectively, as well as 59% of the Enterococci isolated from patients with complicated, healthcare associated UTI (HAUTI) (Table 1). In general, uropathogens from patients admitted to tertiary care hospitals are less fluoroquinolone susceptible than those from out-patients. Clearly, patients admitted to tertiary care hospitals suffer from chronic diseases, urologic surgery, recurrent infectious diseases necessitating antibacterial therapy prior to the actual study, and so forth, so that one or several risk factors favor development of resistance. High rates of fluoroquinolone resistance were found in patients with HAUTIs evaluated in the emergency department [109, 110] and in nursing home residents [111]. Horizontal transmission of one, or few predominating clone(s) in nursing home residents is frequent [2].

3.1.3. Association between Fluoroquinolone Resistance and Production of Extended Spectrum β -Lactamases. Although production of extended spectrum β -lactamases (ESBLs) was not analysed in these studies, it may well be that the increase in both, fluoroquinolone resistance and ESBL-production, are closely associated [112]. 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 [113–116]. *E. coli* strains that produce CTX-M ESBLs, primarily found in community sources, are becoming widely prevalent worldwide [95–97, 113]. For example, in Spain a threefold rise in community-onset UTIs caused by ESBL-producing *E. coli* over a 3-year period from 0.47% (17 of 3,617 isolates) in 2000 to 1.7% (44 of 2,600

TABLE 1: Worldwide prevalence of fluoroquinolone-resistant uropathogens. Data in columns four and five represent total numbers of isolates studied; data in columns six to nine represent fluoroquinolone-resistant isolates in percent of total; figures in column ten show ESBL-positive isolates in percent of total isolates studied; figures in columns eleven and twelve represent ESBL-positive or negative fluoroquinolone-resistant isolates in percent of total numbers of ESBL-positive isolates.

Species	Country	Sampling period	<i>n</i> uUTI	<i>n</i> cUTI	HAUTI uUTI % FQ res.	HAUTI cUTI % FQ res.	CAUTI uUTI % FQ res.	CAUTI cUTI % FQ res.	ESBL pos % of total	% FQ res. of ESBL pos.	% FQ res. of ESBL neg	Ref.
<i>E. coli</i>	ESP	03/03 to 01/03	82	82	—	19.5	8.5	—	—	—	—	[482]
<i>E. coli</i>	GRC	01/05 to 03/06	1,936	—	—	—	2.2	—	—	—	—	[483]
<i>E. coli</i>	PRT	03/04 to 03/06	—	90	—	—	—	98	96	100	—	[120]
<i>E. coli</i>	TUR	2005 to 2006	107	—	—	—	25.2	—	—	—	—	[484]
<i>S. aureus</i>	TUR	2005 to 2006	12	—	—	—	41.7	—	—	—	—	[484]
<i>Enterococcus</i> spp.	TUR	2005 to 2006	5	—	—	—	20.0	—	—	—	—	[484]
<i>E. coli</i>	TUR	01/07 to 12/07	269	34	—	—	22.0	41.0	—	—	—	[90]
<i>E. coli</i>	TUR	—	321	290	—	—	17.0	38.0	71	7.9	92.1	[485]
<i>E. coli</i>	TUR	—	110	—	—	—	15.0	—	—	—	—	[486]
<i>E. coli</i>	LBN	2000	395	—	17.0	—	—	—	—	—	—	[487]
<i>E. coli</i>	LBN	2009	628	—	48.0	—	—	—	—	—	—	[487]
<i>E. coli</i>	IND	08/04 to 07/05	61	—	—	—	69.0	—	—	34.4	65.6	[488]
<i>K. pneumoniae</i>	IND	08/04 to 07/05	22	—	—	—	47.0	—	—	27.3	72.7	[488]
<i>E. coli</i>	IND	06/05 to 12/05	—	508	—	—	—	—	—	29.1	70.9	[489]
<i>K. pneumoniae</i>	IND	06/05 to 12/05	—	—	—	—	—	64.2	—	25.6	74.4	[489]
<i>Enterobacter</i> spp	IND	06/05 to 12/05	—	—	—	—	—	—	—	28.6	71.4	[489]
<i>E. coli</i>	IND	06/04 to 06/05	—	412	—	—	—	—	92	42.4	57.6	[94]
<i>K. pneumoniae</i>	IND	06/04 to 06/05	—	136	—	—	—	—	33	15.2	84.8	[94]
Gram-neg. bacilli	IND	09/01 to 12/01	—	793	—	77.5	—	—	—	71.5	28.5	[490]
Gram pos. cocci	IND	09/01 to 12/02	—	78	—	47.6	—	—	—	—	—	[490]
<i>E. coli</i>	IND	03/11 to 08/11	—	532	—	21	—	—	—	—	—	[491]
<i>E. coli</i>	IND	01/10 to 08/10	—	89	—	62	—	—	—	—	—	[492]
<i>Klebsiella</i> spp.	IND	01/10 to 08/10	—	32	—	48	—	—	—	—	—	[492]
<i>E. coli</i>	PAK	04/05 to 02/06	—	116	—	62.1	—	—	80.3	56.8	43.2	[493]
<i>E. coli</i>	PAK	05/07 to 09/09	—	276	—	77.2	—	—	—	—	—	[494]
<i>E. coli</i>	IRN	03/09 to 06/09	—	620	—	31	—	—	—	—	—	[495]
<i>K. pneumoniae</i>	IRN	03/09 to 06/09	—	115	—	15	—	—	—	—	—	[495]
<i>Enterococcus</i> spp.	IRN	03/09 to 06/09	—	110	—	59	—	—	—	—	—	[495]
<i>P. aeruginosa</i>	IRN	03/09 to 06/09	—	30	—	23	—	—	—	—	—	[495]
<i>S. aureus</i>	IRN	03/09 to 06/09	—	81	—	0.06	—	—	—	—	—	[495]
<i>E. coli</i>	PRK	2006	301	—	—	—	23.4	—	100	11.8	—	[89]

TABLE 1: Continued.

Species	Country	Sampling period	<i>n</i> uUTI	<i>n</i> cUTI	HAUTI uUTI % FQ res.	HAUTI cUTI % FQ res.	CAUTI uUTI % FQ res.	CAUTI cUTI % FQ res.	ESBL pos % of total	% FQ res. of ESBL pos.	% FQ res. of ESBL neg.	Ref.
<i>E. coli</i>	PRK	—	688	—	—	—	—	—	71.8	12.1	87.9	[496]
<i>E. coli</i>	PRK	—	—	160	—	—	—	—	71.8	23.1	76.9	[496]
<i>E. coli</i>	PRK	01/08 to 06/09	1,994	—	—	—	25.4	—	—	—	—	[497]
<i>E. coli</i>	PRK	01/01 to 12/02	232*	419*	—	—	12.7	21.2	—	—	—	[498]
<i>E. coli</i>	PRK	01/08 to 12/09	232*	419*	—	—	88	30.6	—	—	—	[498]
<i>E. coli</i>	HKG	2006 to 2008	271	—	—	—	12.9	—	—	5.2	94.8	[500]
<i>E. coli</i>	ZAF	11/05 to 10/06	87	—	—	—	11.5	—	—	2.6	97.4	[500]
<i>E. coli</i>	ZAF	11/05 to 10/06	—	366	—	17.2	—	—	—	11.9	88.1	[500]
<i>K. pneumoniae</i>	ZAF	11/05 to 10/06	17	—	—	—	11.8	—	—	31.3	68.7	[500]
<i>K. pneumoniae</i>	ZAF	11/05 to 10/06	—	182	—	31.9	—	—	—	40.6	59.4	[500]
<i>E. coli</i>	FRA	05/03 to 04/04	1,217	—	—	—	—	—	—	—	—	[501]
<i>E. coli</i>	ESP	2002 + 2004	5,737	—	—	—	3.7	—	—	—	—	[502]
<i>E. coli</i>	ESP	11/03 to 10/04	3,292	—	—	—	22.7	—	—	—	—	[503]
<i>E. coli</i>	RUS	1998 to 2001	456	—	—	—	18.0	—	—	—	—	[504]
<i>E. coli</i>	GBR	1999 to 2000	1,291	—	—	—	4.5	—	—	—	—	[505]
<i>E. coli</i>	ISR	1999	6,692	—	—	—	2.3	—	—	—	—	[506]
<i>E. coli</i>	USA	08/08 to 03/09	102	253	—	—	6.0	—	—	1.25	98.75	[506]
<i>E. coli</i>	USA	—	357	—	2.0	—	—	—	—	—	—	[507]
<i>E. coli</i>	USA	08/08 to 03/09	—	—	10.0	—	—	—	—	—	—	[109]
<i>E. coli</i>	NLD	1997	—	332	—	29.0	—	—	—	—	—	[111]
<i>E. coli</i>	NLD	1997	—	171	—	22.0	—	—	—	—	—	[111]
<i>Proteus</i> spp.												
<i>E. coli</i>	NLD	2004 + 2009	565	—	—	—	3.0	—	—	—	—	[508]
<i>E. coli</i>	NLD	01/04 to 12/09	—	420	—	12.0	—	—	—	—	—	[130]
<i>E. coli</i>	CHE	01/06 to 08/07	—	345	—	22.0	—	—	—	—	—	[509]
<i>E. coli</i>	CAN	09/05 to 06/06	—	283	—	19.8	—	—	—	3.5	96.5	[263]
<i>P. aeruginosa</i>	CAN	09/05 to 06/06	—	45	—	37.8	—	—	—	—	—	[263]
<i>K. pneumoniae</i>	CAN	09/05 to 06/06	—	51	—	0.0	—	—	—	1.8	98.2	[263]
<i>E. cloacae</i>	CAN	09/05 to 06/06	—	16	—	6.3	—	—	—	—	—	[263]
MSSA	CAN	09/05 to 06/06	—	20	—	20.0	—	—	—	—	—	[263]
<i>E. coli</i>	CAN	01/08 to 12/08	—	510	—	21.4	—	—	—	4.9	95.1	[264]
<i>K. pneumoniae</i>	CAN	01/08 to 12/08	—	98	—	12.2	—	—	—	3.2	96.8	[264]

uUTI: uncomplicated urinary tract infection; cUTI: complicated urinary tract infection; HA-UTI: Healthcare associated urinary tract infection; CA-UTI: community acquired urinary tract infection; ESBL: extended spectrum β -lactamase; Ref: reference; *total number of isolates studied in both sampling periods; ESP: Spain; GRC: Greece; PRT: Portugal; TUR: Turkey; LBN: Lebanon; IND: India; PAK: Pakistan; PRK: South Korea; HKG: Hong Kong; ZAF: South Africa; RUS: Russian Federation; USA: United States of America; NLD: The Netherlands; CHE: Switzerland; CAN: Canada.

isolates) in 2003 was reported, 31% of which (or 0.54% of the total isolates) were resistant to ciprofloxacin [117]. A nationwide study performed in Spain in 2000 revealed that 93% of the ESBL-producing *K. pneumoniae* strains were isolated from inpatients, whereas 51% of ESBL-producing *E. coli* strains were isolated from outpatients [118]. Risk factors for the acquisition of ESBL-producing *E. coli* in non hospitalised 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) [119]. A prospective cohort study in 510 patients with CAUTIs caused by Gram-negative bacteria revealed that ESBL producers were detected in 6.3% of uropathogenic *E. coli* isolated from uncomplicated UTIs and 17.4% of *E. coli* isolates from complicated UTIs ($P < 0.001$), most of which (90.2%) were found to harbour CTX-M-15 [19]. According to multivariate analysis, more than three urinary tract infection episodes in the preceding year (OR 3.8, $P < 0.001$), use of a β -lactam antibiotic in the preceding 3 months (OR 4.6, $P < 0.001$) and prostatic disease (OR 9.6, $P < 0.004$) were found to be associated with ESBL positivity. The percentages of isolates with simultaneous resistance to trimethoprim-sulphamethoxazole, ciprofloxacin, and gentamicin were found to be 4.6% in the ESBL-negative group and 39.2% in the ESBL-positive group ($P < 0.001$) [90]. As the CTX-M type is most common among the CAUTI pathogens it is conceivable that many of these isolates may be genetically related. More than two thirds of unduplicated *E. coli* strains isolated from patients admitted to nine different Portuguese hospitals in three different regions were ESBL producers; all of the CAUTI pathogens produced the CTX-M-15 type β -lactamase. Three quarters of the ESBL producers belonged to one genetic cluster, indicating countrywide dissemination of one single clone [120]. An analysis of selected *E. coli* strains isolated in eight European countries during 2003 to 2006 from patients with uncomplicated cystitis displaying reduced ciprofloxacin susceptibility revealed that 55 different biochemical profiles could be distinguished; although this finding indicates a substantial heterogeneity, about one third of all isolates belonged to two clonal groups O25:H4-ST 131 and O15:K52:H1. ESBL production was detected in 8.1% of all isolates, CTX-M-15 being the most common; strains belonging to the two predominant clonal groups had ciprofloxacin MICs of 16 and ≥ 32 mg/L, respectively [91, 102, 121]. Point source dissemination of ESBL-producers is frequent in patients with uUTIs. *E. coli* ST 131 was the most predominant group and accounted for 23.1% and 46%, respectively, of ESBL-positive isolates overall [91, 102]. Nearly all ST 131 isolates were ciprofloxacin resistant. The intercontinental pandemic spread of the ciprofloxacin-resistant *E. coli* O25:H4:ST 131 clonal group producing CTX-M-15 has been described worldwide in hospital and community settings [122, 123]. The sudden worldwide increase of ESBL-producing *E. coli* is mostly due to the single CTX-M-15 positive clone ST131; foreign travel to high-risk areas, such as the Indian subcontinent, play in part a role in the spread of this clone across different continents

[124]. The isolation of a multidrug-resistant *E. coli* strain of sequence type ST 131 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 ST 131 clonal group, too [125]. Furthermore, plasmid-mediated fluoroquinolone resistance determinants including CTX-M-15 were common in areas of high fluoroquinolone consumption [126] and in nursing home residents in whom a single multiresistant clone spread [127].

3.1.4. Risk Factors for and Impact of Prescribing Habits on Emergence of Fluoroquinolone Resistance. The impact of prescribing of ciprofloxacin on the emergence of fluoroquinolones resistance in uropathogenic *E. coli* was analysed in 72 general practices in the west of Ireland. Over a 4.5 year period (from April 2004 to September 2008) susceptibility and prescribing data were collected and analyzed by a multilevel model with ciprofloxacin-resistance as outcome and prescribing as predictor. The analysis revealed that in "mean" practices with one prescription per month ciprofloxacin resistance was low (3%) whereas in practices with 10 prescriptions per month ciprofloxacin resistance amounted to 5.5% [128]. Analogous effects were noted in patients with CAUTI monitored over a 6-year period in Denver, Colo, USA [129]. In 1999, the initial therapy of uUTI was switched to levofloxacin. The prescriptions increased from 3.1 to 12.7 per 1,000 visits; in parallel, fluoroquinolone resistance increased from 1% to 9%. Risk factors for the acquisition of fluoroquinolone resistant *E. coli* were hospitalization (or for each week of hospitalization = 2.0), and levofloxacin use within the previous year (OR 5.6). Similar risk factors were identified by others, too [130–134]. Additional factors favoring the selection of resistant uropathogens are poor adherence to treatment guidelines [135] and dispensing of antibacterials without prescription [136].

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, 24% in adults and 16% in children, although not used in the pediatric population [137, 138]. The carriage rate was higher than the fluoroquinolone resistance rates among patients with healthcare and community acquired infections (8.3% and 9% in 1992 versus 18% and 17% in 1996, resp.). Increasing fluoroquinolone resistance rates in commensal *E. coli* in children were found in North as well as South America, Africa, and Asia, too [139–145]. Among pediatric blood-stream isolates there was an association between fluoroquinolone resistance and ESBL production [141]. Similarly, the Chinese isolates from pediatric patients are characterized by a high prevalence of plasmid-mediated quinolones resistance; 4.1% were positive for *qnr* and 8.2% for *aac(6')-Ib-cr* genes known to confer low level fluoroquinolone resistance or to inactivate ciprofloxacin, but not moxifloxacin [145]. Isolates from children had relatively high prevalences of ciprofloxacin resistance in the 1990s already although the

use of ciprofloxacin in pediatric populations was approved for treatment of inhalational anthrax (post exposure) in August 2000 and for treatment of cUTI in March 2004. The fluoroquinolone resistance in children could be due to the transmission of resistant isolates between adults and children in families, daycare, or school settings and in previous years to the use of fluoroquinolones in poultry populations. These findings demonstrate that spread of fluoroquinolone resistance due to environmental contamination as well as person to person transmission contributes to an increase in the numbers of resistant isolates independent from selection of resistant strains in diseased patients; this phenomenon may bias resistance statistics. Analogous findings will be reported below for RTI-pathogens. Furthermore, these findings indicate that treatment of fluoroquinolone-naïve patients, that is, 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 uncomplicated UTIs in outpatients are still susceptible to fluoroquinolones, but considerable regional differences in drug susceptibility patterns exist with alarming 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 all those geographic regions in which ESBL producing Gram-negative community-acquired uropathogens are infrequent. Pathogens causing HAUTIs or cUTIs in nursing home patients are less susceptible to fluoroquinolones. Because of the considerable variability of susceptibility patterns in different countries, local epidemiological data are critical in the empiric management of UTIs, in particular in patients with risk factors and nursing home residents. Furthermore, fluoroquinolones exert a MRSA selective potential and exhibit negative epidemiological effects resulting in the selection of multiresistant pathogens. Therefore, fluoroquinolones should be used with caution even in patients with CAUTI and in particular in patients with HAUTI [146–148].

3.2. Respiratory Tract Infections

3.2.1. Community Acquired Respiratory Tract Infections. Although a number of significant pathogens like *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* are associated with community acquired respiratory tract infections (CARTIs) in all age groups [149–151], *S. pneumoniae* is the most frequent one. In the past, three major RTI surveillance studies, the Alexander Project [152], the RTI component of SENTRY [153], and PROTEKT (prospective resistant organism tracking and epidemiology for the ketolide telithromycin, sponsored by Aventis Pharmaceuticals) [154] have provided invaluable data on global antimicrobial resistance in CARTI-pathogens. Penicillin resistance rates in pneumococci varied from 71% in South Korea, 57% in Hong Kong, and 40% to 50% in France, Spain,

and Japan, whereas no penicillin-resistance was detected in Indonesia or the Netherlands [155–161]. Likewise, macrolide resistance among RTI pathogens varied from 0% to 41% [155, 157]. In Taiwan, penicillin and/or macrolide and/or trimethoprim/sulfamethoxazole-resistance amounts to 72%, 92%, and 76%, respectively [162]. 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.

It is important to note that in the studies quoted below the definitions of ciprofloxacin and levofloxacin resistance are based on two different resistant breakpoints, that is, ≥ 4 mg/L for ciprofloxacin and ≥ 8 mg/L for levofloxacin.

No levofloxacin-resistant pneumococci were detected in eight Asian countries from 2002 to 2004 [163, 164]. In Taiwan, only 0.6% of pneumococcal isolates collected from 2000–01 were resistant to levofloxacin [154]; by 2003, 3% of isolates in Taiwan were resistant to levofloxacin [162]. From 192 pneumococcal isolates collected in China from 2001 to 2002, 6.8% were resistant to levofloxacin; 4.2% were resistant to moxifloxacin [160, 165]. In 2008, 6.5% of *S. pneumoniae* isolated from hospitalized patients in Bangkok, Thailand, were resistant to ofloxacin [166]. A national surveillance study in Japan from 1994 to 2002 revealed that levofloxacin resistance rates were below 2% and were stable throughout the observation period; however, an increase in levofloxacin resistance rates from 0% in 1998 to 9.5% in 2000, and 4.8% in 2002 was found among penicillin-resistant pneumococci [161]. Recently, four highly levofloxacin-resistant pneumococci (MIC > 32 mg/L) were detected in Japan among 345 strains collected in Gifu prefecture from May 2006 to July 2006 [167]. Also in Spain, fluoroquinolone resistance rates remain low, ranging from 0.6 to 7% for ciprofloxacin [168–172]. A recent nationwide susceptibility study collected in 34 laboratories 2,559 *S. pneumoniae* isolates from patients with community acquired pneumonia (CAP); only 2.2% and 0.5% of these isolates were ciprofloxacin and levofloxacin resistant [173].

Fluoroquinolone resistance is rare in North America. Surveillance studies in the United States from 1987 to 2009 demonstrated low rates of resistance (0.1 to 1.3%) to levofloxacin [174–195] and to moxifloxacin (0.1%; 216). From 27,828 isolates of *S. pneumoniae* collected in the US during 4 consecutive respiratory seasons from 1998 to 2002, only 1.3% were levofloxacin-resistant [181] although ciprofloxacin has been used in the US since 1987 and has thus exerted a selective pressure on *S. pneumoniae*. Likewise, the prevalence of fluoroquinolone resistance in Canada remained low from 1998 to 2009. Although total per capita outpatient use of fluoroquinolones increased during this 10-year period, levofloxacin and moxifloxacin resistance remained unchanged at <2% in the >26,000 isolates collected [196]. However, a trend for rising levofloxacin resistance from <0.5% to >3% was noted in some regions of North America [85, 179, 180, 190, 191]. The GLOBAL (global landscape on the bacterial activity of levofloxacin) surveillance programme is an initiative intended to detect susceptibility

changes in CARTI pathogens in Europe and Asia [196]. Results from the programme revealed that the susceptibility profiles of 2,395 *S. pneumoniae* isolated from 1997 when the study was initiated till 2007 remained unchanged, that is, $\geq 96\%$ in Asia and $\geq 98.6\%$ in Europe [196]. Analogous data were obtained in the course of the Alexander Project, collecting isolates from Europe, Middle East, Asia, South and North America [157, 197]. Likewise, the MOXIATIV study (a German multicenter study with 29 participating laboratories) demonstrated that 99.3% of the pneumococci were moxifloxacin and levofloxacin susceptible and the MICs of moxifloxacin were as low as those of the prelaunch isolates [198]. These in vitro findings are mirrored by the low prevalence of fluoroquinolone-resistant strains isolated from patients with pneumococcal pneumonia. In 1.2% of the isolates a first step mutation was detected and 6.7% exhibited an efflux phenotype, despite high fluoroquinolone usage [199].

Increasing fluoroquinolone resistance in pneumococci paralleled increased usage of fluoroquinolones in general or 2nd generation quinolones in particular [178, 199–201]. Occasionally, fluoroquinolone resistance resulted in clinical failures in patients with pneumococcal pneumonia having been previously treated empirically with oral fluoroquinolones [160, 185, 202–204]. In total, there were 20 ciprofloxacin and levofloxacin treatment failures reported till January 2005 and reviewed by Fuller and Low [204]. A pretherapy isolate was available in five cases only with MICs ranging from 1 mg/L to 16 mg/L; MICs for the during-therapy isolates ranged from 4 mg/L to >32 mg/L [204]. Thus, the question cannot be answered if resistance may have developed during therapy resulting in clinical failure. This question was recently addressed by Orr et al. [205] who investigated in a tertiary referral hospital in England in 865 patients the incidence and epidemiology of levofloxacin-resistant pneumococci. 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 harboured the same clone [205]. This study revealed that levofloxacin pneumococcal resistance still is uncommon and that in vivo fluoroquinolone resistance development is very rare. If it does occur, strain replacement accounts for the majority of cases. 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 with levofloxacin plus intravenous benzylpenicillin [205]. High-level levofloxacin-resistance (MIC > 8 mg/L) developed under levofloxacin-treatment in eight out of 164 patients with chronic obstructive pulmonary disease whose pretherapy isolates were susceptible [206]. A fatal outcome was described in another patient with chronic obstructive pulmonary disease who was infected with a *S. pneumoniae* strain with a preexisting *parC* mutation; the MIC of levofloxacin for this strain was 1 mg/L, so that the mutation passed unnoticed and the strain was classified as susceptible [207]. 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 was isolated subsequently; this strain harbored a *parC* mutation [208].

The prevalence of first-step fluoroquinolone-resistant *S. pneumoniae* mutants is increasing [195, 200, 208]. Although the subtle changes in MICs of 3rd 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 [209–211]. Three up to 30% of clinical pneumococcal isolates contain mutations in the *gyrA* and/or *parC* loci [179, 209, 212, 213].

These data demonstrate that many pneumococcal isolates with first-step fluoroquinolone resistance may pass unnoticed in routine susceptibility testing because of the high resistance breakpoints. This theory has been proven by two in vitro screening tests [214, 215]. Previously, the resistant breakpoints for ciprofloxacin and levofloxacin were >4 mg/L and >8 mg/L, respectively. Actually, the resistant breakpoints of ciprofloxacin and levofloxacin for *S. pneumoniae* defined by EUCAST are >2 mg/L. The EUCAST provides two comments in this context: 1st, wild type *S. pneumoniae* are not considered susceptible to ciprofloxacin, and 2nd the breakpoints for levofloxacin relate to high dose therapy. However, high levofloxacin doses, that is, 750 mg once 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 an advise on therapy in the patient is limited. Two case reports describing levofloxacin treatment failures confirm the limited predictability of routine in vitro susceptibility testing. First, a 71-year-old male patient was hospitalized due to pneumococcal pneumonia. The pretherapy isolate was levofloxacin susceptible with a MIC of 2 mg/L although it had a point mutation in *gyrA*. The patient was treated with 500 mg iv for 13 days; on day 4 intravenous clarithromycin was added and on day 14 treatment was changed. Initial treatment with levofloxacin failed due to an acquisition of a second mutation in *parC* resulting in a MIC of 16 mg/L [216]. Second, a 79-year-old male patient was hospitalized with bacteremic pneumonia caused by levofloxacin susceptible *S. pneumoniae* with a MIC of 1 mg/L. The patient was treated with 500 mg levofloxacin iv. After initial improvement fever reappeared on day 4, so that amoxicillin was added; but the clinical condition failed to improve and the patient died one day later. This pathogen had a preexisting mutation in *parC*; the post-therapy isolate had an additional mutation in *gyrA* [207]. Both patients had apart from the advanced age additional risk factors like COPD and others.

These clinical examples confirm that first step mutants of *S. pneumoniae* are 1st phenotypically considered to be susceptible and 2nd are primed to acquire additional QRDR mutations conferring high-grade fluoroquinolone resistance resulting in clinical failure [217]. As most first step mutants pass routine susceptibility testing unnoticed they are not effectively detected in surveillance studies, so that these may

be biased. Consequently, routine susceptibility testing of suspicious cases at least should be modified, for example, by using a second fluoroquinolone like ciprofloxacin as an indicator for the acquisition of a first mutation. Furthermore, it should be considered to use a more potent antipneumococcal fluoroquinolone than levofloxacin, for example, a “respiratory fluoroquinolone” like a C-8-methoxyquinolone.

Recently, fluoroquinolone-resistant streptococci were isolated from children. Ciprofloxacin-resistant *S. pneumoniae* were detected in 28% of 847 children of 6 to 60 months of age living in rural Vietnam, about half of which were treated previously with antibacterial agents except fluoroquinolones. This finding could be due to the transmission of already fluoroquinolone-resistant strains within the household from adults to children [218]. Furthermore, ciprofloxacin resistance rates increased significantly ($P < 0.01$) between 1997 and 2006 from 0% to 4.5% in Canadian children aged 0 to 15 years [189]. Elderly are also prone to acquire resistant pneumococci. High fluoroquinolone resistance rates (>10%) were recorded in adults ≥ 65 years old and in patients who acquired pneumococcal infections in nursing homes [178, 190, 193, 201]. A random sample of surveillance isolates collected in the USA between 1998 and 2003 revealed that 16.2% of isolates were recovered from nursing home patients and 6.4% from non-nursing home patients [219].

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 $\geq 4 \mu\text{g}/\text{mL}$) in only 12 cases (<0.1%) [220]. All were HIV-infected children; nine were on therapy for tuberculosis; 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 endemic and clonal spread of fluoroquinolone-resistant pneumococci. Furthermore, horizontal gene transfer may have transformed low-level into high-level levofloxacin-resistant strains [221].

Multiresistant serotype 8 pneumococci (approx. 62% were coresistant to erythromycin, levofloxacin, and tetracycline) causing invasive disease were significantly more frequent in HIV-infected patients than in non-HIV patients admitted to a tertiary care hospital in Madrid, Spain [222], thus indicating that multiresistant pneumococci are a cause for concern in HIV patients.

Despite the global emergence of first- and second step fluoroquinolone-resistant *S. pneumoniae*, the prevalence of resistance in pneumococci isolated from patients suffering from CARTI remained low. Several factors may have contributed to this phenomenon: 1st, 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. 2nd, treatment guidelines may have been adapted recommending the use of a second agent like benzylpenicillin

in, for example, elderly or patients with other risk factors. 3rd, information about patient history and previous antibiotic use is crucial for determining appropriate empirical therapy [190, 223]. 4th, 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 [224–226].

Haemophilus influenzae is generally highly susceptible to fluoroquinolones; global surveillance studies demonstrated that susceptibility to fluoroquinolones remained at or near 100% [197, 227–230]. Resistant isolates have been recovered occasionally [230–237]. For example, during the 1997 through 1998 SENTRY-programme four (0.13%) fluoroquinolone-resistant *H. influenzae* strains were identified [238]. The strains were genetically distinct and had different *gyrA* mutations. Furthermore, clonal outbreaks of fluoroquinolone-resistant *H. influenzae* were observed in long-term care facilities [239–241] and in elderly in Japan [242].

Because of the occurrence of fluoroquinolone-resistant strains, Hirakata et al. [243] 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 to 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 [243].

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 at least should be modified, for example, by using nalidixic acid as an indicator for the acquisition of a first mutation [228, 244]. The presence of *H. influenzae* with reduced levofloxacin-susceptibilities in kindergarten children in Hong Kong is alarming; the MICs of nalidixic acid and levofloxacin were 64–128 mg/L and 0.125 mg/L, respectively [245]. Likewise, the report about a levofloxacin treatment failure in a patient with *H. influenzae* pneumonia is worrying. The 71-year-old patient has been treated with 500 mg levofloxacin once daily; after 7 days the clinical condition had not improved and therapy was changed. Levofloxacin MICs for *H. influenzae* isolated from blood-cultures and bronchial aspirates at day 7 amounted uniformly to 16 mg/L and all the isolates had changes in the QRDR [246].

M. catarrhalis remains fluoroquinolone susceptible to almost 100%, although resistant strains have been detected in a very few single cases [197, 228, 229, 231, 247]. Two treatment failures with clonally unrelated resistant strains have been reported in patients at risk [248].

Conclusion. The 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.

3.2.2. Nosocomial Respiratory Tract Infections. In treatment guidelines and reviews, nosocomial pneumonia is further differentiated into healthcare associated pneumonia (HCAP), hospital acquired pneumonia (HAP), and ventilator associated pneumonia (VAP) [249–254]. Bacterial pathogens most frequently associated with HCAP, HAP, and VAP are methicillin-susceptible and -resistant *S. aureus* (MSSA, MRSA), *Pseudomonas aeruginosa*, *H. influenzae*, *K. pneumoniae*, *E. coli*, and occasionally *S. pneumoniae* and *Acinetobacter* spp. [255]. Resistance surveillance studies differentiating the origin of isolates tested according to pneumonia categories are almost nonexistent; resistance-rates are quoted in very general terms even in some of the guidelines quoted above. Therefore, information compiled below summarises susceptibility data for invasive pneumococci or pathogens isolated from sputa obtained preferably from ICU-patients. *S. pneumoniae* isolated from patients with invasive as well as noninvasive diseases in eight European countries and Latin America were examined in the PneumoWorld Study from 2001 to 2003. Susceptibility testing revealed that fluoroquinolone resistance rates ranged from 0% in Austria, Switzerland, and Belgium to 0.9% in Germany and 1.2 to 1.3% in Italy and Portugal [256]. From the bacteraemic pneumococci isolated from 1999 to 2007 in the UK and Ireland, 14.3% were resistant to ciprofloxacin [257]. Rates of levofloxacin-resistance in invasive *S. pneumoniae* collected by the Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance Program Network (ABCS) remained stable throughout the years at about 0.3% to 0.43% [258, 259]. This finding contradicts reports of seven-valent pneumococcal conjugate vaccine-driven expansion of fluoroquinolone resistant clones [164, 260, 261]; others have hypothesized that a decrease in fluoroquinolone resistance among invasive pneumococci may be due to reduction of absolute numbers of isolates within the vaccine serotypes [262]. Nevertheless, the potential for the clonal expansion and dissemination of fluoroquinolone-resistant strains obtained from the ABCS program has been demonstrated [175]. Clonal spread of levofloxacin resistance in invasive *S. pneumoniae* isolates was identified in Madrid, Spain [176]. Likewise, clonal spread of levofloxacin-resistant pneumococci could be demonstrated in strains from Hong Kong, whereas strains collected in Okinawa, Japan, were not clonally related [177].

All *S. pneumoniae* blood-isolates sampled in 2005–2006 and 2008 from Canadian emergency room- and ICU patients were ciprofloxacin susceptible [263, 264]. Ciprofloxacin-resistance among MSSA- and MRSA-blood isolates collected in 2008 amounted to 8% and 81.6%; ciprofloxacin-resistance in respiratory isolates was 11%, and 95.6%, respectively

[264]. All *H. influenzae* blood-isolates were ciprofloxacin-susceptible [263]. Ciprofloxacin-resistance rates in *E. coli*, *P. aeruginosa*, and *K. pneumoniae* isolated from blood were 21.6%, 16%, and 4.3%, respectively. Eight percent of these *E. coli* isolates were ESBL producers. Ciprofloxacin resistance in respiratory isolates of *E. coli*, *P. aeruginosa*, and *K. pneumoniae* was 31.7%, 18.4%, and 4.5%, respectively [264]. Pathogens isolated from ICU patients not categorized in patients with/without nosocomial RTIs showed variable fluoroquinolone resistance [265]. Pathogens were collected in the USA (283 sites), Canada (87 sites), France (63 sites), Germany (169 sites), and Italy (48 sites) from January 2000 till December 2002. Pneumococci were highly susceptible in all geographic regions. 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 [265]. In ten Asian countries, ciprofloxacin resistances in *P. aeruginosa*, *E. coli*, and *K. pneumoniae* isolated from HAP- and VAP-patients ranged from 4–44%, 26–80%, and 13–68% [266]. Similar rates were reported for Gram-negative species isolated from Indian VAP-patients [267].

Fluoroquinolones have in the past shown good activity against *A. baumannii* [268]; however, over the past decade there has been a constant rise in fluoroquinolone- and multidrug resistance [269, 270]. Fluoroquinolone resistance in *Acinetobacter* spp. isolated from HAP- and VAP-patients in ten Asian countries varied from 23.2 to 92% [250]. 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 [265]. 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% [271].

Conclusion. Pneumococci and haemophilia isolated from HCAP, HAP, and VAP patients are almost all fluoroquinolone-susceptible. MSSA and in particular MRSA are frequently fluoroquinolone-resistant. Enterobacteriaceae and nonfermenters 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.

3.2.3. Cystic Fibrosis. One of the most striking aspects of natural history of *P. aeruginosa* and its association with cystic fibrosis (CF) is the adaptation and heterogeneity exhibited by the organisms as colonisation of the lung develops to a chronic state. In the early stages of colonisation the *P. aeruginosa* population is usually homogeneous with respect to colonial morphology, antigenicity and drug susceptibility. Later, however, considerable heterogeneity is observed and the *P. aeruginosa* population shows a considerable degree of heterogeneous antimicrobial susceptibility with MICs ranging over a broad range from hyper susceptibility to

high-level resistance [272–275]. *P. aeruginosa* being heteroresistant to all relevant antibacterials including ciprofloxacin have been described by these authors. For example, the MIC of ciprofloxacin for one genetically homogeneous isolate as determined by routine methods was 0.5 mg/L prior to ciprofloxacin therapy; however, population analysis revealed that hypersusceptible subpopulations were present at high frequencies and subpopulation with MICs up to 16 times the MIC for the entire population were present at frequencies ranging from 2×10^0 to 5×10^{-2} . The population analysis of the post-exposure isolate showed that the hypersusceptible subpopulations have been eradicated; the subpopulations with 2 to 8 times the pre therapy MIC occurred at frequencies of approx 1×10^{-2} and the subpopulations with 32 and 64 times the pre therapy MIC were present with frequencies of 4- and 2×10^{-4} [275]. Consequently, there is a high probability in CF patients that multiple subpopulations of *P. aeruginosa* with a broad range of MICs will exist, so that in principle a single MIC value for the entire population does not exist. Therefore, selection of colonies for susceptibility testing [276] as well as routine susceptibility testing of mixed morphotypes of *P. aeruginosa* yields inaccurate results; for example, predictability of ciprofloxacin susceptibility and resistance of a single isolate from a CF patient was 87.0% and 41.7%, respectively [277]. Thus, the value of conventional susceptibility-testing of bacteria isolated from CF patients is questionable [278]. In addition, fluoroquinolone resistance emerges in the first few days of therapy and viable counts of the pathogen are reduced minimally. Therefore, the fluoroquinolone used to treat CF patients must exert pleiotropic effects on *P. aeruginosa*; ciprofloxacin, for example, inhibits quorum sensing [279] or modulates immune response [280, 281]. However, it was demonstrated recently in vitro and in patients that antivirulence interventions based on quorum-sensing inhibition with a macrolide diminish natural selection towards reduced virulence and therefore may increase the prevalence of more virulent genotypes [282]. Thus, it has to be studied clinically in CF patients if a fluoroquinolone may exert quorum sensing inhibition at all, and if the virulence of the pathogen may be affected or not.

Furthermore, a common feature of *P. aeruginosa* isolated from CF patients is the very high prevalence of mutator (or hypermutable) strains in contrast to those with an up to 1,000-fold lower spontaneous mutation rate of strains isolated from patients with acute infections [283, 284]. Such hypermutator strains persisted and even amplified (50,000-fold) in contrast to nonhypermutator strains despite adequate, that is, administration of standard doses, exposure to ciprofloxacin [285]. Recent studies have shown that mutators may affect modulation of virulence factors, genetic adaptation to the growth environment in the infected patient, persistence and perhaps also transmissibility [286].

Conventional susceptibility testing—thus not considering the heterogeneous susceptibility pattern of the subpopulations—of *P. aeruginosa* isolates from CF patients revealed that ciprofloxacin resistance in Europe ranged from 13.7% in Bulgaria [287] to approximately 30% in the UK, Spain, Germany, and Italy [288–291]; 37.4% of the US

isolates were ciprofloxacin-resistant [292]. Mucoid strains tended to be less ciprofloxacin susceptible than non mucoid isolates [290]; 27.8% of the non mucoid and 35.3% of the mucoid isolates were susceptible to ciprofloxacin.

Patients with cystic fibrosis suffer from *S. aureus* infections, too. MRSA carriage and infection are becoming increasingly common among CF patients. It appears that healthcare associated-MRSA predominate, but asymptomatic community associated-MRSA colonisation may be a predictor of disease [293]. The emergence and spread of a specific MRSA isolate in Marseille, France, is worrying. This well-adapted multiresistant isolate is closely related to the vancomycin resistant strain Mu50 and spreads rapidly in CF patients [294]. This strain is also characterized by the presence of an antibiotic inducible (e.g., imipenem, tobramycin, ciprofloxacin) bacteriophage which may result in high frequency transfer and the unintended promotion of spread of virulence and resistance determinants.

The presence of hypermutable *P. aeruginosa* and MRSA in CF patients is a threat to the patient and a challenge for any antibacterial agent.

Conclusion. *P. aeruginosa* colonising and infecting CF patients are geno- and phenotypically highly heterogeneous, so that any routine susceptibility testing and resistance surveillance studies are misleading. It is an inevitable consequence of therapy that preexisting resistant subpopulations will be selected, so that resistance will develop rapidly under treatment.

3.3. Skin and Skin Structure Infections. Acute bacterial skin and skin structure infections (ABSSSI) are typically monomicrobial and caused by *S. aureus* and *S. pyogenes* which are also the most common pathogens in complicated bacterial skin and skin structure infections (cBSSSI) which are frequently polymicrobial. However, Gram-negative and anaerobic microbes become more prevalent. 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 [295, 296].

Although *S. pyogenes* were and are still highly susceptible to fluoroquinolones, low incidences ($\leq 8\%$) of ciprofloxacin resistance have been found globally; fluoroquinolone resistance in Japan is almost nonexistent [297–315]. In Belgium, fluoroquinolone resistance increased from 2.8% to 13.1% from 2003 to 2005 and decreased thereafter to 8.9% in 2006 [307]. It is important to note, that in Belgium approx. 55% of the fluoroquinolone-resistant isolates were recovered from children aged less than 16 years [307]. Although fluoroquinolones are contraindicated in children, ciprofloxacin is often used off-label for select life-threatening conditions. Furthermore, older and thus cheap fluoroquinolones are used topically for treatment of otitis media with otorrhoea through tympanostomy tubes in paediatric patients.

In the early days of fluoroquinolone development and clinical use the fluoroquinolones were regarded as potential alternatives to MRSA therapy with a β -lactam or vancomycin. This was due to the fact that resistance to

fluoroquinolones has rarely emerged in the various staphylococcal infection models. Especially in experimental endocarditis caused either by MSSA or MRSA fluoroquinolones proved effective and were not associated with the development of fluoroquinolone resistance in most of the models. In addition, their *in vivo* activity was equivalent or even superior to that of vancomycin or imipenem [2, 316, 317].

Unfortunately, staphylococci acquire resistance to antibacterials quite rapidly as they are genetically highly variable [318]. The determinant for methicillin resistance is located on the so-called *staphylococcus* cassette chromosome *mec* (*SCCmec*). Some of the *SCCmec* elements contain additional genes for antibiotic resistance encoding for aminoglycoside-, tetracycline-, and macrolide-lincosamide-streptogramin-resistance [319, 320]. Furthermore, HA-MRSA tended to develop fluoroquinolone resistance more frequently than MSSA [321, 322]. This phenomenon may be due to the fact that on the chromosomal map of the *S. aureus* genome the *mecA* gene is located between protein A and DNA gyrase genes. Therefore, mutations in the gyrase may have an effect on the expression of *mecA* in HA-MRSA strains [323] and some cell wall associated proteins such as protein A and fibronectin binding proteins [324, 325]. Thus, almost any antibacterial drug class has a methicillin-resistance selective potential [326–328], 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. Hospital admissions in the US for ABSSSI caused by fluoroquinolone resistant MRSA increased from 29% between 2000 and 2004 [329] to 70.3% in 2008 [330]. In addition, fluoroquinolone-resistant HA-MRSA were spread horizontally as were HA-MRSA as such, so that nowadays neither the 2nd- nor the 3rd-generation fluoroquinolones represent alternatives for treatment of HA-MRSA infections [5, 331–338].

In recent years, the emergence of CA-MRSA has complicated the treatment of even ABSSSI [296, 332, 333]. CA-MRSA strains differ in several ways from HA-MRSA strains like composition of the *SCC mec*, the carriage of plasmids encoding resistance to antibacterials of other drug classes and in their associated pathogenicity factors [336]. In contrast to multidrug resistance usually seen in HA-MRSA strains, antibiotic resistance in CA-MRSA is most often limited to macrolides [319, 337–340], so that it has previously been proposed that some 3rd-generation fluoroquinolones could be useful in the treatment of CA-MRSA, since the causative pathogens were usually susceptible to even ciprofloxacin [341–346]. But recently mupirocin, tetracycline, clindamycin, and moxifloxacin (and thus to any commercially available fluoroquinolone) resistance development has been reported [347, 348]. The clone USA 300 became the predominant strain type in the USA and has spread to Europe, South America, and Australia [347, 349, 350]. The lineage USA 100 is frequent, too [351]. Fluoroquinolone resistance in isolates recovered from a phase IV study in patients with cSSSI in the USA and EU from 2004 to 2007 was high; 100% of USA 100-isolates and 42.6% of USA 300 isolates were resistant to gatifloxacin [351]. Community MRSA

isolates in general, and the USA 300 clone in particular are increasingly multidrug resistant, with resistance profiles recently broadening to include clindamycin, tetracycline, mupirocin, and fluoroquinolone agents, in addition to the β -lactams; occasionally, community isolates also display reduced susceptibility to vancomycin or resistance to gentamicin or trimethoprim-sulfamethoxazole [352].

Pathogens collected from 27 USA and 28 EU medical centers in 2009 causing cBSSSI were variably susceptible to fluoroquinolones: levofloxacin resistance in the USA/EU 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 β -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* [353]. 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 [354–356], thus, indicating that resistance rates did not change substantially over time.

Of 175 anaerobic bacteria isolated in the late 1990s from bacterial skin and soft-tissue infections, 27% were levofloxacin-resistant [357]. All *Peptostreptococcus* species isolated from hospitalised patients with diabetic foot wound infection were susceptible to levofloxacin and moxifloxacin; resistance (5–7%) was found in isolates of *B. fragilis*, *Bacteroides ovatus*, and *Prevotella* species collected in 1999 to 2002. [358, 359]. Against *B. fragilis*, moxifloxacin's MIC⁹⁰ was 1.0 μ g/mL. Against other *Bacteroides* species, the MIC⁹⁰ was 2–4 μ g/mL. Moxifloxacin was least active against *Fusobacterium* species other than *F. nucleatum* (MIC⁹⁰, 8 mg/L). Among anaerobic species isolated from patients with moderate to severe diabetic foot infections from 2001 to 2004 in the USA, 24% were fluoroquinolone resistant [356]. In detail, moxifloxacin resistance rates were: 43% *B. fragilis* group, 10% *Fusobacterium* spp., 2% *Porphyromonas* spp., Gram-positive cocci 18%, and Gram-positive rods 12% [283]. As levofloxacin is less active against anaerobes, resistance rates were correspondingly higher. Of all infection sites, decubitus ulcer isolates had the highest resistance rates [360].

Conclusion. In principle, a 3rd generation fluoroquinolone is well suited for treatment of polymicrobial SSSIs because of its broad antibacterial spectrum. 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 heterogeneous susceptibility pattern may limit the use of fluoroquinolones in the treatment of ABSSSIs and cBSSSIs.

3.4. Intra-Abdominal Infections. The Surgical Infection Society and the Infectious Diseases Society of America (IDSA) have recently published guidelines for the diagnosis and treatment of complicated intra-abdominal infections (IAIs). *E. coli*, *Enterococcus* spp., *Bacteroides fragilis*, and other *Bacteroides* species are the most common pathogens associated

with intra-abdominal infections [7, 361]. Intra-abdominal infections 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 as the anaerobic bacteria.

Several surveillance studies have demonstrated that there is a global trend toward decreasing susceptibilities of anaerobes to antibacterial agents since two decades. Although the rates of resistance show clinically important variations between continents, countries, and counties, almost all drug classes—except metronidazole—like beta-lactams including the carbapenems, clindamycin and quinolones lose activity against anaerobes. A dramatic loss of antianaerobic activity of fluoroquinolones in particular has been noted, exceeding 50% in some parts of the world [362–367].

The continuously increasing quinolone resistance amongst anaerobes is surprising because of a variety of reasons: First, previous fluoroquinolones like norfloxacin, ofloxacin, ciprofloxacin, levofloxacin were not used clinically for treatment of anaerobic infections. Nevertheless, surveillance testing in the US between 1994 and 1996, that is, prior to the launch of the first antianaerobic quinolone trovafloxacin, revealed that quinolone resistance ranged from 3% to 8%. Second, quinolone resistance rates increased in 1997 to 13%, although trovafloxacin was approved in December 1997. Quinolone resistance continued to increase to 15% in 1998. Despite the limited use of trovafloxacin in 1998 and its relegation to a restricted therapeutic category in June 1999, frequencies of quinolone resistance increased further, peaking at 25% in 2001 [360, 368]. Furthermore, it has been speculated that third, older fluoroquinolones like norfloxacin, ciprofloxacin, ofloxacin, and levofloxacin may have fostered quinolone resistance development [360, 368]. However, this hypothesis is not convincing either as the older fluoroquinolones have been heavily used since their launch. Furthermore, the older fluoroquinolones are almost inactive against anaerobes [369, 370]. Although very high total concentrations are achieved in the faeces, free and thus antibacterial active concentrations, are low as quinolones are highly and tightly bound to cell debris, DNA, cellulose, and other fecal matter [371]; therefore, norfloxacin, ciprofloxacin, ofloxacin, and levofloxacin suppress growth of fecal aerobic Gram-negative rods but do not affect significantly the anaerobic flora. Anaerobes with increased MICs or quinolone resistance have rarely been isolated from patients during or shortly after a quinolone treatment [372]. Thus, the driving forces for quinolone resistance development are at present unknown.

Very heterogeneous data on quinolone resistance amongst anaerobes have been reported, ranging for example from 27% to 50% in the US [363, 373], and 44.4% in Canada [374], 15% to 25% in Spain [275, 364, 365, 375], and 0% to 32% in Greece [364, 365, 376]. This heterogeneity of susceptibility data within and between countries—which is typical for aerobic species, too—may reflect marked differences in 1st, the patient populations from whom the isolates were obtained (health-care versus community acquired infections—which, however, is almost always not

specified); 2nd, prior antibiotic exposure; 3rd, the patient populations admitted to either tertiary care-or primary care centres; 4th, the sites of isolation; 5th, the limited number of participating centres. Overall, 9% of the European *B. fragilis* group isolates were moxifloxacin-resistant in 2002; a moderate increase to 13.6% was noted in 2009. Geographical differences were detected in 2009, too, with higher resistance rates for moxifloxacin in Scandinavian (21.4%) and Eastern (11.3%) than in Mediterranean countries (5.4%) [365].

A most recent German study with 32 participating centers revealed that moxifloxacin MICs for anaerobes are by one to two titration steps higher than prior to its launch. Resistance rates ranged from 10% to 22% for various anaerobic species except *B. vulgatus*, with 59% of the isolates being resistant. It became evident, too, that resistance rates are higher in isolates obtained from 1st, tertiary care versus primary care centres, 2nd, patients admitted to the ICU versus standard care, and 3rd, health care versus community acquired infections [377].

The resistance epidemiology of quinolone resistance among anaerobes has to be complemented with resistance figures in *Enterobacteriaceae* isolated from patients with intra-abdominal infections in order to cover the entire spectrum of potential pathogens. In general, the situation in Asia is alarming as resistance-rates surpass 60% of the isolates being resistant to ampicillin-sulbactam or a quinolone and producing ESBL [378–384]. ESBL production in *E. coli*, *K. pneumoniae*, or *K. oxytoca* was highly variable in the Asia-Pacific region ranging in total from 4.4% in New Zealand to 77.4% in India. Only 17% and 27% of the ESBL producing *E. coli* and *K. pneumoniae* strains, respectively, were susceptible to ciprofloxacin [379]. In Europe, 11.8% and 17.9% of the *E. coli* and *K. pneumoniae* strains isolated from patients with intra-abdominal infections were ESBL producers [385], ranging from 0% in Lithuania and Switzerland to 30% in Greece. From these, 70% or 78% and 50% or 70% of the community or hospital acquired *E. coli* and *K. pneumoniae* strains were ciprofloxacin resistant. In the US, ESBL production was detected in 4.7% and 17.5% of *E. coli* and *K. pneumoniae* isolates, respectively.

From these, 33% and 19% were susceptible to ciprofloxacin [386]. Ciprofloxacin resistance in a worldwide collection of IAI pathogens amounted to 22.8% in *E. coli*, and 15.6% in *K. pneumoniae* [387]. Both, ESBL production and fluoroquinolone resistance remained high or even increased in 2009–2010 in the Asia-Pacific region, Europe, North- and Latin America; ESBL producers were more frequently isolated from elderly [388–393]. These data confirm—in analogy to the UTI-isolates—the very close correlation between ESBL production and fluoroquinolone resistance in *Enterobacteriaceae* causing IAI. Consequently, fluoroquinolone susceptibility is still high in all those geographic regions in which ESBL-producing Gram-negative bacilli are infrequent. Another clinically relevant finding—again in agreement with UTIs—is that fluoroquinolone resistance was much lower in strains isolated from patients with community acquired intra-abdominal infections 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 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 intra-abdominal infections including mild to moderate infections should be active against both, aerobic and anaerobic pathogens. Consequently, the use of quinolones should be restricted unless resistance rates are lower than 10% [7, 361, 394].

3.5. Sexually Transmitted Diseases. Infections caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most frequent ones among reportable bacterial sexually transmitted diseases (STD) gonorrhoea, syphilis, and chancroid. Infections due to *Chlamydia* spp. were diagnosed almost 4-times more frequently than infections due to *Neisseria* spp. (409.2 cases versus 110.7 cases in the USA in 2009). *Chlamydia* spp. diagnosis increased by 2.8% in 2009 as compared to 2008, and by nearly 20% since 2006, likely due to expanded screening. Gonorrhoea cases declined by 11% overall. Syphilis cases increased, too, while chancroid cases have declined steadily till 2001 and are fluctuating since then. However, *Haemophilus ducreyi*, the causative organisms of chancroid, is difficult to culture, so that this condition may be substantially underdiagnosed. In general, there were large disparities by age, race, and geographical distribution [395–397]. Pelvic inflammatory disease (PID) is a common and serious complication of some sexually transmitted diseases. Two-thirds of cases are considered to be due to sexually-transmitted infections caused by *N. gonorrhoeae* and *C. trachomatis*; one-third (particularly in older women) are commonly polymicrobial. Other pathogens such as *Mycoplasma genitalium* and bacterial vaginosis pathogens (e.g., *Gardnerella vaginalis*, *Mycoplasma hominis*, *Mobiluncus* spp. and other anaerobes) may cause PID, too. Actinomycetes are part of the normal vaginal flora and a rare cause of PID. Therefore, management of PID must take into account in particular the three major pathogens *N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium*.

Coinfections with *C. trachomatis* and *N. gonorrhoeae* are common among young heterosexual patients with gonorrhoea. Therefore, all treatments for STD/PID should cover both, *N. gonorrhoeae* and *C. trachomatis* as well as anaerobes [398, 399], and *M. genitalium* has to be considered [397].

3.5.1. *Neisseria gonorrhoeae*. Initially, *Neisseria* spp. was extremely susceptible to fluoroquinolones with ciprofloxacin MICs of ≤ 0.008 mg/L. However, low level resistance (0.06–0.5 mg/L) was reported shortly after its launch [400–402], followed soon by high-level resistance (MICs of ciprofloxacin > 1.0 mg/L) associated with treatment failures [402–404]. High-level fluoroquinolone resistance is first, more likely to emerge in areas with a high prevalence of low-level resistance; second, it is spread intercontinentally by travellers and an intercity spread and transmission has been reported; third, mono- as well as multi-clonal spread of quinolone-resistant isolates has been reported [405–407].

Typically, several different strain types can be identified by using molecular typing methods; for example, 24 different quinolone-resistant strain types were identified among the isolates having caused an outbreak in California, but only four of these were considered outbreak types and comprised 66% of all the isolates [408]. 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 [409].

Both, low-level and high-level fluoroquinolone resistance has been reported from all parts of the world (reviewed in [410]). Ciprofloxacin resistance in *N. gonorrhoeae* is highest in Asia; resistance rates in China vary from 40 to 100%, depending on the region studied [410–413]. In Korea, ciprofloxacin resistance increased from 9% in 1992, to 84% in 1999, and to 90.5% in 2004 and 83% in 2006 [414, 415]. In India, ciprofloxacin resistance varied from 80.7% in 2002, 97.2% in 2004 to 88.6% in 2006 [416–418]. In Pakistan, ofloxacin-resistance increased from 0% in 1998 to 92.5% in 2009 [419] and ciprofloxacin resistance in isolates collected from 2007 to 2010 in Iran amounted to 53.2% [420]. In Kenya, ciprofloxacin resistance increased from 9.5% in 2007 to 50% in 2009 [421] and ranged in other African countries from 0% in Malawi or Mozambique to 41.9% in South Africa [422]. Quinolone resistance in the Western Pacific Region ranged in 2009 from $\leq 1.5\%$ Fiji, Papua New Guinea and New Caledonia via 35% to 42% in New Zealand and Australia up to $> 95\%$ in Vietnam, Philippines, and Hong Kong, [423]. Gonococcal resistance to ciprofloxacin in the Netherlands, Italy, Greece and in Norway exceed 40% [424–427] which is in the same range as the data previously reported by the “European Surveillance of Sexually Transmitted Infections” (ESSTI) [428] and by the EUROSURVEILLANCE [429]. However, ciprofloxacin-resistance increased to 63% in 17 European countries participating in the European gonococcal antimicrobial surveillance programme, 2009 [430] and was high in the eastern part of the WHO European region, too [431]. Rates of ciprofloxacin resistance amongst the gonococcal isolates rose in Canada from 1.4% in 2001 to 28% in 2006/2007 [432, 433] and the US from $< 1\%$ in 2001 to 6.7% in the first half of 2006 to 14.8% in 2007, decreasing to 13.5% and 9.6% in 2008 and 2009, respectively, increasing again to 12.5% in 2010 [395, 434, 435]. Consequently, quinolones are not recommended as first-line therapy of *N. gonorrhoeae* infections anymore [435–438]. The emergence of multi-drug resistant *N. gonorrhoeae* reduces the treatment-options further [439–444] as such isolates are resistant to quinolones, third generation cephalosporins, and additional agents.

3.5.2. *Chlamydia trachomatis*. Quinolone resistance in *C. pneumoniae* has not been described clinically or even in vitro; however, high-level resistance to ofloxacin, sparfloxacin, and ciprofloxacin occurred in *C. trachomatis* upon serial exposure to subinhibitory quinolone-concentrations [445–449]. However, spontaneous mutation frequencies resulting in moxifloxacin resistance were very low or even nonexistent;

exposure of *C. trachomatis* serovars L₂ and D resulted in emergence of quinolone resistance at a frequency of 2.0–2.2 × 10⁻⁸ in serovar L₂ only, whereas no resistant clones could be elicited in serovar D [450]. It is important to note that these experiments were performed under routine conditions, that is, a relatively high inoculum (approx. 2.7 × 10⁹ inclusion forming units) was exposed to the drug, whereas the bacterial load at the focus of infection is much lower thus reducing the likelihood of drug-induced resistance selection. Nevertheless, fluoroquinolone-resistant strains of *C. trachomatis* have been isolated occasionally [449, 450]. Fluoroquinolone resistance elicited in vitro in *C. trachomatis* serovar L₂ was due to a single nucleotide point mutation in *gyrA*, while no mutations were found in *gyrB*, *parC*, or *parE* genes; no QRDR mutations could be detected in the fluoroquinolone-resistant clinical isolates [451].

3.5.3. *Mycoplasma genitalium*. Surveillance studies for antimicrobial-resistance in general and fluoroquinolone resistance in particular are not existent as culturing of this species from clinical specimens is extremely difficult. Acquired resistance to fluoroquinolones has been described in single cases. Analysis of the *gyrA* and *parC* genes of *M. genitalium* isolated from 6 men in whom levofloxacin therapy failed [452] revealed that in one patient a ParC amino acid change could be detected in the pre- as well as post-therapy isolate, whereas in another patient a ParC-mutation was detectable in the post-therapy isolate only. No QRDR mutations could be detected in strains isolated from the remaining four patients [453]. *M. genitalium* clinical isolates from 28 men with nongonococcal urethritis positive for *M. genitalium* were analyzed by PCR. QRDR-mutations were found in five of these 28 isolates; no alterations were detected in the remaining isolates [454]. The two studies quoted above were performed by noncultural methods, so that no MICs could be determined; thus, an association between QRDR mutations and fluoroquinolone resistance and persistence cannot be proven. Furthermore, it should be considered that the patients in whom persisters could be isolated had been treated with low levofloxacin doses (100 mg t.i.d. for 14 days); in addition, levofloxacin is characterized by a moderate activity against *M. genitalium* while for example, C8-methoxyquinolones are ten times as active [455, 456].

Conclusion. Resistance of *N. gonorrhoeae* to antimicrobials continues to increase worldwide, although considerable geographical variations in resistance exist. Therefore, fluoroquinolones are not recommended as first-line therapy of *N. gonorrhoeae* infections anymore [435–438]. However, local quinolone-treatment options based on local surveillance data may be reasonable, because of 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, too [399]. In case parenteral β-lactam therapy is not feasible, oral use of fluoroquinolones with or without metronidazole is recommended provided treatment is based on results of antimicrobial susceptibility testing [399].

3.6. Traveller's Diarrhea. Enterotoxigenic and enteroaggregative *E. coli* (ETEC and EAEC) are the major causes of bacterial traveler's diarrhea causing up to 80% of acute cases; *Shigella* spp., *Salmonella* spp., and *Campylobacter* spp., as well as viruses and protozoa cause the remainder 20% of cases. Although widely present, the bacterial pathogens show seasonal as well as geographic occurrence patterns [457–460].

In the early days of fluoroquinolone treatment of gastrointestinal infections, ciprofloxacin and other fluoroquinolones were found to be highly active in vitro and clinically effective in the treatment of traveler's diarrhea [461, 462]. However, a study performed during 1997 indicated that the MIC₉₀-values of ciprofloxacin and levofloxacin for enteropathogens collected in India, Jamaica, Mexico, and Kenya were as low as 0.125 mg/L and 0.25 mg/L; however, the individual MICs ranged from <0.0156 to 256 mg/L, thus, indicating that fluoroquinolone-resistant strains have emerged already [460]. Another study assessing the evolution of antimicrobial resistance in EAEC and ETEC causing diarrhea in patients who had traveled to different developing countries, comparing two periods of time, 1994–1997 and 2001–2004 revealed that a statistically significant increase in resistance (*P* < 0.01) was observed for nalidixic acid and ciprofloxacin. Mutations in the *gyrA* gene were found in all nalidixic acid-resistant isolates, whereas mutation(s) in both *gyrA* and *parC* genes were found in the ciprofloxacin-resistant isolates. The prevalence of quinolone-resistant EAEC and ETEC was high among the isolates from patients who had travelled to North Africa (50% of EAEC and 43% of EAEC were resistant to quinolones) and among the isolates from patients who had traveled to the Indian subcontinent (66% of EAEC and 28% to 64% of ETEC were resistant to quinolones). In addition, 33% of the ETEC strains from patients traveling to South-east Asia were also quinolone resistant [463–465]. Results for strains isolated from travelers to India [464], Mexico, Guatemala, India [465], and Ghana [466] confirm that fluoroquinolone resistance increased significantly during the past decade.

Recently, ESBL-producing EAEC were isolated from patients who had traveled to India [467]. Out of 51 EAEC isolates five CTX-M-15 producers were identified which were resistant to fluoroquinolones, too. Three of these five isolates belonged to the same clonal type. ESBL-producing diarrheagenic *E. coli* strains were isolated from children under five years of age in Nicaragua; the ciprofloxacin-MICs ranged up to 8 mg/L [468]. Diarrheagenic *E. coli*, in which, however, ESBL production has not been specified, were isolated from children in Brazil [469] and Vietnam [470]. The isolation of ESBL-producing diarrheagenic pathogens from children suggests that such strains being frequently multidrug-resistant are widespread in the community.

A comparison of the MIC₉₀ values of ciprofloxacin for stains isolated in 1997 and 2006–2008 revealed that the susceptibilities of *C. jejuni*, *Salmonella* spp., and *Shigella* spp. remained unchanged, ranging from 0.06 to 0.125 [465]. However, nalidixic acid and ciprofloxacin are frequently used in several parts of the world for empirical treatment of typhoid fever and other enteric infections, so

that nalidixic acid-resistance was frequent in the 1990s already; some of the nalidixic acid-resistant strains isolated in India, Jamaica, Mexico, and Kenya were cross-resistant to ciprofloxacin [465]. Resistance to fluoroquinolones increased in enteropathogens other than *E. coli* over the past years causing problems in all regions of the world, including the USA and Europe [471, 472]. However, fluoroquinolone resistance differed by race, ethnicity, age, travel, and species. Only 0.5% of *Shigella* spp. strains isolated in the USA were ciprofloxacin resistant [473]; likewise, none of the *Salmonella* spp. and *Shigella* spp. strains isolated from children under five years with diarrhea in rural Mozambique were resistant to ciprofloxacin [474]. On the other hand, nalidixic acid resistance in *Shigella* spp. and *Salmonella* spp. strains examined in Teheran, Iran, increased from 9.2% in 2001 to 42.3% in 2005 [475], and ofloxacin-resistant *Campylobacter* spp. strains collected over a 11 year period in Pakistan increased from 0% in 1992 to 23% in 2002 [476]. In the UK, an increase of ciprofloxacin-resistant *Campylobacter* spp. from 7% in 1995 to 37.5% in 2008 was reported [477] and 80.5% of the *Campylobacter* spp. strains isolated in five different Portuguese cities over a five year period from 2003 to 2007 were ciprofloxacin-resistant [478]. Plasmid-mediated quinolone resistance is frequent among *Salmonella* spp. and *Shigella* spp. [42–45].

Conclusion. The fluoroquinolones have been the most effective antibiotics for the prophylaxis and treatment of bacterial travelers' diarrhea pathogens, but increasing resistance to these agents, mainly among *Campylobacter* species, may limit their benefit in the future [457, 479].

4. Discussion

The emergence of resistance to fluoroquinolones in virtually all species of bacteria was recognized soon after the introduction of these compounds for clinical use [1, 480]. During the last several years, resistance to fluoroquinolones has remained very high among MRSA, *P. aeruginosa* and anaerobes as well as in pathogens isolated from intensive care unit-patients. More worrisome are recent reports of an overall increase in resistance to fluoroquinolones among bacteria causing community-acquired infections, such as *E. coli* and *N. gonorrhoeae*. These surveillance data demonstrate that fluoroquinolone resistance has to be associated with particular bacterial species on the one hand and patient populations on the other hand. This conclusion has been drawn by Acar and Goldstein already in 1997. These authors wrote: "The introduction of fluoroquinolones more than 10 years ago offered clinicians orally and parenterally administrable compounds with a broad spectrum of activity and therapeutic results not seen before for a wide range of infections, including complicated urinary tract infections, gastrointestinal infections, sexually transmitted diseases, respiratory tract infections, and chronic osteomyelitis. Extensive use and misuse of these compounds led to the emergence and spread of resistant strains. Widely varying percentages of resistance to fluoroquinolones have been associated with particular bacterial species, clinical settings,

origins of strains, geographic locations, and local antibiotic policies" [480]. Obviously, not much has changed since then; on the contrary, resistance rates increased to alarming high rates. The continued increase in fluoroquinolone resistance rates affects patient management and necessitates a change in some current guidelines for the treatment of, for example, urinary tract infections [145–147], or even precludes the use of fluoroquinolones in the treatment of severe intra-abdominal infections [8] or sexually transmitted diseases [399, 435–438]. The consequences to be drawn are discussed indication-specifically above.

Although *S. pneumoniae* and *H. influenzae*, causing community acquired respiratory tract infections (CARTIs), remained highly susceptible to fluoroquinolones, 10- to 30% of *H. influenzae* and *S. pneumoniae* causing CARTIs harbored first-step-mutations in the quinolone resistance determining region conferring low-level fluoroquinolone resistance. These mutants pass susceptibility testing unnoticed and are primed to acquire high-level fluoroquinolone resistance rapidly, thus putting the patient at risk. Implementation of a fluoroquinolone therapy in patients harboring such first step mutants, in particular in elderly, immunocompromised patients, and patients with additional risk factors will likely result in the selection of resistance, paralleled by clinical failure.

Of major concern is the association of fluoroquinolone resistance and ESBL-production in Enterobacteriaceae. One- to two thirds of Enterobacteriaceae producing extended spectrum β -lactamases 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 as well as travelers' diarrhea in all those geographic areas in which fluoroquinolone resistance rates and/or ESBL-production is high. The remaining ESBL-producing or plasmid-mediated quinolone resistance mechanisms harboring *Enterobacteriaceae* were low-level quinolone-resistant, thus, being primed to acquire high-level resistance during treatment. Furthermore, fluoroquinolones like ciprofloxacin and levofloxacin select for methicillin resistance in staphylococci. Consequently, their clinical use is limited in those indications in which staphylococci are the predominant pathogens, like skin and skin structure infections. But fluoroquinolones should be used with caution even in the treatment of infections rarely caused by staphylococci like urinary tract infections, because of the MRSA selective potential, thus causing "collateral damage" [146].

The co-selection of fluoroquinolone resistance by β -lactams or aminoglycosides, and vice versa β -lactam- or aminoglycoside resistance by fluoroquinolones demonstrates that chemically unrelated drug classes select for drug-resistant mutants and even multidrug resistant strains, so that the emergence and spread of such strains has compromised the clinical utility of diverse antibacterials.

Successful clones of resistant bacteria are often spread horizontally either due to poor hygiene, transfer of patients from one ward to another or from a hospital to a nursing home, as well as interregional migration and international population mobility. Thus, humans are mobile vectors of drug resistance [481]. Both, exposure of bacterial pathogens

to antibacterials and environmental factors have a role in the emergence and spread of resistance. Furthermore, inappropriate antibiotic policies, poor compliance, suboptimal dosing, diagnostic and laboratory error, ineffective infection control, counterfeit or altered drugs contribute to the selection of resistance. Pleiotropic factors have an impact on the fluoroquinolone resistance epidemiology; as resistance rates vary significantly between and within countries, antibiotic prescribing must be viewed against this background of diverse processes contributing to the emergence and spread of antimicrobial drug resistance.

Conflict of Interests

The author declares that he has no conflict of interest.

References

- [1] A. Dalhoff, "Discovery and development of anti-infectives at Bayer: a personal view. Part III: fluoroquinolones," *SIM News*, vol. 58, no. 3, pp. 92–105, 2008.
- [2] A. Dalhoff, "Quinolone resistance in *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Development during therapy and clinical significance," *Infection*, vol. 22, supplement 2, pp. S111–S121, 1994.
- [3] C. Thauvin-Eliopoulos and G. M. Eliopoulos, "Activity in vitro of the quinolones," in *Quinolone Antimicrobial Agents*, D. C. Hooper and E. Rubinstein, Eds., chapter 5, pp. 91–111, ASM Press, Washington, DC, USA, 3rd edition, 2003.
- [4] A. Dalhoff, "In vitro activities of quinolones," *Expert Opinion on Investigational Drugs*, vol. 8, no. 2, pp. 123–137, 1999.
- [5] A. Dalhoff and F. J. Schmitz, "In vitro antibacterial activity and pharmacodynamics of new quinolones," *European Journal of Clinical Microbiology and Infectious Diseases*, vol. 22, no. 4, pp. 203–221, 2003.
- [6] K. H. Keddy, A. M. Smith, A. Sooka, H. Ismail, and S. Oliver, "Fluoroquinolone-resistant typhoid, South Africa," *Emerging Infectious Diseases*, vol. 16, no. 5, pp. 879–880, 2010.
- [7] D. E. Low, "Quinolone resistance and its clinical relevance," in *Quinolone Antimicrobial Agents*, D. C. Hooper and E. Rubinstein, Eds., chapter 23, pp. 355–386, ASM Press, Washington, DC, USA, 3rd edition, 2003.
- [8] J. S. Solomkin, J. E. Mazuski, J. S. Bradley et al., "Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America," *Clinical Infectious Diseases*, vol. 50, no. 2, pp. 133–164, 2010.
- [9] M. R. Capoor and D. Nair, "Quinolone and cephalosporin resistance in enteric fever," *Journal of Global Infectious Diseases*, vol. 2, pp. 258–262, 2010.
- [10] R. Bax, R. Bywater, G. Cornaglia et al., "Surveillance of antimicrobial resistance—what, how and whither?" *Clinical Microbiology and Infection*, vol. 7, no. 6, pp. 316–325, 2001.
- [11] R. Masterton, "The importance and future of antimicrobial surveillance studies," *Clinical Infectious Diseases*, vol. 47, no. 1, pp. S21–S31, 2008.
- [12] A. Dalhoff, "Resistance surveillance studies: a multifaceted problem—the fluoroquinolone example," *Infection*. In press.
- [13] K. Drlica, M. Malik, R. J. Kerns, and X. Zhao, "Quinolone-mediated bacterial death," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 2, pp. 385–392, 2008.
- [14] K. Drlica and X. Zhao, "DNA gyrase, topoisomerase IV, and the 4-quinolones," *Microbiology and Molecular Biology Reviews*, vol. 61, no. 3, pp. 377–392, 1997.
- [15] X. Zhao, C. Xu, J. Domagala, and K. Drlica, "DNA topoisomerase targets of the fluoroquinolones: a strategy for avoiding bacterial resistance," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 25, pp. 13991–13996, 1997.
- [16] D. C. Hooper, "Mechanisms of fluoroquinolone resistance," *Drug Resistance Updates*, vol. 2, no. 1, pp. 38–55, 1999.
- [17] D. C. Hooper, "Mechanisms of action and resistance of older and newer fluoroquinolones," *Clinical Infectious Diseases*, vol. 31, supplement 2, pp. S24–S28, 2000.
- [18] D. C. Hooper, "Fluoroquinolone resistance among Gram-positive cocci," *The Lancet Infectious Diseases*, vol. 2, no. 9, pp. 530–538, 2002.
- [19] G. A. Jacoby, "Mechanisms of resistance to quinolones," *Clinical Infectious Diseases*, vol. 41, no. 2, supplement, pp. S120–S126, 2005.
- [20] P. M. Hawkey, "Mechanisms of quinolone action and microbial response," *Journal of Antimicrobial Chemotherapy*, vol. 51, supplement 1, pp. 29–35, 2003.
- [21] V. H. Tam, A. Louie, T. R. Fritsche et al., "Impact of drug-exposure intensity and duration of therapy on the emergence of *Staphylococcus aureus* resistance to a quinolone antimicrobial," *Journal of Infectious Diseases*, vol. 195, no. 12, pp. 1818–1827, 2007.
- [22] D. Ince and D. C. Hooper, "Quinolone resistance due to reduced target enzyme expression," *Journal of Bacteriology*, vol. 185, no. 23, pp. 6883–6892, 2003.
- [23] G. C. Walker, "Mutagenesis and inducible responses to deoxyribonucleic acid damage in *Escherichia coli*," *Microbiological Reviews*, vol. 48, no. 1, pp. 60–93, 1984.
- [24] A. R. Fernández De Henestrosa, T. Ogi, S. Aoyagi et al., "Identification of additional genes belonging to the LexA regulon in *Escherichia coli*," *Molecular Microbiology*, vol. 35, no. 6, pp. 1560–1572, 2000.
- [25] J. Courcelle, A. Kodursky, B. Peter, P. Brown, and P. Hanawalt, "Comparative gene expression profiles following UV exposure in wild-type and SOS-deficient *Escherichia coli*," *Genetics*, vol. 158, no. 1, pp. 41–64, 2001.
- [26] P. Ysern, B. Clerch, M. Castano, I. Gibert, J. Barbe, and M. Llagostera, "Induction of SOS genes in *Escherichia coli* and mutagenesis in *Salmonella typhimurium* by fluoroquinolones," *Mutagenesis*, vol. 5, no. 1, pp. 63–66, 1990.
- [27] M. Malik, X. Zhao, and K. Drlica, "Lethal fragmentation of bacterial chromosomes mediated by DNA gyrase and quinolones," *Molecular Microbiology*, vol. 61, no. 3, pp. 810–825, 2006.
- [28] M. Wang, G. A. Jacoby, D. M. Mills, and D. C. Hooper, "SOS regulation of *qnrB* expression," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 2, pp. 821–823, 2009.
- [29] S. Da Re, F. Garnier, E. Guérin, S. Campoy, F. Denis, and M. C. Ploy, "The SOS response promotes *qnrB* quinolone-resistance determinant expression," *EMBO Reports*, vol. 10, no. 8, pp. 929–933, 2009.
- [30] R. T. Cirz, J. K. Chin, D. R. Andes, V. de Crécy-Lagard, W. A. Craig, and F. E. Romesberg, "Inhibition of mutation and combating the evolution of antibiotic resistance," *PLoS Biology*, vol. 3, no. 6, article e176, 2005.
- [31] R. T. Cirz, M. B. Jones, N. A. Gingles et al., "Complete and SOS-mediated response of *Staphylococcus aureus* to the antibiotic ciprofloxacin," *Journal of Bacteriology*, vol. 189, no. 2, pp. 531–539, 2007.

- [32] T. Dörr, K. Lewis, and M. Vulić, "SOS response induces persistence to fluoroquinolones in *Escherichia coli*," *PLoS Genetics*, vol. 5, no. 12, Article ID e1000760, 2009.
- [33] M. B. Avison, "New approaches to combating antimicrobial drug resistance," *Genome Biology*, vol. 6, no. 13, article 243, 2005.
- [34] E. López, M. Elez, I. Matic, and J. Blázquez, "Antibiotic-mediated recombination: ciprofloxacin stimulates SOS-independent recombination of divergent sequences in *Escherichia coli*," *Molecular Microbiology*, vol. 64, no. 1, pp. 83–93, 2007.
- [35] C. Miller, L. E. Thomsen, C. Gaggero, R. Mosseri, H. Ingmer, and S. N. Cohen, "SOS response induction by β -lactams and bacterial defense against antibiotic lethality," *Science*, vol. 305, no. 5690, pp. 1629–1631, 2004.
- [36] E. Maiques, C. Úbeda, S. Campoy et al., " β -lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in *Staphylococcus aureus*," *Journal of Bacteriology*, vol. 188, no. 7, pp. 2726–2729, 2006.
- [37] C. S. Lewin and S. G. B. Amyes, "The role of the SOS response in bacteria exposed to zidovudine or trimethoprim," *Journal of Medical Microbiology*, vol. 34, no. 6, pp. 329–332, 1991.
- [38] J. W. Beaber, B. Hochhut, and M. K. Waldor, "SOS response promotes horizontal dissemination of antibiotic resistance genes," *Nature*, vol. 427, no. 6969, pp. 72–74, 2004.
- [39] J. H. Tran and G. A. Jacoby, "Mechanism of plasmid-mediated quinolone resistance," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 8, pp. 5638–5642, 2002.
- [40] L. Poirel, V. Cattoir, and P. Nordmann, "Is plasmid-mediated quinolone resistance a clinically significant problem?" *Clinical Microbiology and Infection*, vol. 14, no. 4, pp. 295–297, 2008.
- [41] A. Robicsek, J. Strahilevitz, G. A. Jacoby et al., "Fluoroquinolone-modifying enzyme: a new adaptation of a common aminoglycoside acetyltransferase," *Nature Medicine*, vol. 12, no. 1, pp. 83–88, 2006.
- [42] J. Strahilevitz, G. A. Jacoby, D. C. Hooper, and A. Robicsek, "Plasmid-mediated quinolone resistance: a multifaceted threat," *Clinical Microbiology Reviews*, vol. 22, no. 4, pp. 664–689, 2009.
- [43] L. Poirel, V. Cattoir, and P. Nordmann, "Plasmid-mediated quinolone-resistance; interactions between human, animal, and environmental ecologies," *Frontiers in Microbiology*, vol. 3, pp. 1–7, 2012.
- [44] J. M. Rodríguez-Martínez, M. E. Cano, C. Velasco, L. Martínez-Martínez, and A. Pascual, "Plasmid-mediated quinolone resistance: an update," *Journal of Infection and Chemotherapy*, vol. 17, no. 2, pp. 149–182, 2011.
- [45] L. Martínez-Martínez, A. Pascual, and G. A. Jacoby, "Quinolone resistance from a transferable plasmid," *The Lancet*, vol. 351, no. 9105, pp. 797–799, 1998.
- [46] G. Jacoby, V. Cattoir, D. Hooper et al., "*qnr* gene nomenclature," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 7, pp. 2297–2299, 2008.
- [47] M. H. C. Baquirin and M. Barlow, "Evolution and recombination of the plasmidic *qnr* alleles," *Journal of Molecular Evolution*, vol. 67, no. 1, pp. 103–110, 2008.
- [48] A. Robicsek, G. A. Jacoby, and D. C. Hooper, "The worldwide emergence of plasmid-mediated quinolone resistance," *The Lancet Infectious Diseases*, vol. 6, no. 10, pp. 629–640, 2006.
- [49] L. Poirel, J. M. Rodríguez-Martínez, H. Mammari, A. Liard, and P. Nordmann, "Origin of plasmid-mediated quinolone resistance determinant QnrA," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 8, pp. 3523–3525, 2005.
- [50] L. Poirel, M. Van De Loo, H. Mammari, and P. Nordmann, "Association of plasmid-mediated quinolone resistance with extended-spectrum β -lactamase VEB-1," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 7, pp. 3091–3094, 2005.
- [51] C. Montero, G. Mateu, R. Rodríguez, and H. Takiff, "Intrinsic resistance of *Mycobacterium smegmatis* to fluoroquinolones may be influenced by new pentapeptide protein MfpA," *Antimicrobial Agents and Chemotherapy*, vol. 45, no. 12, pp. 3387–3392, 2001.
- [52] S. Arsène and R. Leclercq, "Role of a *qnr*-like, gene in the intrinsic resistance of *Enterococcus faecalis* to fluoroquinolones," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 9, pp. 3254–3258, 2007.
- [53] J. M. Rodríguez-Martínez, C. Velasco, A. Briaies, I. García, M. C. Conejo, and A. Pascual, "Qnr-like pentapeptide repeat proteins in Gram-positive bacteria," *Journal of Antimicrobial Chemotherapy*, vol. 61, no. 6, pp. 1240–1243, 2008.
- [54] K. Shimizu, K. Kikuchi, T. Sasaki et al., "Smqnr, a new chromosome-carried quinolone resistance gene in *Stenotrophomonas maltophilia*," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 10, pp. 3823–3825, 2008.
- [55] C. Velasco, J. M. Rodríguez-Martínez, A. Briaies, P. Díaz de Alba, J. Calvo, and A. Pascual, "Smaqnr, a new chromosome-encoded quinolone resistance determinant in *Serratia marcescens*," *The Journal of antimicrobial chemotherapy*, vol. 65, no. 2, pp. 239–242, 2010.
- [56] P. Nordmann and L. Poirel, "Emergence of plasmid-mediated resistance to quinolones in *Enterobacteriaceae*," *Journal of Antimicrobial Chemotherapy*, vol. 56, no. 3, pp. 463–469, 2005.
- [57] A. Hernandez, M. B. Sanchez, and J. L. Martinez, "Quinolone-resistance: much more than predicted," *Frontiers in Microbiology*, vol. 2, pp. 1–6, 2011.
- [58] P. Lascols, I. Podglajen, C. Verdet et al., "A plasmid-borne *Shewanella algae* gene, *qnrA3*, and its possible transfer in vivo between *Kluyvera ascorbata* and *Klebsiella pneumoniae*," *Journal of Bacteriology*, vol. 190, no. 15, pp. 5217–5223, 2008.
- [59] V. Cattoir, L. Poirel, C. Aubert, C.-J. Soussy, and P. Nordmann, "Unexpected occurrence of plasmid-mediated quinolone resistance determinants in environmental *Aeromonas* spp.," *Emerging Infectious Diseases*, vol. 14, no. 2, pp. 231–237, 2008.
- [60] L. Poirel, A. Liard, J. M. Rodríguez-Martínez, and P. Nordmann, "Vibrionaceae as a possible source of Qnr-like quinolone resistance determinants," *Journal of Antimicrobial Chemotherapy*, vol. 56, no. 6, pp. 1118–1121, 2005.
- [61] M. W. Vetting, H. P. Chi, S. S. Hegde, G. A. Jacoby, D. C. Hooper, and J. S. Blanchard, "Mechanistic and structural analysis of aminoglycoside N-acetyltransferase AAC(6′)-Ib and its bifunctional, fluoroquinolone-active AAC(6′)-Ib-cr variant," *Biochemistry*, vol. 47, no. 37, pp. 9825–9835, 2008.
- [62] E. Ruiz, A. A. Ocampo-Sosa, J. Alcoba-Flórez et al., "Changes in ciprofloxacin resistance levels in *Enterobacter aerogenes* isolates associated with variable expression of the *aac(6′)-Ib-cr* gene," *Antimicrobial Agents and Chemotherapy*, vol. 56, no. 2, pp. 1097–1100, 2012.
- [63] I. Frasson, A. Cavallaro, C. Bergo, S. N. Richter, and G. Palù, "Prevalence of *aac(6′)-Ib-cr* plasmid-mediated and chromosome-encoded fluoroquinolone resistance in *Enterobacteriaceae* in Italy," *Gut Pathogens*, vol. 3, no. 1, Article ID 12, 2011.

- [64] C. C. Sanders and C. Watanakunakorn, "Emergence of resistance to β -lactams, aminoglycosides, and quinolones during combination therapy for infection due to *Serratia marcescens*," *Journal of Infectious Diseases*, vol. 153, no. 3, pp. 617–619, 1986.
- [65] B. Périchon, P. Courvalin, and M. Galimand, "Transferable resistance to aminoglycosides by methylation of G1405 in 16S rRNA and to hydrophilic fluoroquinolones by QepA-mediated efflux in *Escherichia coli*," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 7, pp. 2464–2469, 2007.
- [66] K. Yamane, J. I. Wachino, S. Suzuki et al., "New plasmid-mediated fluoroquinolone efflux pump, QepA, found in an *Escherichia coli* clinical isolate," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 9, pp. 3354–3360, 2007.
- [67] H. B. Kim, M. Wang, C. H. Park, G. A. Jacoby, and D. C. Hooper, "oqxAB encoding a multidrug efflux pump in human clinical isolates of *Enterobacteriaceae*," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 8, pp. 3582–3584, 2009.
- [68] L. H. Hansen, L. B. Jensen, H. I. Sørensen, and S. J. Sørensen, "Substrate specificity of the OqxAB multidrug resistance pump in *Escherichia coli* and selected enteric bacteria," *Journal of Antimicrobial Chemotherapy*, vol. 60, no. 1, pp. 145–147, 2007.
- [69] L. H. Hansen, E. Johannesen, M. Burmølle, A. H. Sørensen, and S. J. Sørensen, "Plasmid-encoded multidrug efflux pump conferring resistance to olaquinox in *Escherichia coli*," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 9, pp. 3332–3337, 2004.
- [70] S. K. Morgan-Linnell, L. B. Boyd, D. Steffen, and L. Zechiedrich, "Mechanisms accounting for fluoroquinolone resistance in *Escherichia coli* clinical isolates," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 1, pp. 235–241, 2009.
- [71] E. Cambau, S. Matrat, X. S. Pan et al., "Target specificity of the new fluoroquinolone besifloxacin in *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Escherichia coli*," *Journal of Antimicrobial Chemotherapy*, vol. 63, no. 3, pp. 443–450, 2009.
- [72] M. J. Everett, Y. F. Jin, V. Ricci, and L. J. V. Piddock, "Contributions of individual mechanisms to fluoroquinolone resistance in 36 *Escherichia coli* strains isolated from humans and animals," *Antimicrobial Agents and Chemotherapy*, vol. 40, no. 10, pp. 2380–2386, 1996.
- [73] M. Oethinger, I. Podglajen, W. V. Kern, and S. B. Levy, "Overexpression of the marA or soxS regulatory gene in clinical topoisomerase mutants of *Escherichia coli*," *Antimicrobial Agents and Chemotherapy*, vol. 42, no. 8, pp. 2089–2094, 1998.
- [74] J. D. Goldman, D. G. White, and S. B. Levy, "Multiple antibiotic resistance (mar) locus protects *Escherichia coli* from rapid cell killing by fluoroquinolones," *Antimicrobial Agents and Chemotherapy*, vol. 40, no. 5, pp. 1266–1269, 1996.
- [75] H. Okusu, D. Ma, and H. Nikaido, "AcrAB efflux pump plays a major role in the antibiotic resistance phenotype of *Escherichia coli* multiple-antibiotic-resistance (Mar) mutants," *Journal of Bacteriology*, vol. 178, no. 1, pp. 306–308, 1996.
- [76] A. Mazzariol, Y. Tokue, T. M. Kanegawa, G. Cornaglia, and H. Nikaido, "High-level fluoroquinolone-resistant clinical isolates of *Escherichia coli* overproduce multidrug efflux protein AcrA," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 12, pp. 3441–3443, 2000.
- [77] M. Oethinger, W. V. Kern, A. S. Jellen-Ritter, L. M. McMurry, and S. B. Levy, "Ineffectiveness of topoisomerase mutations in mediating clinically significant fluoroquinolone resistance in *Escherichia coli* in the absence of the AcrAB efflux pump," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 1, pp. 10–13, 2000.
- [78] H. Wang, J. L. Dzik-Fox, M. Chen, and S. B. Levy, "Genetic characterization of highly fluoroquinolone-resistant clinical *Escherichia coli* strains from China: role of acrR mutations," *Antimicrobial Agents and Chemotherapy*, vol. 45, no. 5, pp. 1515–1521, 2001.
- [79] Q. C. Truong, J. C. Van Nguyen, D. Shlaes, L. Gutmann, and N. J. Moreau, "A novel, double mutation in DNA gyrase A of *Escherichia coli* conferring resistance to quinolone antibiotics," *Antimicrobial Agents and Chemotherapy*, vol. 41, no. 1, pp. 85–90, 1997.
- [80] D. C. Hooper, "Mechanism of quinolones resistance," in *Quinolone Antimicrobial Agents*, D. C. Hooper and E. Rubinstein, Eds., pp. 41–67, ASM Press, Washington, DC, USA, 3rd edition, 2003.
- [81] D. C. Hooper, "Efflux pumps and nosocomial antibiotic resistance: a primer for hospital epidemiologists," *Clinical Infectious Diseases*, vol. 40, no. 12, pp. 1811–1817, 2005.
- [82] F. Van Bambeke, J. M. Pagès, and V. J. Lee, "Inhibitors of bacterial efflux pumps as adjuvants in antibacterial therapy and diagnostic tools for detection of resistance by efflux," *Frontiers in Anti-Infective Drug Discovery*, vol. 1, pp. 138–175, 2010.
- [83] L. J. V. Piddock, "Multidrug-resistance efflux pumps—not just for resistance," *Nature Reviews Microbiology*, vol. 4, no. 8, pp. 629–636, 2006.
- [84] J. A. Karlowsky, L. J. Kelly, C. Thornsberry, M. E. Jones, and D. F. Sahn, "Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States," *Antimicrobial Agents and Chemotherapy*, vol. 46, no. 8, pp. 2540–2545, 2002.
- [85] J. A. Karlowsky, C. Thornsberry, D. E. Peterson, D. C. Mayfield, and D. F. Sahn, "Antimicrobial resistance among *Escherichia coli* urinary tract isolates in the United States: a current view provided by electronic surveillance," *Infectious Diseases in Clinical Practice*, vol. 10, no. 2, pp. 87–92, 2001.
- [86] K. Gupta, D. Scholes, and W. E. Stamm, "Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women," *Journal of the American Medical Association*, vol. 281, no. 8, pp. 736–738, 1999.
- [87] G. G. Zhanel, T. L. Hisanaga, N. M. Laing et al., "Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA)," *International Journal of Antimicrobial Agents*, vol. 27, no. 6, pp. 468–475, 2006.
- [88] AMR Trends Report Epidemiological services. British Columbia Centre for Disease Control, "Antimicrobial resistance trends in the province of British Columbia," AMR Trends Report, 2009, <http://www.bccdc.ca/>.
- [89] M. E. Kim, U. S. Ha, and Y. H. Cho, "Prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in female outpatients in South Korea: a multicentre study in 2006," *International Journal of Antimicrobial Agents*, vol. 31, supplement 1, pp. 15–18, 2008.
- [90] Ö. K. Azap, H. Arslan, K. Serefhanoglu et al., "Risk factors for extended-spectrum β -lactamase positivity in uropathogenic *Escherichia coli* isolated from community-acquired urinary

- tract infections," *Clinical Microbiology and Infection*, vol. 16, no. 2, pp. 147–151, 2010.
- [91] J. R. Johnson, M. Menard, B. Johnston, M. A. Kuskowski, K. Nichol, and G. G. Zhanel, "Epidemic clonal groups of *Escherichia coli* as a cause of antimicrobial-resistant urinary tract infections in Canada, 2002 to 2004," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 7, pp. 2733–2739, 2009.
- [92] N. Woodford, M. E. Ward, M. E. Kaufmann et al., "Community and hospital spread of *Escherichia coli* producing CTX-M extended-spectrum β -lactamases in the UK," *Journal of Antimicrobial Chemotherapy*, vol. 54, no. 4, pp. 735–743, 2004.
- [93] J. R. Johnson, B. Johnston, C. Clabots, M. A. Kuskowski, and M. Castanheira, "*Escherichia coli* sequence type ST131 as the major cause of serious multidrug-resistant *E. Coli* infections in the United States," *Clinical Infectious Diseases*, vol. 51, no. 3, pp. 286–294, 2010.
- [94] B. N. Selvakumar and R. Jasmine, "Antibiotic susceptibility of ESBL-producing urinary isolates at a Tertiary Care Hospital in Tiruchirappalli South India," *Journal of Medical Sciences*, vol. 7, no. 3, pp. 443–446, 2007.
- [95] J. D. D. Pitout, D. L. Church, D. B. Gregson et al., "Molecular epidemiology of CTX-M-producing *Escherichia coli* in the calgary health region: emergence of CTX-M-15-producing isolates," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 4, pp. 1281–1286, 2007.
- [96] J. D. Pitout and K. B. Laupland, "Extended-spectrum β -lactamase-producing *Enterobacteriaceae*: an emerging public-health concern," *The Lancet Infectious Diseases*, vol. 8, no. 3, pp. 159–166, 2008.
- [97] R. Cantón, A. Novais, A. Valverde et al., "Prevalence and spread of extended-spectrum β -lactamase-producing *Enterobacteriaceae* in Europe," *Clinical Microbiology and Infection*, vol. 14, supplement 1, pp. 144–153, 2008.
- [98] A. R. Manges, H. Tabor, P. Tellis, C. Vincent, and P.-P. Tellier, "Endemic and epidemic lineages of *Escherichia coli* that cause urinary tract infections," *Emerging Infectious Diseases*, vol. 14, no. 10, pp. 1575–1583, 2008.
- [99] A. R. Manges, J. R. Johnson, B. Foxman, T. T. O'Bryan, K. E. Fullerton, and L. W. Riley, "Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group," *New England Journal of Medicine*, vol. 345, no. 14, pp. 1007–1013, 2001.
- [100] P. R. S. Lagacé-Wiens, K. A. Nichol, L. E. Nicolle et al., "ESBL subtypes in fluoroquinolone-resistant and fluoroquinolone-susceptible ESBL-producing *Escherichia coli* urinary isolates in Manitoba," *Canadian Journal of Infectious Diseases and Medical Microbiology*, vol. 18, no. 2, pp. 133–137, 2007.
- [101] A. Takahashi, T. Muratani, M. Yasuda et al., "Genetic profiles of fluoroquinolone-resistant *Escherichia coli* isolates obtained from patients with cystitis: phylogeny, virulence factors, PAI_{usp} subtypes, and mutation patterns," *Journal of Clinical Microbiology*, vol. 47, no. 3, pp. 791–795, 2009.
- [102] G. Peirano, D. Richardson, J. Nigrin et al., "High prevalence of ST131 isolates producing CTX-M-15 and CTX-M-14 among extended-spectrum- β -lactamase-producing *Escherichia coli* isolates from Canada," *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 3, pp. 1327–1330, 2010.
- [103] G. Kahlmeter, "An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS project," *Journal of Antimicrobial Chemotherapy*, vol. 51, no. 1, pp. 69–76, 2003.
- [104] K. G. Naber, G. Schito, H. Botto, J. Palou, and T. Mazzei, "Surveillance Study in Europe and Brazil on Clinical Aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for Empiric Therapy," *European Urology*, vol. 54, no. 5, pp. 1164–1178, 2008.
- [105] G. C. Schito, K. G. Naber, H. Botto et al., "The ARES study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections," *International Journal of Antimicrobial Agents*, vol. 34, no. 5, pp. 407–413, 2009.
- [106] Y. Neuzillet, K. G. Naber, G. Schito, L. Gualco, and H. Botto, "French results of the ARES Study: clinical aspects and epidemiology of antimicrobial resistance in female patients with cystitis. Implications for empiric therapy," *Medecine et Maladies Infectieuses*, vol. 42, no. 2, pp. 66–75, 2012.
- [107] F. M. E. Wagenlehner, C. Wagenlehner, O. Savov, L. Guaico, G. Schito, and K. G. Naber, "Clinical aspects and epidemiology of uncomplicated cystitis in women. German results of the ARES study," *Urologe A*, vol. 49, no. 2, pp. 253–261, 2010.
- [108] J. Palou, C. Pigrau, I. Molina, J. M. Ledesma, and J. Angulo, "Etiology and sensitivity of uropathogens identified in uncomplicated lower urinary tract infections in women (ARESC Study): implications on empiric therapy," *Medicina Clinica*, vol. 136, no. 1, pp. 1–7, 2011.
- [109] T. Khawcharoenporn, S. Vasoo, E. Ward, and K. Singh, "High rates of quinolone resistance among urinary tract infections in the ED," *American Journal of Emergency Medicine*, vol. 30, no. 1, pp. 68–74, 2012.
- [110] D. A. Talan, A. Krishnadasan, F. M. Abrahamian, W. E. Stamm, and G. J. Moran, "Prevalence and risk factor analysis of trimethoprim-sulfamethoxazole- and fluoroquinolone-resistant *Escherichia coli* infection among emergency department patients with pyelonephritis," *Clinical Infectious Diseases*, vol. 47, no. 9, pp. 1150–1158, 2008.
- [111] M. Vromen, A. J. A. M. Van Der Ven, A. Knols, and E. E. Stobberingh, "Antimicrobial resistance patterns in urinary isolates from nursing home residents. Fifteen years of data reviewed," *Journal of Antimicrobial Chemotherapy*, vol. 44, no. 1, pp. 113–116, 1999.
- [112] J. D. D. Pitout, P. Nordmann, K. B. Laupland, and L. Poirel, "Emergence of *Enterobacteriaceae* producing extended-spectrum β -lactamases (ESBLs) in the community," *Journal of Antimicrobial Chemotherapy*, vol. 56, no. 1, pp. 52–59, 2005.
- [113] J. D. D. Pitout, N. D. Hanson, D. L. Church, and K. B. Laupland, "Population-based laboratory surveillance for *Escherichia coli*-producing extended-spectrum β -Lactamases: importance of community isolates with blaCTX-M genes," *Clinical Infectious Diseases*, vol. 38, no. 12, pp. 1736–1741, 2004.
- [114] J. D. D. Pitout, "Infections with extended-spectrum β -lactamase-producing *Enterobacteriaceae*: changing epidemiology and drug treatment choices," *Drugs*, vol. 70, no. 3, pp. 313–333, 2010.
- [115] D. M. Livermore, R. Canton, M. Gniadkowski et al., "CTX-M: changing the face of ESBLs in Europe," *Journal of Antimicrobial Chemotherapy*, vol. 59, no. 2, pp. 165–174, 2007.
- [116] D. M. Livermore and P. M. Hawkey, "CTX-M: changing the face of ESBLs in the UK," *Journal of Antimicrobial Chemotherapy*, vol. 56, no. 3, pp. 451–454, 2005.
- [117] E. Calbo, V. Romání, M. Xercavins et al., "Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum β -lactamases," *Journal of*

- Antimicrobial Chemotherapy*, vol. 57, no. 4, pp. 780–783, 2006.
- [118] J. R. Hernández, A. Pascual, R. Cantón et al., “Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in Spanish hospitals (GEIH-BLEE Project 2002),” *Enfermedades Infecciosas y Microbiología Clínica*, vol. 21, no. 2, pp. 77–82, 2003.
- [119] J. Rodríguez-Baño, M. D. Navarro, L. Romero et al., “Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in nonhospitalized patients,” *Journal of Clinical Microbiology*, vol. 42, no. 3, pp. 1089–1094, 2004.
- [120] N. Mendonça, J. Leitão, V. Manageiro, E. Ferreira, and M. Caniça, “Spread of extended-spectrum β -lactamase CTX-M-producing *Escherichia coli* clinical isolates in community and nosocomial environments in Portugal,” *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 6, pp. 1946–1955, 2007.
- [121] S. Cagnacci, L. Gualco, E. Debbia, G. C. Schito, and A. Marchese, “European emergence of ciprofloxacin-resistant *Escherichia coli* clonal groups O25:H4-ST 131 and O15:K52:H1 causing community-acquired uncomplicated cystitis,” *Journal of Clinical Microbiology*, vol. 46, no. 8, pp. 2605–2612, 2008.
- [122] M. H. Nicolas-Chanoine, J. Blanco, V. Leflon-Guibout et al., “Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15,” *Journal of Antimicrobial Chemotherapy*, vol. 61, no. 2, pp. 273–281, 2008.
- [123] B. A. Rogers, H. E. Sidjabat, and D. L. Paterson, “*Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain,” *Journal of Antimicrobial Chemotherapy*, vol. 66, no. 1, Article ID dkq415, pp. 1–14, 2011.
- [124] G. Peirano and J. D. D. Pitout, “Molecular epidemiology of *Escherichia coli* producing CTX-M β -lactamases: the worldwide emergence of clone ST131 O25:H4,” *International Journal of Antimicrobial Agents*, vol. 35, no. 4, pp. 316–321, 2010.
- [125] J. R. Johnson, J. T. Anderson, C. Clabots, B. Johnston, and M. Cooperstock, “Within-household sharing of a fluoroquinolone-resistant *Escherichia coli* sequence type st131 strain causing pediatric osteoarticular infection,” *Pediatric Infectious Disease Journal*, vol. 29, no. 5, pp. 473–475, 2010.
- [126] C. Longhi, M. P. Conte, M. Marazzato et al., “Plasmid-mediated fluoroquinolone resistance determinants in *Escherichia coli* from community-uncomplicated urinary tract infection in an area of high prevalence of quinolone resistance,” *European Journal of Clinical Microbiology and Infectious Diseases*. In press.
- [127] H. Dhanji, M. Doumith, P. J. Rooney et al., “Molecular epidemiology of fluoroquinolone-resistant ST131 *Escherichia coli* producing CTX-M extended-spectrum β -lactamases in nursing homes in Belfast, UK,” *Journal of Antimicrobial Chemotherapy*, vol. 66, no. 2, Article ID dkq463, pp. 297–303, 2011.
- [128] A. Vellinga, A. W. Murphy, B. Hanahoe, K. Bennett, and M. Cormican, “A multilevel analysis of trimethoprim and ciprofloxacin prescribing and resistance of uropathogenic *Escherichia coli* in general practice,” *Journal of Antimicrobial Chemotherapy*, vol. 65, no. 7, Article ID dkq149, pp. 1514–1520, 2010.
- [129] L. Johnson, A. Sabel, W. J. Burman et al., “Emergence of fluoroquinolone-resistance in outpatient urinary *Escherichia coli* isolates,” *American Journal of Medicine*, vol. 121, no. 10, pp. 876–884, 2008.
- [130] W. E. van der Starre, C. van Nieuwkoop, S. Paltansing et al., “Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection,” *Journal of Antimicrobial Chemotherapy*, vol. 66, no. 3, Article ID dkq465, pp. 650–656, 2011.
- [131] P. Rattanaumpawan, P. C. Tolomeo, W. B. Bilker, and E. Lautenbach, “Risk factors for fluoroquinolone-resistance in nosocomial urinary tract infections caused by Gram-negative bacilli,” in *Proceedings of the 5th Decennial International Conference Health-Associated Infections*, Abstract no. 317, Atlanta, Ga, USA, March 2010.
- [132] P. Rattanaumpawan, P. Tolomeo, W. B. Bilker, N. O. Fishman, and E. Lautenbach, “Risk factors for fluoroquinolone resistance in Enterococcus urinary tract infections in hospitalized patients,” *Epidemiology and Infection*, vol. 139, no. 6, pp. 955–961, 2011.
- [133] G. A. Vasquez, H. R. Siu, E. M. Luna, K. C. Reyes, and M. J. Zervos, “Risk factors for quinolone-resistant *Escherichia coli* urinary tract infection,” *Infectious Diseases in Clinical Practice*, vol. 17, no. 5, pp. 309–313, 2009.
- [134] C. Y. Lin, S. H. Huang, T. C. Chen, P. L. Lu, W. R. Lin, and Y. H. Chen, “Risk factors of ciprofloxacin resistance in urinary *Escherichia coli* isolates,” *Journal of Microbiology, Immunology and Infection*, vol. 41, no. 4, pp. 325–331, 2008.
- [135] C. Llor, G. Rabanaque, A. López, and J. M. Cots, “The adherence of GPs to guidelines for the diagnosis and treatment of lower urinary tract infections in women is poor,” *Family Practice*, vol. 28, no. 3, pp. 294–299, 2011.
- [136] D. Plachouras, D. Kavatha, A. Antoniadou et al., “Dispensing of antibiotics without prescription in Greece, 2008: another link in the antibiotic resistance chain,” *Eurosurveillance*, vol. 15, no. 7, pp. 1–4, 2010.
- [137] J. Garau, M. Xercavins, M. Rodríguez-Carballeira et al., “Emergence and dissemination of quinolone-resistant *Escherichia coli* in the community,” *Antimicrobial Agents and Chemotherapy*, vol. 43, no. 11, pp. 2736–2741, 1999.
- [138] J. Oteo, E. Lázaro, F. J. De Abajo, F. Baquero, and J. Campos, “Antimicrobial-resistant invasive *Escherichia coli*, Spain,” *Emerging Infectious Diseases*, vol. 11, no. 4, pp. 546–553, 2005.
- [139] A. Bartoloni, L. Pallecchi, C. Fiorelli et al., “Increasing resistance in commensal *Escherichia coli*, Bolivia and Peru,” *Emerging Infectious Diseases*, vol. 14, no. 2, pp. 338–340, 2008.
- [140] M. B. Zaidi, E. Zamora, P. Diaz, L. Tollefson, P. J. Fedorka-Cray, and M. L. Headrick, “Risk factors for fecal quinolone-resistant *Escherichia coli* in Mexican children,” *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 6, pp. 1999–2001, 2003.
- [141] J. Y. Kim, E. Lautenbach, J. Chu et al., “Fluoroquinolone resistance in pediatric bloodstream infections because of *Escherichia coli* and *Klebsiella* species,” *American Journal of Infection Control*, vol. 36, no. 1, pp. 70–73, 2008.
- [142] X. Qin, Y. Razia, J. R. Johnson et al., “Ciprofloxacin-resistant gram-negative bacilli in the fecal microflora of children,” *Antimicrobial Agents and Chemotherapy*, vol. 50, no. 10, pp. 3325–3329, 2006.
- [143] H. D. Kalter, R. H. Gilman, L. H. Moulton, A. R. Cullotta, L. Cabrera, and B. Velapatño, “Risk factors for antibiotic-resistant *Escherichia coli* carriage in young children in Peru: community-based cross-sectional prevalence study,” *American Journal of Tropical Medicine and Hygiene*, vol. 82, no. 5, pp. 879–888, 2010.
- [144] I. O. Enabulele, S. C. Yah, E. O. Yusuf, and N. O. Eghafona, “Emerging quinolones resistant transfer genes among

- gram-negative bacteria, isolated from faeces of HIV/AIDS patients attending some Clinics and Hospitals in the City of Benin, Edo State, Nigeria," *Online Journal of Health and Allied Sciences*, vol. 5, no. 3, 2006.
- [145] C. Han, Y. Yang, M. Wang et al., "The prevalence of plasmid-mediated quinolone resistance determinants among clinical isolates of ESBL or AmpC-producing *Escherichia coli* from Chinese pediatric patients," *Microbiology and Immunology*, vol. 54, no. 3, pp. 123–128, 2010.
- [146] F. M. E. Wagenlehner, G. Schmiemann, U. Hoyme et al., "National S3 guideline on uncomplicated urinary tract infection: recommendations for treatment and management of uncomplicated community-acquired bacterial urinary tract infections in adult patients," *Urologe A*, vol. 50, no. 2, pp. 153–169, 2011.
- [147] D. L. Paterson, "Collateral damage" from cephalosporin or quinolone antibiotic therapy," *Clinical Infectious Diseases*, vol. 38, no. 4, pp. S341–S345, 2004.
- [148] P. R. Hsueh, D. J. Hoban, Y. Carmeli et al., "Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region," *Journal of Infection*, vol. 63, no. 2, pp. 114–123, 2011.
- [149] P. P. Gleason, T. P. Meehan, J. M. Fine, D. H. Galusha, and M. J. Fine, "Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia," *Archives of Internal Medicine*, vol. 159, no. 21, pp. 2562–2572, 1999.
- [150] B. J. Marston, J. F. Plouffe, T. M. File et al., "Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance study in Ohio," *Archives of Internal Medicine*, vol. 157, no. 15, pp. 1709–1718, 1997.
- [151] J. Eller, A. Ede, T. Schaberg, M. S. Niederman, H. Mauch, and H. Lode, "Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function," *Chest*, vol. 113, no. 6, pp. 1542–1548, 1998.
- [152] D. Felmingham, "A multicentre collaborative study of the antimicrobial susceptibility of community-acquired, lower respiratory tract pathogens 1992–1993: the Alexander Project," *Journal of Antimicrobial Chemotherapy*, vol. 38, pp. 1–57, 1996.
- [153] L. White and D. S. Reeves, "PROTEKT: an innovative surveillance programme for RTI pathogens," *Journal of Antimicrobial Chemotherapy*, vol. 50, supplement S1, pp. 1–70, 2002.
- [154] D. J. Hoban, G. V. Doern, A. C. Fluit, M. Roussel-Delvallez, and R. N. Jones, "Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveillance Program, 1997–1999," *Clinical Infectious Diseases*, vol. 32, no. 10, pp. S81–S93, 2001.
- [155] R. Cantón, E. Loza, M. Isabel Morosini, and F. Baquero, "Antimicrobial resistance amongst isolates of *Streptococcus pyogenes* and *Staphylococcus aureus* in the PROTEKT antimicrobial surveillance programme during 1999–2000," *Journal of Antimicrobial Chemotherapy*, vol. 50, no. 1, pp. 9–24, 2002.
- [156] D. Felmingham, R. R. Reinert, Y. Hirakata, and A. Rodloff, "Increasing prevalence of antimicrobial resistance among isolates of *Streptococcus pneumoniae* from the PROTEKT surveillance study, and comparative in vitro activity of the ketolide, telithromycin," *Journal of Antimicrobial Chemotherapy*, vol. 50, no. 1, pp. 25–37, 2002.
- [157] D. Felmingham, A. R. White, M. R. Jacobs et al., "The Alexander Project: the benefits from a decade of surveillance," *Journal of Antimicrobial Chemotherapy*, vol. 56, no. 2, pp. ii3–ii21, 2005.
- [158] D. J. Farrell, I. Morrissey, S. Bakker, and D. Felmingham, "Molecular characterization of macrolide resistance mechanisms among *Streptococcus pneumoniae* and *Streptococcus pyogenes* isolated from the PROTEKT 1999–2000 study," *Journal of Antimicrobial Chemotherapy*, vol. 50, no. 1, pp. 39–47, 2002.
- [159] D. F. Sahm, M. E. Jones, M. L. Hickey, D. R. Diakun, S. V. Mani, and C. Thornsbury, "Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe, 1997–1998," *Journal of Antimicrobial Chemotherapy*, vol. 45, no. 4, pp. 457–466, 2000.
- [160] P. L. Ho, T. L. Que, D. N. C. Tsang, T. K. Ng, K. H. Chow, and W. H. Seto, "Emergence of fluoroquinolone resistance among multiply resistant strains of *Streptococcus pneumoniae* in Hong Kong," *Antimicrobial Agents and Chemotherapy*, vol. 43, no. 5, pp. 1310–1313, 1999.
- [161] K. Yamaguchi and A. Ohno, "Investigation of the susceptibility trends in Japan to fluoroquinolones and other antimicrobial agents in a nationwide collection of clinical isolates: a longitudinal analysis from 1994 to 2002," *Diagnostic Microbiology and Infectious Disease*, vol. 52, no. 2, pp. 135–143, 2005.
- [162] Y. J. Lau, P. R. Hsueh, Y. C. Liu et al., "Comparison of in vitro activities of tigecycline with other antimicrobial agents against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in Taiwan," *Microbial Drug Resistance*, vol. 12, no. 2, pp. 130–135, 2006.
- [163] J. H. Song, W. S. Oh, C. I. Kang et al., "Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens," *International Journal of Antimicrobial Agents*, vol. 31, no. 2, pp. 107–114, 2008.
- [164] J. H. Song, S. I. Jung, K. S. Ko et al., "High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP study)," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 6, pp. 2101–2107, 2004.
- [165] Z. Tiemei, F. Xiangqun, and L. Youning, "Resistance phenotypes and genotypes of erythromycin-resistant *Streptococcus pneumoniae* isolates in Beijing and Shenyang, China," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 10, pp. 4040–4041, 2004.
- [166] S. Srifuengfung, C. Tribuddharat, K. Chokephaibulkit, and S. Comerungsee, "Fluoroquinolone resistance in *Streptococcus pneumoniae* from a university hospital, Thailand," *Journal of the Medical Association of Thailand*, vol. 93, supplement 5, pp. S35–S39, 2010.
- [167] Y. Matsukawa, Y. Yamagishi, H. Mikamo et al., "Epidemiological analysis of *Streptococcus pneumoniae* in Gifu prefecture," *Japanese Journal of Antibiotics*, vol. 63, no. 3, pp. 224–241, 2010.
- [168] A. G. De La Campa, L. Balsalobre, C. Ardanuy et al., "Fluoroquinolone resistance in penicillin-resistant *Streptococcus pneumoniae* Clones, Spain," *Emerging Infectious Diseases*, vol. 10, no. 10, pp. 1751–1759, 2004.
- [169] J. Aspa, O. Rajas, F. R. De Castro et al., "Drug-resistant pneumococcal pneumonia: clinical relevance and related factors," *Clinical Infectious Diseases*, vol. 38, no. 6, pp. 787–798, 2004.

- [170] E. Pérez-Trallero, C. Fernandez-Mazarrasa, C. García-Rey et al., "Antimicrobial susceptibilities of 1,684 *Streptococcus pneumoniae* and 2,039 *Streptococcus pyogenes* isolates and their ecological relationships: results of a 1-year (1998-1999) multicenter surveillance study in Spain," *Antimicrobial Agents and Chemotherapy*, vol. 45, no. 12, pp. 3334–3340, 2001.
- [171] M. I. Morosini, E. Loza, R. Del Campo, F. Almaraz, F. Baquero, and R. Cantón, "Fluoroquinolone-resistant *Streptococcus pneumoniae* in Spain: activities of garenoxacin against clinical isolates including strains with altered topoisomerases," *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 8, pp. 2692–2695, 2003.
- [172] C. García-Rey, L. Aguilar, and F. Baquero, "Influences of different factors on prevalence of ciprofloxacin resistance in *Streptococcus pneumoniae* in Spain," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 12, pp. 3481–3482, 2000.
- [173] E. Pérez-Trallero, J. E. Martín-Herrero, A. Mazón et al., "Antimicrobial resistance among respiratory pathogens in Spain: latest data and changes over 11 years (1996-1997 to 2006-2007)," *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 7, pp. 2953–2959, 2010.
- [174] G. V. Doern, K. P. Heilmann, H. K. Huynh, P. R. Rhomberg, S. L. Coffman, and A. B. Brueggemann, "Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999-2000, including a comparison of resistance rates since 1994-1995," *Antimicrobial Agents and Chemotherapy*, vol. 45, no. 6, pp. 1721–1729, 2001.
- [175] M. W. R. Pletz, L. McGee, J. Jorgensen et al., "Levofloxacin-resistant invasive *Streptococcus pneumoniae* in the United States: evidence for clonal spread and the impact of conjugate pneumococcal vaccine," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 9, pp. 3491–3497, 2004.
- [176] I. Rodríguez-Avial, B. Ramos, E. Ríos, E. Cercenado, M. Ordobás, and J. C. Sanz, "Clonal spread of levofloxacin-resistant *Streptococcus pneumoniae* invasive isolates in Madrid, Spain, 2007 to 2009," *Antimicrobial Agents and Chemotherapy*, vol. 55, no. 5, pp. 2469–2471, 2011.
- [177] S. Sunagawa, J. Fujita, F. Higa et al., "Comparison of drug sensitivity and genotypes of clinically isolated strains of levofloxacin-resistant *Streptococcus pneumoniae* obtained from Okinawa Island, the Japanese main island and Hong Kong," *Journal of Antibiotics*, vol. 64, no. 8, pp. 539–545, 2011.
- [178] K. Waites and S. Brown, "Antimicrobial resistance among isolates of respiratory tract infection pathogens from the southern United States: data from the PROTEKT US surveillance program 2000/2001," *Southern Medical Journal*, vol. 96, no. 10, pp. 974–985, 2003.
- [179] A. B. Brueggemann, S. L. Coffman, P. Rhomberg et al., "Fluoroquinolone resistance in *Streptococcus pneumoniae* in United States since 1994-1995," *Antimicrobial Agents and Chemotherapy*, vol. 46, no. 3, pp. 680–688, 2002.
- [180] D. M. Johnson, H. S. Sader, T. R. Fritsche, D. J. Biedenbach, and R. N. Jones, "Susceptibility trends of *Haemophilus influenzae* and *Moraxella catarrhalis* against orally administered antimicrobial agents: five-year report from the SENTRY Antimicrobial Surveillance Program," *Diagnostic Microbiology and Infectious Disease*, vol. 47, no. 1, pp. 373–376, 2003.
- [181] D. F. Sahn, J. A. Karlowsky, L. J. Kelly et al., "Need for annual surveillance of antimicrobial resistance in *Streptococcus pneumoniae* in the United States: 2-year longitudinal analysis," *Antimicrobial Agents and Chemotherapy*, vol. 45, no. 4, pp. 1037–1042, 2001.
- [182] R. N. Jones and M. A. Pfaller, "Macrolide and fluoroquinolone (Levofloxacin) resistances among *Streptococcus pneumoniae* strains: significant trends from the SENTRY antimicrobial surveillance program (North America, 1997–1999)," *Journal of Clinical Microbiology*, vol. 38, no. 11, pp. 4298–4299, 2000.
- [183] M. E. Jones, J. A. Karlowsky, R. Blosser-Middleton et al., "Longitudinal assessment of antipneumococcal susceptibility in the United States," *Antimicrobial Agents and Chemotherapy*, vol. 46, no. 8, pp. 2651–2655, 2002.
- [184] D. F. Sahn, D. E. Peterson, I. A. Critchley, and C. Thornsberrry, "Analysis of ciprofloxacin activity against *Streptococcus pneumoniae* after 10 years of use in the United States," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 9, pp. 2521–2524, 2000.
- [185] S. Pottumarthy, T. R. Fritsche, H. S. Sader, M. G. Stilwell, and R. N. Jones, "Susceptibility patterns of *Streptococcus pneumoniae* isolates in North America (2002–2003): contemporary in vitro activities of amoxicillin/clavulanate and 15 other antimicrobial agents," *International Journal of Antimicrobial Agents*, vol. 25, no. 4, pp. 282–289, 2005.
- [186] M. E. Jones, R. S. Blosser-Middleton, C. Thornsberrry, J. A. Karlowsky, and D. F. Sahn, "The activity of levofloxacin and other antimicrobials against clinical isolates of *Streptococcus pneumoniae* collected worldwide during 1999–2002," *Diagnostic Microbiology and Infectious Disease*, vol. 47, no. 4, pp. 579–586, 2003.
- [187] I. A. Critchley, S. D. Brown, M. M. Traczewski, G. S. Tillotson, and N. Janjic, "National and regional assessment of antimicrobial resistance among community-acquired respiratory tract pathogens identified in a 2005–2006 U.S. faropenem surveillance study," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 12, pp. 4382–4389, 2007.
- [188] A. W. Karchmer, "Increased antibiotic resistance in respiratory tract pathogens: PROTEKT US—an update," *Clinical Infectious Diseases*, vol. 39, no. 3, pp. S142–S150, 2004.
- [189] O. G. Vanderkooi, D. E. Low, K. Green, J. E. Powis, and A. McGeer, "Predicting antimicrobial resistance in invasive pneumococcal infections," *Clinical Infectious Diseases*, vol. 40, no. 9, pp. 1288–1297, 2005.
- [190] H. J. Adam, D. J. Hoban, A. S. Gin, and G. G. Zhanel, "Association between fluoroquinolone usage and a dramatic rise in ciprofloxacin-resistant *Streptococcus pneumoniae* in Canada, 1997–2006," *International Journal of Antimicrobial Agents*, vol. 34, no. 1, pp. 82–85, 2009.
- [191] G. G. Zhanel, L. Palatnick, K. A. Nichol, T. Bellyou, D. E. Low, and D. J. Hoban, "Antimicrobial resistance in respiratory tract *Streptococcus pneumoniae* isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002," *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 6, pp. 1867–1874, 2003.
- [192] J. Powis, A. McGeer, K. Green et al., "In vitro antimicrobial susceptibilities of *Streptococcus pneumoniae* clinical isolates obtained in Canada in 2002," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 9, pp. 3305–3311, 2004.
- [193] R. J. Davidson, R. Melano, and K. R. Forward, "Antimicrobial resistance among invasive isolates of *Streptococcus pneumoniae* collected across Canada," *Diagnostic Microbiology and Infectious Disease*, vol. 59, no. 1, pp. 75–80, 2007.
- [194] G. G. Zhanel, K. Ennis, L. Vercaigne et al., "A critical review of the fluoroquinolones: focus on respiratory tract infections," *Drugs*, vol. 62, no. 1, pp. 13–59, 2002.
- [195] J. A. Karlowsky, C. Thornsberrry, M. E. Jones, A. T. Evangelista, I. A. Critchley, and D. F. Sahn, "Factors associated with relative rates of antimicrobial resistance among *Streptococcus pneumoniae* in the United States: results from the TRUST

- surveillance program (1998–2002),” *Clinical Infectious Diseases*, vol. 36, no. 8, pp. 963–970, 2003.
- [196] C. M. Pillar, C. Thornsberry, and D. F. Sahm, “Susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* collected across Europe and Asia to levofloxacin and other respiratory agents; results from GLOBAL surveillance (1997–2007),” *Penetration*, pp. 14–22, 2010.
- [197] M. R. Jacobs, D. Felmingham, P. C. Appelbaum, R. Grungerb, and the Alexander Project group, “The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory infection to commonly used antibacterial agents,” *Journal of Antimicrobial Chemotherapy*, vol. 52, no. 2, pp. 229–246, 2003.
- [198] E. Jacobs, A. Dalhoff, and G. Korfmann, “Susceptibility patterns of bacterial isolates from hospitalised patients with respiratory tract infections (MOXIAKTIV Study),” *International Journal of Antimicrobial Agents*, vol. 33, no. 1, pp. 52–57, 2009.
- [199] M. W. Pletz, M. van der Linden, H. von Baum, C. B. Duesberg, K. P. Klugman, and T. Welte, “Low prevalence of fluoroquinolone resistant strains and resistance precursor strains in *Streptococcus pneumoniae* from patients with community-acquired pneumonia despite high fluoroquinolone usage,” *International Journal of Medical Microbiology*, vol. 301, no. 1, pp. 53–57, 2011.
- [200] S. M. Bhavnani, J. P. Hammel, R. N. Jones, and P. G. Ambrose, “Relationship between increased levofloxacin use and decreased susceptibility of *Streptococcus pneumoniae* in the United States,” *Diagnostic Microbiology and Infectious Disease*, vol. 51, no. 1, pp. 31–37, 2005.
- [201] D. K. Chen, A. McGeer, J. C. De Azavedo, and D. E. Low, “Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada,” *New England Journal of Medicine*, vol. 341, no. 4, pp. 233–229, 1999.
- [202] R. Davidson, R. Cavalcanti, J. L. Brunton et al., “Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia,” *New England Journal of Medicine*, vol. 346, no. 10, pp. 747–750, 2002.
- [203] C. Urban, N. Rahman, X. Zhao et al., “Fluoroquinolone-resistant *Streptococcus pneumoniae* associated with levofloxacin therapy,” *Journal of Infectious Diseases*, vol. 184, no. 6, pp. 794–798, 2001.
- [204] J. D. Fuller and D. E. Low, “A review of *Streptococcus pneumoniae* infection treatment failures associated with fluoroquinolone resistance,” *Clinical Infectious Diseases*, vol. 41, no. 1, pp. 118–121, 2005.
- [205] D. Orr, P. Wilkinson, L. Moyce, S. Martin, R. George, and B. Pichon, “Incidence and epidemiology of levofloxacin resistance in *Streptococcus pneumoniae*: experience from a tertiary referral hospital in England,” *Journal of Antimicrobial Chemotherapy*, vol. 65, no. 3, Article ID dkp463, pp. 449–452, 2009.
- [206] E. Pérez-Trallero, J. M. Marimón, A. González, M. Ercibengoa, and J. Larruskain, “In vivo development of high-level fluoroquinolone resistance in *Streptococcus pneumoniae* in chronic obstructive pulmonary disease,” *Clinical Infectious Diseases*, vol. 41, no. 4, pp. 560–564, 2005.
- [207] M. De Cueto, J. M. Rodríguez, M. J. Soriano, L. López-Cerero, J. Venero, and A. Pascual, “Fatal levofloxacin failure in treatment of a bacteremic patient infected with *Streptococcus pneumoniae* with a preexisting parC mutation,” *Journal of Clinical Microbiology*, vol. 46, no. 4, pp. 1558–1560, 2008.
- [208] M. W. R. Pletz, L. McGee, O. Burkhardt, H. Lode, and K. P. Klugman, “Ciprofloxacin treatment failure in a patient with resistant *Streptococcus pneumoniae* infection following prior ciprofloxacin therapy,” *European Journal of Clinical Microbiology and Infectious Diseases*, vol. 24, no. 1, pp. 58–60, 2005.
- [209] D. E. Low, “Quinolone resistance among pneumococci: therapeutic and diagnostic implications,” *Clinical Infectious Diseases*, vol. 38, supplement 4, pp. S357–S362, 2004.
- [210] K. Weiss, C. Restieri, R. Gauthier et al., “A nosocomial outbreak of fluoroquinolone-resistant *Streptococcus pneumoniae*,” *Clinical Infectious Diseases*, vol. 33, no. 4, pp. 517–522, 2001.
- [211] S. Bhavnani, J. P. Hammel, and R. N. Jones, “Relationship between increased levofloxacin use and decreased susceptibility to *Streptococcus pneumoniae*: report from the ARREST Program [abstract K-1397],” in *Proceedings of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC ’03)*, American Society for Microbiology, Chicago, Ill, USA, September 2003.
- [212] G. V. Doern, S. S. Richter, A. Miller et al., “Antimicrobial resistance among *Streptococcus pneumoniae* in the United States: have we begun to turn the corner on resistance to certain antimicrobial classes?” *Clinical Infectious Diseases*, vol. 41, no. 2, pp. 139–148, 2005.
- [213] D. E. Low, “Fluoroquinolone-resistant pneumococci: maybe resistance isn’t futile?” *Clinical Infectious Diseases*, vol. 40, no. 2, pp. 236–238, 2005.
- [214] S. Lim, D. Bast, A. McGeer, J. De Azavedo, and D. E. Low, “Antimicrobial susceptibility breakpoints and first-step parC mutations in *Streptococcus pneumoniae*: redefining fluoroquinolone resistance,” *Emerging Infectious Diseases*, vol. 9, no. 7, pp. 833–837, 2003.
- [215] K. N. Schurek, H. J. Adam, D. J. Hoban, and G. G. Zhanel, “Call for the international adoption of microbiological breakpoints for fluoroquinolones and *Streptococcus pneumoniae*,” *International Journal of Antimicrobial Agents*, vol. 28, no. 3, pp. 266–269, 2006.
- [216] E. Pérez-Trallero, J. M. Marimón, L. Iglesias, and J. Larruskain, “Fluoroquinolone and macrolide treatment failure in pneumococcal pneumonia and selection of multidrug-resistant isolates,” *Emerging Infectious Diseases*, vol. 9, no. 9, pp. 1159–1162, 2003.
- [217] M. B. Kays, D. W. Smith, M. F. Wack, and G. A. Denys, “Levofloxacin treatment failure in a patient with fluoroquinolone-resistant *Streptococcus pneumoniae* pneumonia,” *Pharmacotherapy*, vol. 22, no. 3, pp. 395–399, 2002.
- [218] N. Q. Hoa, N. V. Trung, M. Larsson et al., “Decreased *Streptococcus pneumoniae* susceptibility to oral antibiotics among children in rural Vietnam: a community study,” *BMC Infectious Diseases*, vol. 10, article 85, 2010.
- [219] M. W. R. Pletz, A. P. Shergill, L. McGee, B. Beall, C. G. Whitney, and K. P. Klugman, “Prevalence of first-step mutants among levofloxacin-susceptible invasive isolates of *Streptococcus pneumoniae* in the United States,” *Antimicrobial Agents and Chemotherapy*, vol. 50, no. 4, pp. 1561–1563, 2006.
- [220] A. von Gottberg, K. P. Klugman, C. Cohen et al., “Emergence of levofloxacin-non-susceptible *Streptococcus pneumoniae* and treatment for multidrug-resistant tuberculosis in children in South Africa: a cohort observational surveillance study,” *The Lancet*, vol. 371, no. 9618, pp. 1108–1113, 2008.
- [221] N. Wolter, M. Du Plessis, A. Von Gottberg, L. De Gouveia, and K. P. Klugman, “Molecular characterization of emerging non-levofloxacin-susceptible pneumococci isolated from children in South Africa,” *Journal of Clinical Microbiology*, vol. 47, no. 5, pp. 1319–1324, 2009.

- [222] J. C. Sanz, E. Cercenado, M. Marín et al., "Multidrug-resistant pneumococci (serotype 8) causing invasive disease in HIV+ patients," *Clinical Microbiology and Infection*, vol. 17, no. 7, pp. 1094–1098, 2011.
- [223] A. Pantosti and M. L. Moro, "Antibiotic use: the crystal ball for predicting antibiotic resistance," *Clinical Infectious Diseases*, vol. 40, no. 9, pp. 1298–1300, 2005.
- [224] S. H. Gillespie, L. L. Voelker, and A. Dickens, "Evolutionary barriers to quinolone resistance in *Streptococcus pneumoniae*," *Microbial Drug Resistance*, vol. 8, no. 2, pp. 79–84, 2002.
- [225] C. N. Johnson, D. E. Briles, W. H. Benjamin, S. K. Hollingshead, and K. B. Waites, "Relative fitness of fluoroquinolone-resistant *Streptococcus pneumoniae*," *Emerging Infectious Diseases*, vol. 11, no. 6, pp. 814–820, 2005.
- [226] D. E. Rozen, L. McGee, B. R. Levin, and K. P. Klugman, "Fitness costs of fluoroquinolone resistance in *Streptococcus pneumoniae*," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 2, pp. 412–416, 2007.
- [227] S. D. Brown and M. J. Rybak, "Antimicrobial susceptibility of *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* collected from patients across the USA, in 2001–2002, as part of the PROTEKT US study," *Journal of Antimicrobial Chemotherapy*, vol. 54, supplement 1, pp. i7–i15, 2004.
- [228] D. F. Sahn, N. P. Brown, D. C. Draghi, A. T. Evangelista, Y. C. Yee, and C. Thornsberrry, "Tracking resistance among bacterial respiratory tract pathogens: summary of findings of the TRUST Surveillance Initiative, 2001–2005," *Postgraduate medicine*, vol. 120, supplement 3, pp. 8–15, 2008.
- [229] I. Morrissey, K. Maher, L. Williams, J. Shackcloth, D. Felmingham, and R. Reynolds, "Non-susceptibility trends among *Haemophilus influenzae* and *Moraxella catarrhalis* from community-acquired respiratory tract infections in the UK and Ireland, 1999–2007," *Journal of Antimicrobial Chemotherapy*, vol. 62, supplement 2, pp. ii97–ii103, 2008.
- [230] S. L. Barriere and J. A. Hindler, "Ciprofloxacin-resistant *Haemophilus influenzae* infection in a patient with chronic lung disease," *Annals of Pharmacotherapy*, vol. 27, no. 3, pp. 309–310, 1993.
- [231] D. J. Biedenbach and R. N. Jones, "Five-year analysis of *Haemophilus influenzae* isolates with reduced susceptibility to fluoroquinolones: prevalence results from the SENTRY antimicrobial surveillance program," *Diagnostic Microbiology and Infectious Disease*, vol. 46, no. 1, pp. 55–61, 2003.
- [232] J. Campos, F. Román, M. Georgiou et al., "Long-term persistence of ciprofloxacin-resistant *Haemophilus influenzae* in patients with cystic fibrosis," *Journal of Infectious Diseases*, vol. 174, no. 6, pp. 1345–1347, 1996.
- [233] E. Elliott, D. Oosthuizen, M. M. Johnson, and L. J. V. Piddock, "Fluoroquinolone resistance in *Haemophilus influenzae*," *Journal of Antimicrobial Chemotherapy*, vol. 52, no. 4, pp. 734–735, 2003.
- [234] M. Georgiou, R. Muñoz, F. Román et al., "Ciprofloxacin-resistant *Haemophilus influenzae* strains possess mutations in analogous positions of *GyrA* and *ParC*," *Antimicrobial Agents and Chemotherapy*, vol. 40, no. 7, pp. 1741–1744, 1996.
- [235] I. M. Gould, K. J. Forbes, and G. S. Gordon, "Quinolone resistant *Haemophilus influenzae*," *Journal of Antimicrobial Chemotherapy*, vol. 33, no. 1, pp. 187–188, 1994.
- [236] M. Pérez-Vázquez, F. Román, B. Aracil, R. Cantón, and J. Campos, "In vitro activities of garenoxacin (BMS-28756) against *Haemophilus influenzae* isolates with different fluoroquinolone susceptibilities," *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 11, pp. 3539–3541, 2003.
- [237] J. Vila, J. Ruiz, F. Sanchez et al., "Increase in quinolone resistance in a *Haemophilus influenzae* strain isolated from a patient with recurrent respiratory infections treated with ofloxacin," *Antimicrobial Agents and Chemotherapy*, vol. 43, no. 1, pp. 161–162, 1999.
- [238] D. J. Biedenbach and R. N. Jones, "Fluoroquinolone-resistant *Haemophilus influenzae*: frequency of occurrence and analysis of confirmed strains in the SENTRY antimicrobial surveillance program (North and Latin America)," *Diagnostic Microbiology and Infectious Disease*, vol. 36, no. 4, pp. 255–259, 2000.
- [239] J. Nazir, C. Urban, N. Mariano et al., "Quinolone-resistant *Haemophilus influenzae* in a long-term care facility: clinical and molecular epidemiology," *Clinical Infectious Diseases*, vol. 38, no. 11, pp. 1564–1569, 2004.
- [240] X. Li, N. Mariano, J. J. Rahal, C. M. Urban, and K. Drlica, "Quinolone-resistant *Haemophilus influenzae* in a long-term-care facility: nucleotide sequence characterization of alterations in the genes encoding DNA gyrase and DNA topoisomerase IV," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 9, pp. 3570–3572, 2004.
- [241] C. M. Chang, T. L. Lauderdale, H. C. Lee et al., "Colonisation of fluoroquinolone-resistant *Haemophilus influenzae* among nursing home residents in southern Taiwan," *Journal of Hospital Infection*, vol. 75, no. 4, pp. 304–308, 2010.
- [242] S. I. Yokota, Y. Ohkoshi, K. Sato, and N. Fujii, "Emergence of fluoroquinolone-resistant *Haemophilus influenzae* strains among elderly patients but not among children," *Journal of Clinical Microbiology*, vol. 46, no. 1, pp. 361–365, 2008.
- [243] Y. Hirakata, K. Ohmori, M. Mikuriya et al., "Antimicrobial activities of piperacillin-tazobactam against *Haemophilus influenzae* isolates, including β -lactamase-negative ampicillin-resistant and β -lactamase-positive amoxicillin-clavulanate-resistant isolates, and mutations in their quinolone resistance-determining regions," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 10, pp. 4225–4230, 2009.
- [244] N. P. Brenwald, J. M. Andrews, G. Jevons, and R. Wise, "Detection of ciprofloxacin resistance in *Haemophilus influenzae* using nalidixic acid and BSAC methodology," *Journal of Antimicrobial Chemotherapy*, vol. 51, no. 5, pp. 1311–1312, 2003.
- [245] P.-L. Ho, K. H. Chow, C. C. Mak et al., "Decreased levofloxacin susceptibility in *Haemophilus influenzae* in children, Hong Kong," *Emerging Infectious Diseases*, vol. 10, no. 11, pp. 1960–1962, 2004.
- [246] T. Bastida, M. Pérez-Vázquez, J. Campos et al., "Levofloxacin treatment failure in *Haemophilus influenzae* pneumonia," *Emerging Infectious Diseases*, vol. 9, no. 11, pp. 1475–1478, 2003.
- [247] H. H. Balkhy, Z. A. Memish, A. Shibl, A. Elbashier, and A. Osoba, "In vitro activity of quinolones against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* in Saudi Arabia," *Eastern Mediterranean Health Journal*, vol. 11, no. 1–2, pp. 36–44, 2005.
- [248] J. R. Dippersio, R. N. Jones, T. Barrett, G. V. Doern, and M. A. Pfaller, "Fluoroquinolone-resistant *Moraxella catarrhalis* in a patient with pneumonia: report from the SENTRY antimicrobial surveillance program (1998)," *Diagnostic Microbiology and Infectious Disease*, vol. 32, no. 2, pp. 131–135, 1998.
- [249] N. M. Joseph, S. Sista, T. K. Dutta, A. S. Badhe, and S. C. Parija, "Ventilator-associated pneumonia: a review," *European Journal of Internal Medicine*, vol. 21, no. 5, pp. 360–368, 2010.

- [250] G. W. Soo Hoo, Y. E. Wen, T. V. Nguyen, and M. B. Goetz, "Impact of clinical guidelines in the management of severe hospital-acquired pneumonia," *Chest*, vol. 128, no. 4, pp. 2778–2787, 2005.
- [251] T. M. File, "Recommendations for treatment of Hospital-acquired and ventilator-associated pneumonia: review of recent international guidelines," *Clinical Infectious Diseases*, vol. 51, supplement 1, pp. S42–S47, 2010.
- [252] A. Torres, M. Ferrer, and J. R. Badia, "Treatment guidelines and outcomes of Hospital-acquired and ventilator-associated pneumonia," *Clinical Infectious Diseases*, vol. 51, supplement 1, pp. S48–S53, 2010.
- [253] A. Torres and J. Rello, "Update in community-acquired and nosocomial pneumonia 2009," *American Journal of Respiratory and Critical Care Medicine*, vol. 181, no. 8, pp. 782–787, 2010.
- [254] A. Torres, S. Ewig, H. Lode, and J. Carlet, "Defining, treating and preventing hospital acquired pneumonia: European perspective," *Intensive Care Medicine*, vol. 35, no. 1, pp. 9–29, 2009.
- [255] M. H. Kollef, A. Shorr, Y. P. Tabak, V. Gupta, L. Z. Liu, and R. S. Johannes, "Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia," *Chest*, vol. 128, no. 6, pp. 3854–3862, 2005.
- [256] R. R. Reinert, S. Reinert, M. Van Der Linden, M. Y. Cil, A. Al-Lahham, and P. Appelbaum, "Antimicrobial susceptibility of *Streptococcus pneumoniae* in eight European countries from 2001 to 2003," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 7, pp. 2903–2913, 2005.
- [257] D. J. Farrell, D. Felmingham, J. Shackcloth et al., "Non-susceptibility trends and serotype distributions among *Streptococcus pneumoniae* from community-acquired respiratory tract infections and from bacteraemias in the UK and Ireland, 1999 to 2007," *Journal of Antimicrobial Chemotherapy*, vol. 62, no. 2, pp. ii87–ii95, 2008.
- [258] Centers for Disease Control and Prevention, "Active bacterial core surveillance report. Emerging infection program network, *Streptococcus pneumoniae*," 2007, <http://www.cdc.gov/ncidod/abcs/reports-findings/survreports/spneu07.pdf>.
- [259] Centers for Disease Control and Prevention, "Active bacterial core surveillance report. Emerging infection program network, *Streptococcus pneumoniae*," 2009, <http://www.cdc.gov/ncidod/abcs/reports-findings/survreports/spneu09.pdf>.
- [260] T. A. Davies, Y. C. Yee, K. Amsler, R. Goldschmidt, D. F. Sahm, and A. T. Evangelista, "Sporadic occurrences of fluoroquinolone-resistant *Streptococcus pneumoniae* in the United States: longitudinal analysis of institutions from the New England and West South Central regions during the TRUST 4-9 (2000–2005) Surveillance Studies," *Postgraduate medicine*, vol. 120, no. 3, pp. 25–31, 2008.
- [261] A. G. De La Campa, C. Ardanuy, L. Balsalobre et al., "Changes in fluoroquinolone-resistant *Streptococcus pneumoniae* after 7-valent conjugate vaccination, Spain," *Emerging Infectious Diseases*, vol. 15, no. 6, pp. 905–911, 2009.
- [262] C. G. Whitney, M. M. Farley, J. Hadler et al., "Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine," *New England Journal of Medicine*, vol. 348, no. 18, pp. 1737–1746, 2003.
- [263] G. G. Zhanel, M. DeCorby, N. Laing et al., "Antimicrobial-resistant pathogens in intensive care units in Canada: results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005–2006," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 4, pp. 1430–1437, 2008.
- [264] G. G. Zhanel, M. DeCorby, H. Adam et al., "Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: results of the Canadian Ward Surveillance study (CANWARD 2008)," *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 11, pp. 4684–4693, 2010.
- [265] M. E. Jones, D. C. Draghi, C. Thornsberry, J. A. Karlowsky, D. F. Sahm, and R. P. Wenzel, "Emerging resistance among bacterial pathogens in the intensive care unit—a European and North American surveillance study (2000–2002)," *Annals of Clinical Microbiology and Antimicrobials*, vol. 3, article 14, 2004.
- [266] E. N. Lagamayo, "Antimicrobial resistance in major pathogens of hospital-acquired pneumonia in Asian countries," *American Journal of Infection Control*, vol. 36, no. 4, supplement, pp. S101–S108, 2008.
- [267] N. Goel, U. Chaudhary, R. Aggarwal, and K. Bala, "Antibiotic sensitivity pattern of gram negative bacilli isolated from the lower respiratory tract of ventilated patients in the intensive care unit," *Indian Journal of Critical Care Medicine*, vol. 13, no. 3, pp. 148–151, 2009.
- [268] P. G. Higgins, K. Coleman, and S. G. B. Amyes, "Bactericidal and bacteriostatic activity of gemifloxacin against *Acinetobacter* spp. *in vitro*," *Journal of Antimicrobial Chemotherapy*, vol. 45, no. 4, pp. 71–77, 2000.
- [269] J. A. Karlowsky, D. C. Draghi, M. E. Jones, C. Thornsberry, I. R. Friedland, and D. F. Sahm, "Surveillance for antimicrobial susceptibility among clinical isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from hospitalized patients in the United States, 1998 to 2001," *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 5, pp. 1681–1688, 2003.
- [270] F. Perez, A. M. Hujer, K. M. Hujer, B. K. Decker, P. N. Rather, and R. A. Bonomo, "Global challenge of multidrug-resistant *Acinetobacter baumannii*," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 10, pp. 3471–3484, 2007.
- [271] H. Alishkan, Ş. Çolakoğlu, T. Turunç et al., "Four years monitorization of antibiotic sensitivity rates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains isolated from patients in intensive care unit and inpatient clinics," *Mikrobiyoloji Bulteni*, vol. 42, no. 2, pp. 321–329, 2008.
- [272] J. R. W. Govan, C. Doherty, and S. Glass, "Rational parameters for antibiotic therapy in patients with cystic fibrosis," *Infection*, vol. 15, no. 4, pp. 300–307, 1987.
- [273] S. Pournaras, A. Ikonomidis, A. Markogiannakis, N. Spanakis, A. N. Maniatis, and A. Tsakris, "Characterization of clinical isolates of *Pseudomonas aeruginosa* heterogeneously resistant to carbapenems," *Journal of Medical Microbiology*, vol. 56, no. 1, pp. 66–70, 2007.
- [274] N. Bagge, M. Hentzer, J. B. Andersen, O. Ciofu, M. Givskov, and N. Høiby, "Dynamics and Spatial Distribution of β -Lactamase Expression in *Pseudomonas aeruginosa* Biofilms," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 4, pp. 1168–1174, 2004.
- [275] A. Dalhoff, "Clinical perspectives of quinolone resistance in *Pseudomonas aeruginosa*," in *Pseudomonas aeruginosa in Human Disease. Antibiot Chemother*, J. Y. Homma, H. Tanimoto, I. A. Holder, N. Høiby, and G. Döring, Eds., vol. 44, pp. 221–239, Karger, Basel, Switzerland, 1991.
- [276] J. D. Perry, L. Laine, S. Hughes, A. Nicholson, A. Galloway, and F. K. Gould, "Recovery of antimicrobial-resistant *Pseudomonas aeruginosa* from sputa of cystic fibrosis patients by culture on selective media," *Journal of Antimicrobial Chemotherapy*, vol. 61, no. 5, pp. 1057–1061, 2008.
- [277] G. L. Morlin, D. L. Hedges, A. L. Smith, and J. L. Burns, "Accuracy and cost of antibiotic susceptibility testing of

- mixed morphotypes of *Pseudomonas aeruginosa*,” *Journal of Clinical Microbiology*, vol. 32, no. 4, pp. 1027–1030, 1994.
- [278] J. E. Foweraker, C. R. Laughton, D. F. J. Brown, and D. Bilton, “Phenotypic variability of *Pseudomonas aeruginosa* in sputa from patients with acute infective exacerbation of cystic fibrosis and its impact on the validity of antimicrobial susceptibility testing,” *Journal of Antimicrobial Chemotherapy*, vol. 55, no. 6, pp. 921–927, 2005.
- [279] M. E. Skindersoe, M. Alhede, R. Phipps et al., “Effects of antibiotics on quorum sensing in *Pseudomonas aeruginosa*,” *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 10, pp. 3648–3663, 2008.
- [280] A. Dalhoff and I. Shalit, “Immunomodulatory effects of quinolones,” *The Lancet Infectious Diseases*, vol. 3, no. 6, pp. 359–371, 2003.
- [281] A. Dalhoff, “Immunomodulatory activities of fluoroquinolones,” *Infection*, vol. 33, supplement 2, pp. 55–70, 2005.
- [282] T. Köhler, G. G. Perron, A. Buckling, and C. van Delden, “Quorum sensing inhibition selects for virulence and cooperation in *Pseudomonas aeruginosa*,” *PLoS Pathogens*, vol. 6, no. 5, article e1000883, 2010.
- [283] A. Oliver, R. Cantón, P. Campo, F. Baquero, and J. Blázquez, “High frequency of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis lung infection,” *Science*, vol. 288, no. 5469, pp. 1251–1253, 2000.
- [284] A. Oliver, F. Baquero, and J. Blázquez, “The mismatch repair system (mutS, mutL and uvrD genes) in *Pseudomonas aeruginosa*: molecular characterization of naturally occurring mutants,” *Molecular Microbiology*, vol. 43, no. 6, pp. 1641–1650, 2002.
- [285] M. D. Maciá, N. Borrell, M. Segura, C. Gómez, J. L. Pérez, and A. Oliver, “Efficacy and potential for resistance selection of antipseudomonal treatments in a mouse model of lung infection by hypermutable *Pseudomonas aeruginosa*,” *Antimicrobial Agents and Chemotherapy*, vol. 50, no. 3, pp. 975–983, 2006.
- [286] A. Oliver and A. Mena, “Bacterial hypermutation in cystic fibrosis, not only for antibiotic resistance,” *Clinical Microbiology and Infection*, vol. 16, no. 7, pp. 798–808, 2010.
- [287] T. Strateva, G. Petrova, P. Perenovska, and I. Mitov, “Bulgarian cystic fibrosis *Pseudomonas aeruginosa* isolates: antimicrobial susceptibility and neuraminidase-encoding gene distribution,” *Journal of Medical Microbiology*, vol. 58, no. 5, pp. 690–692, 2009.
- [288] M. I. Morosini, M. García-Castillo, E. Loza, M. Pérez-Vázquez, F. Baquero, and R. Cantón, “Breakpoints for predicting *Pseudomonas aeruginosa* susceptibility to inhaled tobramycin in cystic fibrosis patients: use of high-range Etest strips,” *Journal of Clinical Microbiology*, vol. 43, no. 9, pp. 4480–4485, 2005.
- [289] T. L. Pitt, M. Sparrow, M. Warner, and M. Stefanidou, “Survey of resistance of *Pseudomonas aeruginosa* from UK patients with cystic fibrosis to six commonly prescribed antimicrobial agents,” *Thorax*, vol. 58, no. 9, pp. 794–796, 2003.
- [290] T. Schülin, “In vitro activity of the aerosolized agents colistin and tobramycin and five intravenous agents against *Pseudomonas aeruginosa* isolated from cystic fibrosis patients in southwestern Germany,” *Journal of Antimicrobial Chemotherapy*, vol. 49, no. 2, pp. 403–406, 2002.
- [291] G. Manno, M. Cruciani, L. Romano et al., “Antimicrobial use and *Pseudomonas aeruginosa* susceptibility profile in a cystic fibrosis centre,” *International Journal of Antimicrobial Agents*, vol. 25, no. 3, pp. 193–197, 2005.
- [292] J. L. Burns, L. Saiman, S. Whittier et al., “Comparison of agar diffusion methodologies for antimicrobial susceptibility testing of *Pseudomonas aeruginosa* isolates from cystic fibrosis patients,” *Journal of Clinical Microbiology*, vol. 38, no. 5, pp. 1818–1822, 2000.
- [293] M. Z. David and R. S. Daum, “Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic,” *Clinical Microbiology Reviews*, vol. 23, no. 3, pp. 616–687, 2010.
- [294] J. M. Rolain, P. François, D. Hernandez et al., “Genomic analysis of an emerging multiresistant *Staphylococcus aureus* strain rapidly spreading in cystic fibrosis patients revealed the presence of an antibiotic inducible bacteriophage,” *Biology Direct*, vol. 4, article 1, 2009.
- [295] M. S. Dryden, “Complicated skin and soft tissue infection,” *Journal of Antimicrobial Chemotherapy*, vol. 65, supplement 3, Article ID dkq302, pp. iii35–iii44, 2010.
- [296] P. Giordano, K. Weber, G. Gesin, and J. Kubert, “Skin and skin structure infections: treatment with newer generation fluoroquinolones,” *Therapeutics and Clinical Risk Management*, vol. 3, no. 2, pp. 309–317, 2007.
- [297] A. L. Barry, M. A. Pfaller, P. C. Fuchs, and R. R. Packer, “In vitro activities of 12 orally administered antimicrobial agents against four species of bacterial respiratory pathogens from U.S. Medical Centers in 1992 and 1993,” *Antimicrobial Agents and Chemotherapy*, vol. 38, no. 10, pp. 2419–2425, 1994.
- [298] J. M. Blondeau, D. Church, Y. Yaschuk, and J. Bjarnason, “In vitro activity of several antimicrobial agents against 1003 isolates of *Streptococcus pyogenes* collected from Western Canada,” *International Journal of Antimicrobial Agents*, vol. 12, no. 1, pp. 67–70, 1999.
- [299] J. A. A. Hoogkamp-Korstanje and J. Roelofs-Willems, “Comparative in vitro activity of moxifloxacin against Gram-positive clinical isolates,” *Journal of Antimicrobial Chemotherapy*, vol. 45, no. 1, pp. 31–39, 2000.
- [300] S. S. Yan, M. L. Fox, S. M. Holland, F. Stock, V. J. Gill, and D. F. Fedorko, “Resistance to multiple fluoroquinolones in a clinical isolate of *Streptococcus pyogenes*: identification of gyrA and parC and specification of point mutations associated with resistance,” *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 11, pp. 3196–3198, 2000.
- [301] D. J. Biedenbach, M. A. Toleman, T. R. Walsh, and R. N. Jones, “Characterization of fluoroquinolone-resistant β -hemolytic *Streptococcus* spp. isolated in North America and Europe including the first report of fluoroquinolone-resistant *Streptococcus dysgalactiae* subspecies equisimilis: report from the SENTRY Antimicrobial Surveillance Program (1997–2004),” *Diagnostic Microbiology and Infectious Disease*, vol. 55, no. 2, pp. 119–127, 2006.
- [302] S. S. Richter, D. J. Diekema, K. P. Heilmann et al., “Fluoroquinolone resistance in *Streptococcus pyogenes*,” *Clinical Infectious Diseases*, vol. 36, no. 3, pp. 380–383, 2003.
- [303] R. R. Reinert, R. Lütticken, and A. Al-Lahham, “High-level fluoroquinolone resistance in a clinical *Streptococcus pyogenes* isolate in Germany,” *Clinical Microbiology and Infection*, vol. 10, no. 7, pp. 659–662, 2004.
- [304] S. Malhotra-Kumar, C. Lammens, S. Chapelle, C. Mallentjer, J. Weyler, and H. Goossens, “Clonal spread of fluoroquinolone non-susceptible *Streptococcus pyogenes*,” *Journal of Antimicrobial Chemotherapy*, vol. 55, no. 3, pp. 320–325, 2005.
- [305] A. Rivera, M. Rebollo, F. Sánchez et al., “Characterisation of fluoroquinolone-resistant clinical isolates of *Streptococcus pyogenes* in Barcelona, Spain,” *Clinical Microbiology and Infection*, vol. 11, no. 9, pp. 759–761, 2005.

- [306] L. van Heirstraeten, G. Leten, C. Lammens, H. Goosens, and S. Malhotra-Kumar, "Increase in fluoroquinolone non-susceptibility among clinical *Streptococcus pyogenes* in Belgium during 2007–10," *Journal of Antimicrobial Chemotherapy*. In press.
- [307] S. Malhotra-Kumar, L. Van Heirstraeten, C. Lammens, S. Chapelle, and H. Goossens, "Emergence of high-level fluoroquinolone resistance in emm 6 *Streptococcus pyogenes* and in vitro resistance selection with ciprofloxacin, levofloxacin and moxifloxacin," *Journal of Antimicrobial Chemotherapy*, vol. 63, no. 5, pp. 886–894, 2009.
- [308] R. Pires, C. Ardanuy, D. Rolo et al., "Emergence of ciprofloxacin-nonsusceptible *Streptococcus pyogenes* isolates from healthy children and pediatric patients in Portugal," *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 6, pp. 2677–2680, 2010.
- [309] K. Arai, Y. Hirakata, H. Yano et al., "Emergence of fluoroquinolone-resistant *Streptococcus pyogenes* in Japan by a point mutation leading to a new amino acid substitution," *Journal of Antimicrobial Chemotherapy*, vol. 66, no. 3, Article ID dkq477, pp. 494–498, 2011.
- [310] R. Alonso, E. Mateo, G. Ezpeleta, and R. Cisterna, "Characterisation of levofloxacin-resistant clinical isolates of *Streptococcus pyogenes* in Bilbao, Spain," *International Journal of Antimicrobial Agents*, vol. 30, no. 2, pp. 183–185, 2007.
- [311] D. E. Bessen, "Population biology of the human restricted pathogen, *Streptococcus pyogenes*," *Infection, Genetics and Evolution*, vol. 9, no. 4, pp. 581–593, 2009.
- [312] J. Powis, A. McGeer, C. Duncan et al., "Prevalence and characterization of invasive isolates of *Streptococcus pyogenes* with reduced susceptibility to fluoroquinolones," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 5, pp. 2130–2132, 2005.
- [313] P. R. Smeesters, A. Vergison, D. C. Junior, and L. Van Melderden, "Emerging fluoroquinolone-non-susceptible group A streptococci in two different paediatric populations," *International Journal of Antimicrobial Agents*, vol. 34, no. 1, pp. 44–49, 2009.
- [314] T. Ikebe, K. Hirasawa, R. Suzuki et al., "Antimicrobial susceptibility survey of *Streptococcus pyogenes* isolated in Japan from patients with severe invasive group A streptococcal infections," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 2, pp. 788–790, 2005.
- [315] T. Wajima, S. Y. Murayama, K. Sunaoshi, E. Nakayama, K. Sunakawa, and K. Ubukata, "Distribution of emm type and antibiotic susceptibility of group A streptococci causing invasive and noninvasive disease," *Journal of Medical Microbiology*, vol. 57, no. 11, pp. 1383–1388, 2008.
- [316] P. Ball, "Emergent resistance to ciprofloxacin amongst *Pseudomonas aeruginosa* and *Staphylococcus aureus*: clinical significance and therapeutic approaches," *Journal of Antimicrobial Chemotherapy*, vol. 26, supplement f, pp. 165–179, 1990.
- [317] M. E. Mulligan, P. J. Ruane, L. Johnston et al., "Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization," *American Journal of Medicine*, vol. 82, no. 4 A, pp. 215–219, 1987.
- [318] J. R. Fitzgerald, D. E. Sturdevant, S. M. Mackie, S. R. Gill, and J. M. Musser, "Evolutionary genomics of *Staphylococcus aureus*: insights into the origin of methicillin-resistant strains and the toxic shock syndrome epidemic," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 15, pp. 8821–8826, 2001.
- [319] B. Berger-Bächi and S. Rohrer, "Factors influencing methicillin resistance in staphylococci," *Archives of Microbiology*, vol. 178, no. 3, pp. 165–171, 2002.
- [320] S. Deresinski, "Methicillin-resistant *Staphylococcus aureus*: an evolutionary, epidemiologic, and therapeutic odyssey," *Clinical Infectious Diseases*, vol. 40, no. 4, pp. 562–573, 2005.
- [321] A. Dalhoff and S. Schubert, "Dichotomous selection of high-level oxacillin resistance in *Staphylococcus aureus* by fluoroquinolones," *International Journal of Antimicrobial Agents*, vol. 36, no. 3, pp. 216–221, 2010.
- [322] R. A. Venezia, B. E. Domaracki, A. M. Evans, K. E. Preston, and E. M. Graffunder, "Selection of high-level oxacillin resistance in heteroresistant *Staphylococcus aureus* by fluoroquinolone exposure," *Journal of Antimicrobial Chemotherapy*, vol. 48, no. 3, pp. 375–381, 2001.
- [323] C. Bisognano, P. E. Vaudaux, D. P. Lew, E. Y. W. Ng, and D. C. Hooper, "Increased expression of fibronectin-binding proteins by fluoroquinolone-resistant *Staphylococcus aureus* exposed to subinhibitory levels of ciprofloxacin," *Antimicrobial Agents and Chemotherapy*, vol. 41, no. 5, pp. 906–913, 1997.
- [324] C. Bisognano, P. Vaudaux, P. Rohner, D. P. Lew, and D. C. Hooper, "Induction of fibronectin-binding proteins and increased adhesion of quinolone-resistant *Staphylococcus aureus* by subinhibitory levels of ciprofloxacin," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 6, pp. 1428–1437, 2000.
- [325] A. P. Johnson, H. M. Aucken, S. Cavendish et al., "Dominance of EMRSA-15 and -16 among MRSA causing nosocomial bacteraemia in the UK: analysis of isolates from the European Antimicrobial Resistance Surveillance System (EARSS)," *Journal of Antimicrobial Chemotherapy*, vol. 48, no. 1, pp. 143–144, 2001.
- [326] G. Dziekan, A. Hahn, K. Thüne et al., "Methicillin-resistant *Staphylococcus aureus* in a teaching hospital: investigation of nosocomial transmission using a matched case-control study," *Journal of Hospital Infection*, vol. 46, no. 4, pp. 263–270, 2000.
- [327] S. G. Weber, H. S. Gold, D. C. Hooper, A. W. Karchmer, and Y. Carmeli, "Fluoroquinolones and the Risk for Methicillin-resistant *Staphylococcus aureus* in Hospitalized Patients," *Emerging Infectious Diseases*, vol. 9, no. 11, pp. 1415–1422, 2003.
- [328] E. M. Graffunder and R. A. Venezia, "Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials," *Journal of Antimicrobial Chemotherapy*, vol. 49, no. 6, pp. 999–1005, 2002.
- [329] J. Edelsberg, C. Taneja, M. Zervos et al., "Trends in US hospital admissions for skin and soft tissue infections," *Emerging Infectious Diseases*, vol. 15, no. 9, pp. 1516–1518, 2009.
- [330] R. N. Jones, R. E. Mendes, and H. S. Sader, "Ceftaroline activity against pathogens associated with complicated skin and skin structure infections: results from an international surveillance study," *Journal of Antimicrobial Chemotherapy*, vol. 65, supplement 4, Article ID dkq252, pp. iv17–iv31, 2010.
- [331] H. M. Blumberg, D. Rimland, D. J. Carroll, P. Terry, and I. K. Wachsmuth, "Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant *Staphylococcus aureus*," *Journal of Infectious Diseases*, vol. 163, no. 6, pp. 1279–1285, 1991.

- [332] G. M. Knight, E. L. Budd, L. Whitney et al., "Shift in dominant hospital-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) clones over time," *Journal of Antimicrobial Chemotherapy*. In press.
- [333] C. Liu, A. Bayer, S. E. Cosgrove et al., "Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary," *Clinical Infectious Diseases*, vol. 52, no. 3, pp. 285–292, 2011.
- [334] H. F. Chambers, "Community-associated MRSA—resistance and virulence converge," *New England Journal of Medicine*, vol. 352, no. 14, pp. 1485–1487, 2005.
- [335] B. A. Diep, G. G. Stone, L. Basuino et al., "The arginine catabolic mobile element and staphylococcal chromosomal cassette mec linkage: convergence of virulence and resistance in the USA300 clone of methicillin-resistant *Staphylococcus aureus*," *Journal of Infectious Diseases*, vol. 197, no. 11, pp. 1523–1530, 2008.
- [336] S. Monecke, G. Coombs, A. C. Shore et al., "A field guide to pandemic, epidemic and sporadic clones of methicillin-resistant *Staphylococcus aureus*," *PLoS ONE*, vol. 6, no. 4, Article ID e17936, 2011.
- [337] A. V. Groom, D. H. Wolsey, T. S. Naimi et al., "Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community," *Journal of the American Medical Association*, vol. 286, no. 10, pp. 1201–1205, 2001.
- [338] E. J. Gorak, S. M. Yamada, and J. D. Brown, "Community-acquired methicillin-resistant *Staphylococcus aureus* in hospitalized adults and children without known risk factors," *Clinical Infectious Diseases*, vol. 29, no. 4, pp. 797–800, 1999.
- [339] P. D. Fey, B. Saïd-Salim, M. E. Rupp et al., "Comparative molecular analysis of community- or hospital-acquired methicillin-resistant *Staphylococcus aureus*," *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 1, pp. 196–203, 2003.
- [340] M. F. Q. Kluytmans-VandenBergh and J. A. J. W. Kluytmans, "Community-acquired methicillin-resistant *Staphylococcus aureus*: current perspectives," *Clinical Microbiology and Infection*, vol. 12, supplement 1, pp. 9–15, 2006.
- [341] E. A. Eady and J. H. Cove, "Staphylococcal resistance revisited: community-acquired methicillin resistant *Staphylococcus aureus*—an emerging problem for the management of skin and soft tissue infections," *Current Opinion in Infectious Diseases*, vol. 16, no. 2, pp. 103–124, 2003.
- [342] B. Shopsin, X. Zhao, B. N. Kreiswirth, G. S. Tillotson, and K. Drlica, "Are the new quinolones appropriate treatment for community-acquired methicillin-resistant *Staphylococcus aureus*?" *International Journal of Antimicrobial Agents*, vol. 24, no. 1, pp. 32–34, 2004.
- [343] G. J. Beilman, G. Sandifer, D. Skarda et al., "Emerging infections with community-associated methicillin-resistant *Staphylococcus aureus* in outpatients at an Army Community Hospital," *Surgical Infections*, vol. 6, no. 1, pp. 87–92, 2005.
- [344] J. von Freyberg, S. Scherpe, M. A. Horstkotte, and J. K. Knobloch, "Activity of moxifloxacin against community-acquired MRSA and other quinolone-susceptible MRSA isolates," in *Proceedings of the 16th European Congress of Clinical Microbiology and Infectious Diseases*, Abstract No 305, Nice, France, April 2004.
- [345] Y. L. Su, W. F. Hong, C. Sutherland, A. C. DeRyke, and D. P. Nicolau, "Antibacterial effects of moxifloxacin and levofloxacin simulating epithelial lining fluid concentrations against community-acquired methicillin-resistant: *Staphylococcus aureus*," *Drugs in R and D*, vol. 8, no. 2, pp. 69–77, 2007.
- [346] W. Witte, "Community-acquired methicillin-resistant *Staphylococcus aureus*: what do we need to know?" *Clinical Microbiology and Infection*, vol. 15, supplement 7, pp. 17–25, 2009.
- [347] L. L. Han, L. K. McDougal, R. J. Gorwitz et al., "High frequencies of clindamycin and tetracycline resistance in methicillin-resistant *Staphylococcus aureus* pulsed-field type USA300 isolates collected at a Boston ambulatory health center," *Journal of Clinical Microbiology*, vol. 45, no. 4, pp. 1350–1352, 2007.
- [348] E. J. C. Goldstein, D. M. Citron, Y. A. Warren, K. L. Tyrrell, and M. J. Rybak, "Virulence characteristics of community-associated *Staphylococcus aureus* and in vitro activities of moxifloxacin alone and in combination against community-associated and healthcare-associated methicillin-resistant and -susceptible *S. aureus*," *Journal of Medical Microbiology*, vol. 57, no. 4, pp. 452–456, 2008.
- [349] F. C. Tenover and R. V. Goering, "Methicillin-resistant *Staphylococcus aureus* strain USA300: origin and epidemiology," *Journal of Antimicrobial Chemotherapy*, vol. 64, no. 3, pp. 441–446, 2009.
- [350] C. Liu, C. J. Graber, M. Karr et al., "A population-based study of the incidence and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* disease in San Francisco, 2004–2005," *Clinical Infectious Diseases*, vol. 46, no. 11, pp. 1637–1646, 2008.
- [351] R. E. Mendes, H. S. Sader, L. M. Deshpande, B. A. Diep, H. F. Chambers, and R. N. Jones, "Characterization of baseline methicillin-resistant *Staphylococcus aureus* isolates recovered from phase IV clinical trial for linezolid," *Journal of Clinical Microbiology*, vol. 48, no. 2, pp. 568–574, 2010.
- [352] K. Chua, F. Laurent, G. Coombs, M. L. Grayson, and B. P. Howden, "Not community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA)! A clinician's guide to community MRSA—its evolving antimicrobial resistance and implications for therapy," *Clinical Infectious Diseases*, vol. 52, no. 1, pp. 99–114, 2011.
- [353] G. V. Doern, R. N. Jones, M. A. Pfaller, K. C. Kugler, and M. L. Beach, "Bacterial pathogens isolated from patients with skin and soft tissue infections: frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997)," *Diagnostic Microbiology and Infectious Disease*, vol. 34, no. 1, pp. 65–72, 1999.
- [354] H. S. Sader, R. N. Jones, and J. B. Silva, "Skin and soft tissue infections in Latin American medical centers: Four-year assessment of the pathogen frequency and antimicrobial susceptibility patterns," *Diagnostic Microbiology and Infectious Disease*, vol. 44, no. 3, pp. 281–288, 2002.
- [355] M. E. Jones, J. A. Karlowsky, D. C. Draghi, C. Thornsberry, D. F. Sahm, and D. Nathwani, "Epidemiology and antibiotic susceptibility of bacteria causing skin and soft tissue infections in the USA and Europe: a guide to appropriate antimicrobial therapy," *International Journal of Antimicrobial Agents*, vol. 22, no. 4, pp. 406–419, 2003.
- [356] D. M. Citron, E. J. C. Goldstein, C. V. Merriam, B. A. Lipsky, and M. A. Abramson, "Bacteriology of moderate-to-severe diabetic foot infections and in vitro activity of antimicrobial agents," *Journal of Clinical Microbiology*, vol. 45, no. 9, pp. 2819–2828, 2007.
- [357] H. M. Wexler, E. Molitoris, D. Molitoris, and S. M. Finegold, "In vitro activity of levofloxacin against a selected group of anaerobic bacteria isolated from skin and soft tissue infections," *Antimicrobial Agents and Chemotherapy*, vol. 42, no. 4, pp. 984–986, 1998.

- [358] E. J. C. Goldstein, D. M. Citron, and C. A. Nesbit, "Diabetic foot infections: bacteriology and activity of 10 oral antimicrobial agents against bacteria isolated from consecutive cases," *Diabetes Care*, vol. 19, no. 6, pp. 638–641, 1996.
- [359] C. E. Edmiston, C. J. Krepel, G. R. Seabrook et al., "In vitro activities of moxifloxacin against 900 aerobic and anaerobic surgical isolates from patients with intra-abdominal and diabetic foot infections," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 3, pp. 1012–1016, 2004.
- [360] Y. Golan, L. A. McDermott, N. V. Jacobus et al., "Emergence of fluoroquinolone resistance among *Bacteroides* species," *Journal of Antimicrobial Chemotherapy*, vol. 52, no. 2, pp. 208–213, 2003.
- [361] Infectious Diseases Society of America, "Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections," *Clinical Infectious Diseases*, vol. 50, no. 1, pp. 133–164, 2010.
- [362] H. M. Wexler, "Bacteroides: the good, the bad, and the nitty-gritty," *Clinical Microbiology Reviews*, vol. 20, no. 4, pp. 593–621, 2007.
- [363] D. R. Snyderman, N. V. Jacobus, L. A. McDermott et al., "Lessons learned from the anaerobe survey historical perspective and review of the most recent data (2005–2007)," *Clinical Infectious Diseases*, vol. 50, 1, pp. S26–S33, 2010.
- [364] M. Hedberg, C. E. Nord, G. Feierl et al., "Antimicrobial susceptibility of *Bacteroides fragilis* group isolates in Europe," *Clinical Microbiology and Infection*, vol. 9, no. 6, pp. 475–488, 2003.
- [365] E. Nagy and E. Urbán, "Antimicrobial susceptibility of *Bacteroides fragilis* group isolates in Europe: 20 years of experience," *Clinical Microbiology and Infection*, vol. 17, no. 3, pp. 371–379, 2011.
- [366] C. Y. Liu, Y. T. Huang, C. H. Liao, L. C. Yen, H. Y. Lin, and P. R. Hsueh, "Increasing trends in antimicrobial resistance among clinically important anaerobes and bacteroides fragilis isolates causing nosocomial infections: emerging resistance to carbapenems," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 9, pp. 3161–3168, 2008.
- [367] L. M. Koeth, C. E. Good, P. C. Appelbaum et al., "Surveillance of susceptibility patterns in 1297 Europeans and US anaerobic and capnophilic isolates to co-amoxiclav and five other antimicrobials agents," *Journal of Antimicrobial Chemotherapy*, vol. 53, no. 6, pp. 1039–1044, 2004.
- [368] D. W. Hecht, "Prevalence of antibiotic resistance in anaerobic bacteria: worrisome developments," *Clinical Infectious Diseases*, vol. 39, no. 1, pp. 92–97, 2004.
- [369] P. C. Appelbaum, "Quinolone activity against anaerobes," *Drugs*, vol. 58, no. 2, pp. 60–64, 1999.
- [370] R. Schaumann and A. C. Rodloff, "Activities of quinolones against obligately anaerobic bacteria," *Anti-Infective Agents in Medicinal Chemistry*, vol. 6, no. 1, pp. 49–56, 2007.
- [371] C. Edlund, L. Lindqvist, and C. E. Nord, "Norfloxacin binds to human fecal material," *Antimicrobial Agents and Chemotherapy*, vol. 32, no. 12, pp. 1869–1874, 1988.
- [372] A. Sullivan, "Effect of antimicrobial agents on the ecological balance of human microflora," *The Lancet Infectious Diseases*, vol. 1, no. 2, pp. 101–114, 2001.
- [373] E. J. C. Goldstein, D. M. Citron, Y. A. Warren, K. L. Tyrrell, C. V. Merriam, and H. Fernandez, "In vitro activity of moxifloxacin against 923 anaerobes isolated from human intra-abdominal infections," *Antimicrobial Agents and Chemotherapy*, vol. 50, no. 1, pp. 148–155, 2006.
- [374] J. A. Karlowsky, A. J. Walkty, H. J. Adam, M. R. Baxter, D. J. Hoban, and G. G. Zhanel, "Prevalence of antimicrobial resistance among clinical isolates of *Bacteroides fragilis* Group in Canada in 2010–2011: CANWARD Surveillance study," *Antimicrobial Agents and Chemotherapy*, vol. 56, no. 3, pp. 1247–1252, 2012.
- [375] C. Betriu, E. Culebras, M. Gómez, F. López, I. Rodríguez-Avil, and J. J. Picazo, "Resistance trends of the *Bacteroides fragilis* group over a 10-year period, 1997 to 2006, in Madrid, Spain," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 7, pp. 2686–2690, 2008.
- [376] J. Papaparaskevas, A. Pantazatou, A. Katsandri et al., "Moxifloxacin resistance is prevalent among *Bacteroides* and *Prevotella* species in Greece," *Journal of Antimicrobial Chemotherapy*, vol. 62, no. 1, pp. 137–141, 2008.
- [377] H. Seifert and A. Dalhoff, "Comparative in vitro activities of moxifloxacin and six other antimicrobial agents against anaerobic bacterial isolates causing intraabdominal infection: results from the PRISMA study," *Journal of Antimicrobial Chemotherapy*, vol. 65, no. 11, pp. 2405–2410, 2010.
- [378] W. C. Ko and P. R. Hsueh, "Increasing extended-spectrum β -lactamase production and quinolone resistance among Gram-negative bacilli causing intra-abdominal infections in the Asia/Pacific region: data from the Smart Study 2002–2006," *Journal of Infection*, vol. 59, no. 2, pp. 95–103, 2009.
- [379] S. P. Hawser, S. K. Bouchillon, D. J. Hoban, R. E. Badal, P. R. Hsueh, and D. L. Paterson, "Emergence of high levels of extended-spectrum- β -lactamase-producing gram-negative bacilli in the Asia-Pacific region: data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, 2007," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 8, pp. 3280–3284, 2009.
- [380] D. Yagci, F. Yoruk, A. Azap, and O. Memikoglu, "Prevalence and risk factors for selection of quinolone-resistant *Escherichia coli* strains in fecal flora of patients receiving quinolone therapy," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 3, pp. 1287–1289, 2009.
- [381] E. Lautenbach, J. P. Metlay, M. G. Weiner et al., "Gastrointestinal tract colonization with fluoroquinolone-resistant *Escherichia coli* in hospitalized patients: changes over time in risk factors for resistance," *Infection Control and Hospital Epidemiology*, vol. 30, no. 1, pp. 18–24, 2009.
- [382] A. Apisarnthanarak, P. Kiratisin, P. Saifon, R. Kitphati, S. Dejsirilert, and L. M. Mundy, "Clinical and molecular epidemiology of community-onset, extended-spectrum β -lactamase-producing *Escherichia coli* infections in Thailand: A case-case-control study," *American Journal of Infection Control*, vol. 35, no. 9, pp. 606–612, 2007.
- [383] J. Rodríguez-Baño, E. Picón, P. Gijón et al., "Community-onset bacteremia due to extended-spectrum β -lactamase-producing *Escherichia coli*: risk factors and prognosis," *Clinical Infectious Diseases*, vol. 50, no. 1, pp. 40–48, 2010.
- [384] Q. Yang, H. Wang, M. Chen et al., "Surveillance of antimicrobial susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002–2009 Study for Monitoring Antimicrobial Resistance Trends (SMART)," *International Journal of Antimicrobial Agents*, vol. 36, no. 6, pp. 507–512, 2010.
- [385] S. P. Hawser, S. K. Bouchillon, D. J. Hoban, R. E. Badal, R. Cantón, and F. Baquero, "Incidence and Antimicrobial Susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* with extended-spectrum β -lactamases in community- and hospital-associated intra-abdominal infections in Europe: results of the 2008 Study for Monitoring Antimicrobial

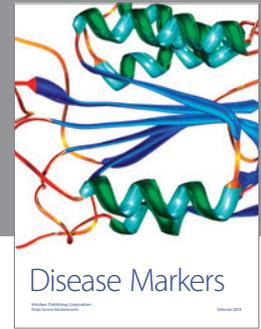
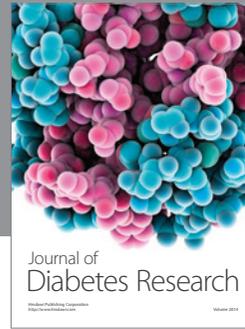
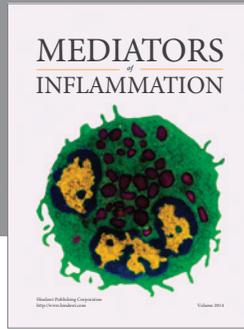
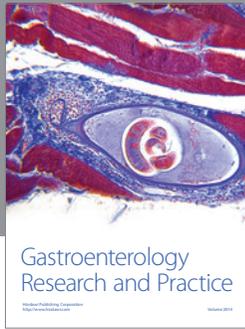
- Resistance Trends (SMART)," *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 7, pp. 3043–3046, 2010.
- [386] D. J. Hoban, S. K. Bouchillon, S. P. Hawser, R. E. Badal, V. J. LaBombardi, and J. DiPersio, "Susceptibility of Gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007–2008: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART)," *Antimicrobial Agents and Chemotherapy*, vol. 54, no. 7, pp. 3031–3034, 2010.
- [387] D. L. Paterson, F. Rossi, F. Baquero et al., "In vitro susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART)," *Journal of Antimicrobial Chemotherapy*, vol. 55, no. 6, pp. 965–973, 2005.
- [388] Y. H. Chen, P. R. Hsueh, R. E. Badal et al., "Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria," *Journal of Infection*, vol. 62, no. 4, pp. 280–291, 2011.
- [389] S. P. Hawser, S. K. Bouchillon, C. Lascols et al., "Susceptibility of European *Escherichia coli* clinical isolates from intra-abdominal infections, extended-spectrum β -lactamase occurrence, resistance distribution, and molecular characterization of ertapenem-resistant isolates (SMART 2008–2009)," *Clinical Microbiology and Infection*, vol. 18, no. 3, pp. 253–259, 2011.
- [390] R. Badal, S. Hawser, S. Bouchillon, D. Hoban, M. Hackel, and A. Johnson, "Antimicrobial susceptibility trends of Enterobacteriaceae from intra-abdominal infections in Europe: SMART 2001–2010," in *Proceedings of the 21st European Congress of Clinical Microbiology and Infectious Diseases and 27th International Congress of Chemotherapy*, Abstract no. P 565, Milan, Italy, 2011.
- [391] R. Cantón, E. Loza, J. Aznar et al., "Sensibilidad de microorganismos gramnegativos de infecciones intraabdominales y evolución de los aislados con β -lactamasas de espectro extendido en el estudio smart en españa (2002–2010)," *Revista Espanola de Quimioterapia*, vol. 24, no. 4, pp. 223–232, 2011.
- [392] S. P. Hawser, R. E. Badal, S. K. Bouchillon, and D. J. Hoban, "Trending eight years of in vitro activity of ertapenem and comparators against *Escherichia coli* from intra-abdominal infections in North America—SMART 2002–2009," *Journal of Chemotherapy*, vol. 23, no. 5, pp. 266–272, 2011.
- [393] M. V. Villegas, M. G. Blanco, J. Sifuentes-Osornio, and F. Rossi, "Increasing prevalence of extended-spectrum-beta-lactamase among Gram-negative bacilli in Latin America—2008 update from the Study for Monitoring Antimicrobial Resistance Trends (SMART)," *Brazilian Journal of Infectious Diseases*, vol. 15, no. 1, pp. 34–39, 2011.
- [394] R. Wiest, A. Krag, and A. Gerbes, "Spontaneous bacterial peritonitis: recent guidelines and beyond," *Gut*, vol. 61, no. 2, pp. 297–310, 2012.
- [395] Centers for Disease Control and Prevention, "Sexually transmitted diseases in the United States, 2008. Sexually transmitted diseases surveillance, 2008," <http://www.cdc.gov/std/stats/>.
- [396] M. Kemp, J. J. Christensen, S. Lautenschlager, M. Vall-Mayans, and H. Moi, "European guideline for the management of chancroid, 2011," *International Journal of STD and AIDS*, vol. 22, no. 5, pp. 241–244, 2011.
- [397] P. Judlin, "Current concepts in managing pelvic inflammatory disease," *Current Opinion in Infectious Diseases*, vol. 23, no. 1, pp. 83–87, 2010.
- [398] GRASP Steering Group, *The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) Year 2007 Report*, Health Protection Agency, London, UK, 2008.
- [399] K. A. Workowski and S. Berman, "Sexually transmitted diseases treatment guidelines, 2010," *Morbidity and Mortality Weekly Report*, vol. 59, no. 12 RR, pp. 1–113, 2010.
- [400] W. R. Gransden, C. A. Warren, I. Phillips, M. Hodges, and D. Barlow, "Decreased susceptibility of *Neisseria gonorrhoeae* to ciprofloxacin," *The Lancet*, vol. 335, no. 8680, p. 51, 1990.
- [401] A. E. Jephcott and A. Turner, "Ciprofloxacin resistance in gonococci," *The Lancet*, vol. 335, no. 8682, p. 165, 1990.
- [402] C. A. Ison, P. J. Woodford, H. Madders, and E. Claydon, "Drift in susceptibility of *Neisseria gonorrhoeae* to ciprofloxacin and emergence of therapeutic failure," *Antimicrobial Agents and Chemotherapy*, vol. 42, no. 11, pp. 2919–2922, 1998.
- [403] H. Birley, P. McDonald, P. Carey, and J. Fletcher, "High level ciprofloxacin resistance in *Neisseria gonorrhoeae*," *Genitourinary Medicine*, vol. 70, no. 4, pp. 292–293, 1994.
- [404] Centers for Disease Control and Prevention, "Fluoroquinolone resistance in *Neisseria gonorrhoeae*—Colorado and Washington, 1995," *Morbidity and Mortality Weekly Report*, vol. 44, no. 41, pp. 761–764, 1995.
- [405] S. R. Morris, J. S. Knapp, D. F. Moore et al., "Using strain typing to characterise a fluoroquinolone-resistant *Neisseria gonorrhoeae* transmission network in southern California," *Sexually Transmitted Infections*, vol. 84, no. 4, pp. 290–291, 2008.
- [406] M. Pérez-Losada, K. A. Crandall, M. C. Bash, M. Dan, J. Zenilman, and R. P. Viscidi, "Distinguishing importation from diversification of quinolone-resistant *Neisseria gonorrhoeae* by molecular evolutionary analysis," *BMC Evolutionary Biology*, vol. 7, article 84, 2007.
- [407] D. Yong, T. S. Kim, J. R. Choi et al., "Epidemiological characteristics and molecular basis of fluoroquinolone-resistant *Neisseria gonorrhoeae* strains isolated in Korea and nearby countries," *Journal of Antimicrobial Chemotherapy*, vol. 54, no. 2, pp. 451–455, 2004.
- [408] S. R. Morris, D. F. Moore, P. B. Hannah et al., "Strain typing and antimicrobial resistance of fluoroquinolone-resistant *Neisseria gonorrhoeae* causing a California infection outbreak," *Journal of Clinical Microbiology*, vol. 47, no. 9, pp. 2944–2949, 2009.
- [409] J. W. Tapsall, E. A. Limnios, and D. Murphy, "Analysis of trends in antimicrobial resistance in *Neisseria gonorrhoeae* isolated in Australia, 1997–2006," *Journal of Antimicrobial Chemotherapy*, vol. 61, no. 1, pp. 150–155, 2008.
- [410] J. Tapsall, "Antimicrobial resistance in *Neisseria gonorrhoeae*," *World Health Organisation*, Section B, pp. 14–58, 2001, WHO/CDS/CSR/DRS/2001.3.
- [411] B. Wang, J. S. Xu, C. X. Wang et al., "Antimicrobial susceptibility of *Neisseria gonorrhoeae* isolated in Jiangsu Province, China, with a focus on fluoroquinolone resistance," *Journal of Medical Microbiology*, vol. 55, no. 9, pp. 1251–1255, 2006.
- [412] L. Tazi, M. Pérez-Losada, W. Gu et al., "Population dynamics of *Neisseria gonorrhoeae* in Shanghai, China: a comparative study," *BMC Infectious Diseases*, vol. 10, article 13, 2010.
- [413] Y. Yang, M. Liao, W. M. Gu et al., "Antimicrobial susceptibility and molecular determinants of quinolone resistance in *Neisseria gonorrhoeae* isolates from Shanghai," *Journal of*

- Antimicrobial Chemotherapy*, vol. 58, no. 4, pp. 868–872, 2006.
- [414] J. Yoo, C. Yoo, Y. Cho, H. Park, H.-B. Oh, and W. K. Seong, “Antimicrobial resistance patterns (1999–2002) and characterization of ciprofloxacin-resistant *Neisseria gonorrhoeae* in Korea,” *Sexually Transmitted Diseases*, vol. 31, no. 5, pp. 305–310, 2004.
- [415] H. Lee, S. G. Hong, Y. Soe et al., “Trends in antimicrobial resistance of *Neisseria gonorrhoeae* isolated from Korean patients from 2000 to 2006,” *Sexually Transmitted Diseases*, vol. 38, no. 11, pp. 1082–1086, 2011.
- [416] M. Bala, K. Ray, S. M. Gupta, S. Muralidhar, and R. K. Jain, “Changing trends of antimicrobial susceptibility patterns of *Neisseria gonorrhoeae* in India and the emergence of ceftriaxone less susceptible *N. gonorrhoeae* strains,” *Journal of Antimicrobial Chemotherapy*, vol. 60, no. 3, pp. 582–586, 2007.
- [417] M. Bala, K. Ray, and S. M. Gupta, “Antimicrobial resistance pattern of *Neisseria gonorrhoeae* isolates from peripheral health centres and STD clinic attendees of a tertiary care centre in India,” *International Journal of STD and AIDS*, vol. 19, no. 6, pp. 378–380, 2008.
- [418] S. Sethi, D. Sharma, S. D. Mehta et al., “Emergence of ciprofloxacin resistant *Neisseria gonorrhoeae* in north India,” *Indian Journal of Medical Research*, vol. 123, no. 5, pp. 707–710, 2006.
- [419] K. Jabeen, S. Nizamuddin, S. Irfan, E. Khan, F. Malik, and A. Zafar, “Increasing trend of resistance to penicillin, tetracycline, and fluoroquinolone resistance in *Neisseria gonorrhoeae* from Pakistan (1992–2009),” *Journal of Tropical Medicine*, vol. 2011, Article ID 960501, 5 pages, 2011.
- [420] M. Bokaeian, M. I. Qureshi, S. Dabiri, and A. H. M. Fard, “An investigation on antibiotic resistance of *Neisseria gonorrhoeae* isolated from gonorrheal patients in Zahedan, Iran from 2007 to 2010,” *African Journal of Microbiology Research*, vol. 5, no. 17, pp. 2455–2459, 2011.
- [421] S. D. Mehta, I. Maclean, J. O. Ndinya-Achola et al., “Emergence of quinolone resistance and cephalosporin MIC creep in *Neisseria gonorrhoeae* isolates from a cohort of young men in Kisumu, Kenya, 2002 to 2009,” *Antimicrobial Agents and Chemotherapy*, vol. 55, no. 8, pp. 3882–3888, 2011.
- [422] D. A. Lewis, “Antimicrobial-resistant gonorrhoea in Africa: an important public health threat in need of a regional gonococcal antimicrobial surveillance programme,” *Southern African Journal of Epidemiology and Infection*, vol. 26, no. 4, pp. 215–220, 2011.
- [423] M. Lahra, “The WHO Western Pacific and SAouth East Asian Gonococcal Antimicrobial Surveillance Programmes,” *Communicable Diseases Intelligence*, vol. 35, no. 1, pp. 2–7, 2011.
- [424] F. D. H. Koedijk, M. G. Van Veen, A. J. De Neeling, G. B. Linde, and M. A. B. Van Der Sande, “Increasing trend in gonococcal resistance to ciprofloxacin in the Netherlands, 2006–8,” *Sexually Transmitted Infections*, vol. 86, no. 1, pp. 41–45, 2010.
- [425] S. Starnino, I. Dal Conte, A. Matteelli et al., “Trend of ciprofloxacin resistance in *Neisseria gonorrhoeae* strains isolated in Italy and analysis of the molecular determinants,” *Diagnostic Microbiology and Infectious Disease*, vol. 67, no. 4, pp. 350–354, 2010.
- [426] E. Tzelepi, M. Daniilidou, V. Miriagou, E. Siatravani, E. Pavlidou, and A. Flietakis, “Cluster of multidrug-resistant *Neisseria gonorrhoeae* with reduced susceptibility to the newer cephalosporins in Northern Greece,” *Journal of Antimicrobial Chemotherapy*, vol. 62, no. 3, pp. 637–639, 2008.
- [427] I. Jakopanec, K. Borgen, and P. Aavitsland, “The epidemiology of gonorrhoea in Norway, 1993–2007: past victories, future challenges,” *BMC Infectious Diseases*, vol. 9, article 33, 2009.
- [428] I. M. C. Martin, S. Hoffmann, and C. A. Ison, “European Surveillance of Sexually Transmitted Infections (ESSTI): the first combined antimicrobial susceptibility data for *Neisseria gonorrhoeae* in Western Europe,” *Journal of Antimicrobial Chemotherapy*, vol. 58, no. 3, pp. 587–593, 2006.
- [429] H. J. de Vries, J. J. van der Helm, M. F. Schim van der Loeff, and A. P. van Dam, “Multidrug-resistant *Neisseria gonorrhoeae* with reduced cefotaxime susceptibility is increasingly common in men who have sex with men, Amsterdam, the Netherlands,” *Euro surveillance*, vol. 14, no. 37, pp. 1–6, 2009.
- [430] M. J. Cole, M. Unemo, S. Hoffmann, S. A. Chisholm, C. A. Ison, and M. J. van de Laar, “The European gonococcal antimicrobial surveillance programme, 2009,” *Euro Surveillance*, vol. 16, no. 42, 2011.
- [431] M. Unemo, E. Shipitsyna, and M. Domeika, “Gonorrhoea surveillance, laboratory diagnosis and antimicrobial susceptibility testing of *Neisseria gonorrhoeae* in 11 countries of the eastern part of the WHO European region,” *Acta Pathologica, Microbiologica et Immunologica Scandinavica*, vol. 119, no. 9, pp. 643–649, 2011.
- [432] K. V. Ota, F. Jamieson, D. N. Fisman et al., “Prevalence of and risk factors for quinolone-resistant *Neisseria gonorrhoeae* infection in Ontario,” *Canadian Medical Association Journal*, vol. 180, no. 3, pp. 287–290, 2009.
- [433] A. E. Singh, S. Plitt, C. Boyington et al., “Antimicrobial resistance in gonorrhoea: the influence of epidemiologic and laboratory surveillance data on treatment guidelines: Alberta, Canada 2001–2007,” *Sexually Transmitted Diseases*, vol. 36, no. 10, pp. 665–669, 2009.
- [434] Centers for Disease Control and Prevention, “Sexually transmitted diseases surveillance,” 2010, <http://www.cdc.gov/std/stats10/gonorrhea.htm>.
- [435] C. Del Rio, G. Hall, E. W. Hook et al., “Update to CDC’s sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections,” *Morbidity and Mortality Weekly Report*, vol. 56, no. 14, pp. 332–336, 2007.
- [436] C. Bignell, “2009 European (IUSTI/WHO) guideline on the diagnosis and treatment of gonorrhoea in adults,” *International Journal of STD and AIDS*, vol. 20, no. 7, pp. 453–457, 2009.
- [437] C. Bignell and M. Fitzgerald, “UK national guideline for the management of gonorrhoea in adults, 2011,” *International Journal of STD and AIDS*, vol. 22, no. 10, pp. 541–547, 2011.
- [438] C. A. Ison, “Antimicrobial resistance in sexually transmitted infections in the developed world: implications for rational treatment,” *Current Opinion in Infectious Diseases*, vol. 25, no. 1, pp. 73–78, 2012.
- [439] J. Tapsall, “Multidrug-resistant *Neisseria gonorrhoeae*,” *Canadian Medical Association Journal*, vol. 180, no. 3, pp. 268–269, 2009.
- [440] M. Ohnishi, D. Golparian, K. Shimuta et al., “Is *Neisseria gonorrhoeae* initiating a future era of untreatable gonorrhoea?: detailed characterization of the first strain with high-level resistance to ceftriaxone,” *Antimicrobial Agents and Chemotherapy*, vol. 55, no. 7, pp. 3538–3545, 2011.
- [441] M. Ohnishi, T. Saika, S. Hoshina et al., “Ceftriaxone-resistant *Neisseria gonorrhoeae*, Japan,” *Emerging Infectious Diseases*, vol. 17, no. 1, pp. 148–149, 2011.

- [442] K. A. Workowski, S. M. Berman, and J. M. Douglas, "Emerging antimicrobial resistance in *Neisseria gonorrhoeae*: urgent need to strengthen prevention strategies," *Annals of Internal Medicine*, vol. 148, no. 8, pp. 606–613, 2008.
- [443] M. Bala, "Characterization of profile of multidrug-resistant *Neisseria gonorrhoeae* using old and new definitions in india over a decade: 2000–2009," *Sexually Transmitted Diseases*, vol. 38, no. 11, pp. 1056–1058, 2011.
- [444] C. A. Ison and S. Alexander, "Antimicrobial resistance in *Neisseria gonorrhoeae* in the UK: surveillance and management," *Expert Review of Anti-Infective Therapy*, vol. 9, no. 10, pp. 867–876, 2011.
- [445] S. Dessus-Babus, C. M. Bébéar, A. Charron, C. Bébéar, and B. De Barbeyrac, "Sequencing of gyrase and topoisomerase IV quinolone-resistance- determining regions of *Chlamydia trachomatis* and characterization of quinolone-resistant mutants obtained in vitro," *Antimicrobial Agents and Chemotherapy*, vol. 42, no. 10, pp. 2474–2481, 1998.
- [446] I. Morrissey, H. Salman, S. Bakker, D. Farrell, C. M. Bébéar, and G. Ridgway, "Serial passage of *Chlamydia spp.* in sub-inhibitory fluoroquinolone concentrations," *Journal of Antimicrobial Chemotherapy*, vol. 49, no. 5, pp. 757–761, 2002.
- [447] S. Takahashi, T. Hagiwara, S. Shiga, T. Hirose, and T. Tsukamoto, "In vitro analysis of the change in resistance of *Chlamydia trachomatis* under exposure to sub-MIC levofloxacin for a therapeutic term," *Chemotherapy*, vol. 46, no. 6, pp. 402–407, 2000.
- [448] J. Rupp, W. Solbach, and J. Gieffers, "Variation in the mutation frequency determining quinolone resistance in *Chlamydia trachomatis* serovars L₂ and D," *Journal of Antimicrobial Chemotherapy*, vol. 61, no. 1, pp. 91–94, 2008.
- [449] S. Yokoi, M. Yasuda, S. I. Ito et al., "Uncommon occurrence of fluoroquinolone resistance-associated alterations in GyrA and ParC in clinical strains of *Chlamydia trachomatis*," *Journal of Infection and Chemotherapy*, vol. 10, no. 5, pp. 262–267, 2004.
- [450] M. M. Shkarupeta, V. N. Lazarev, T. A. Akopian, T. S. Afrikanova, and V. M. Govorun, "Analysis of antibiotic resistance markers in *Chlamydia trachomatis* clinical isolates obtained after ineffective antibiotic therapy," *Bulletin of Experimental Biology and Medicine*, vol. 143, no. 6, pp. 713–717, 2007.
- [451] J. Rupp, A. Gebert, W. Solbach, and M. Maass, "Serine-to-asparagine substitution in the GyrA gene leads to quinolone resistance in moxifloxacin-exposed *Chlamydia pneumoniae*," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 1, pp. 406–407, 2005.
- [452] S. I. Maeda, M. Tamaki, K. Kojima et al., "Association of *Mycoplasma genitalium* persistence in the urethra with recurrence of nongonococcal urethritis," *Sexually Transmitted Diseases*, vol. 28, no. 8, pp. 472–476, 2001.
- [453] T. Deguchi, S. I. Maeda, M. Tamaki et al., "Analysis of the gyrA and parC genes of *Mycoplasma genitalium* detected in first-pass urine of men with non-gonococcal urethritis before and after fluoroquinolone treatment," *Journal of Antimicrobial Chemotherapy*, vol. 48, no. 5, pp. 742–744, 2001.
- [454] Y. Shimada, T. Deguchi, K. Nakane et al., "Emergence of clinical strains of *Mycoplasma genitalium* harbouring alterations in ParC associated with fluoroquinolone resistance," *International Journal of Antimicrobial Agents*, vol. 36, no. 3, pp. 255–258, 2010.
- [455] R. Hamasuna, J. S. Jensen, and Y. Osada, "Antimicrobial susceptibilities of *Mycoplasma genitalium* strains examined by broth dilution and quantitative PCR," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 11, pp. 4938–4939, 2009.
- [456] C. M. Bébéar, B. De Barbeyrac, S. Pereyre, H. Renaudin, M. Clerc, and C. Bébéar, "Activity of moxifloxacin against the urogenital mycoplasmas *Ureaplasma spp.*, *Mycoplasma hominis* and *Mycoplasma genitalium* and *Chlamydia trachomatis*," *Clinical Microbiology and Infection*, vol. 14, no. 8, pp. 801–805, 2008.
- [457] H. L. DuPont, "Therapy for and prevention of traveler's diarrhea," *Clinical Infectious Diseases*, vol. 45, supplement 1, pp. S78–S84, 2007.
- [458] D. N. Taylor, A. L. Bourgeois, C. D. Ericsson et al., "A randomized, double-blind, multicenter study of rifaximin compared with placebo and with ciprofloxacin in the treatment of travelers' diarrhea," *American Journal of Tropical Medicine and Hygiene*, vol. 74, no. 6, pp. 1060–1066, 2006.
- [459] Z. D. Jiang, B. Lowe, M. P. Verenkar et al., "Prevalence of enteric pathogens among international travelers with diarrhea acquired in Kenya (Mombasa), India (Goa), or Jamaica (Montego Bay)," *Journal of Infectious Diseases*, vol. 185, no. 4, pp. 497–502, 2002.
- [460] H. Gomi, Z. D. Jiang, J. A. Adachi et al., "In vitro antimicrobial susceptibility testing of bacterial enteropathogens causing traveler's diarrhea in four geographic regions," *Antimicrobial Agents and Chemotherapy*, vol. 45, no. 1, pp. 212–216, 2001.
- [461] G. M. Eliopoulos and C. T. Eliopoulos, "Activity in vitro of the quinolones," in *Quinolone Antimicrobials*, D. C. Hooper and J. S. Wolfson, Eds., vol. 1993, pp. 161–193, American Society for Microbiology, Washington, DC, USA, 2nd edition, 2005.
- [462] H. L. DuPont, "Use of quinolones for treatment and prophylaxis of bacterial gastrointestinal infections," in *Quinolone Antimicrobials*, D. C. Hooper and J. S. Wolfson, Eds., vol. 1993, pp. 329–337, American Society for Microbiology, Washington, DC, USA, 2nd edition, 2005.
- [463] E. Mendez Arancibia, C. Pitart, J. Ruiz, F. Marco, J. Gascón, and J. Vila, "Evolution of antimicrobial resistance in enteroaggregative *Escherichia coli* and enterotoxigenic *Escherichia coli* causing traveller's diarrhoea," *Journal of Antimicrobial Chemotherapy*, vol. 64, no. 2, pp. 343–347, 2009.
- [464] J. Vila, M. Vargas, J. Ruiz, M. Corachan, M. T. J. De Anta, and J. Gascon, "Quinolone resistance in enterotoxigenic *Escherichia coli* causing diarrhea in travelers to India in comparison with other geographical areas," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 6, pp. 1731–1733, 2000.
- [465] J. Ouyang-Latimer, S. Jafri, A. VanTassel et al., "In vitro antimicrobial susceptibility of bacterial enteropathogens isolated from international travelers to Mexico, Guatemala, and India from 2006 to 2008," *Antimicrobial Agents and Chemotherapy*, vol. 55, no. 2, pp. 874–878, 2011.
- [466] S. S. Namboodiri, J. A. Opintan, R. S. Lijek, M. J. Newman, and I. N. Okeke, "Quinolone resistance in *Escherichia coli* from Accra, Ghana," *BMC Microbiology*, vol. 11, article 44, 2011.
- [467] E. Guiral, E. Mendez-Arancibia, S. M. Soto et al., "CTX-M-15-producing enteroaggregative *Escherichia coli* as cause of travelers' diarrhea," *Emerging Infectious Diseases*, vol. 17, no. 10, pp. 1950–1953, 2011.
- [468] E. Amaya, D. Reyes, S. Vilchez et al., "Antibiotic resistance patterns of intestinal *Escherichia coli* isolates from Nicaraguan children," *Journal of Medical Microbiology*, vol. 60, no. 2, pp. 216–222, 2011.

- [469] P. G. Garcia, V. L. Silva, and C. G. Diniz, "Occurrence and antimicrobial drug susceptibility patterns of commensal and diarrheagenic *Escherichia coli* in fecal microbiota from children with and without diarrhea," *Journal of Microbiology*, vol. 49, no. 1, pp. 46–52, 2011.
- [470] T. V. Nguyen, P. V. Le, C. H. Le, and A. Weintraub, "Antibiotic resistance in diarrheagenic *Escherichia coli* and *Shigella* strains isolated from children in Hanoi, Vietnam," *Antimicrobial Agents and Chemotherapy*, vol. 49, no. 2, pp. 816–819, 2005.
- [471] M. Kosek, C. Bern, and R. L. Guerrant, "The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000," *Bulletin of the World Health Organization*, vol. 81, no. 3, pp. 197–204, 2003.
- [472] CDC, "National antimicrobial resistance monitoring system for enteric bacteria (NARMS): human isolates final report 2010," Tech. Rep., US Department of Health and Human Services, CDC, Atlanta, Ga, USA, 2012.
- [473] B. Shiferaw, S. Solghan, A. Palmer et al., "Antimicrobial susceptibility patterns of shigella isolates in foodborne diseases active surveillance network (foodnet) sites, 2000–2010," *Clinical Infectious Diseases*, vol. 54, supplement 5, pp. S458–S463, 2012.
- [474] I. Mandomando, D. Jaintilal, M. J. Pons et al., "Antimicrobial susceptibility and mechanisms of resistance in *Shigella* and *Salmonella* isolates from children under five years of age with diarrhea in rural Mozambique," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 6, pp. 2450–2454, 2009.
- [475] M. Ashtiani, M. Monajemzadeh, and L. Kashi, "Trends in antimicrobial resistance of fecal *Shigella* and *Salmonella* isolates in Tehran, Iran," *Indian Journal of Pathology and Microbiology*, vol. 52, no. 1, pp. 52–55, 2009.
- [476] N. G. Ibrahim, A. Zafar, and R. Hasan, "Evaluation of frequency of isolation and trends in antibiotic resistance among *Campylobacter* isolates over 11 year period," *Journal of the Pakistan Medical Association*, vol. 54, no. 6, pp. 291–294, 2004.
- [477] A. J. Cody, L. Clarke, I. C. Bowler, and K. E. Dingle, "Ciprofloxacin-resistant campylobacteriosis in the UK," *The Lancet*, vol. 376, no. 9757, p. 1987, 2010.
- [478] A. Vicente, R. Barros, A. Florinda, A. Silva, and T. Hanscheid, "High rates of fluoroquinolone-resistant *Campylobacter* in Portugal—need for surveillance," *Euro Surveillance*, vol. 13, no. 6, 2008.
- [479] B. A. Connor, "Travelers' diarrhea. Self treatable conditions," Centers for Disease Control and Prevention, <http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-2-the-pre-travel-consultation/self-treatable-conditions.htm>.
- [480] J. F. Acar and F. W. Goldstein, "Trends in bacterial resistance to fluoroquinolones," *Clinical Infectious Diseases*, vol. 24, no. 1, pp. S67–S73, 1997.
- [481] D. W. MacPherson, B. D. Gushulak, W. B. Baine et al., "Population mobility, globalization, and antimicrobial drug resistance," *Emerging Infectious Diseases*, vol. 15, no. 11, pp. 1727–1732, 2009.
- [482] J. I. Alós, M. G. Serrano, J. L. Gómez-Garcés, and J. Perianes, "Antibiotic resistance of *Escherichia coli* from community-acquired urinary tract infections in relation to demographic and clinical data," *Clinical Microbiology and Infection*, vol. 11, no. 3, pp. 199–203, 2005.
- [483] I. Katsarolis, G. Poulakou, S. Athanasia et al., "Acute uncomplicated cystitis: from surveillance data to a rationale for empirical treatment," *International Journal of Antimicrobial Agents*, vol. 35, no. 1, pp. 62–67, 2010.
- [484] C. Aypak, A. Altunsoy, and N. Düzgün, "Empiric antibiotic therapy in acute uncomplicated urinary tract infections and fluoroquinolone resistance: a prospective observational study," *Annals of Clinical Microbiology and Antimicrobials*, vol. 8, no. 1, pp. 27–33, 2009.
- [485] H. Arslan, Ö. K. Azap, Ö. Ergönül et al., "Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey," *Journal of Antimicrobial Chemotherapy*, vol. 56, no. 5, pp. 914–918, 2005.
- [486] M. Eryilmaz, M. E. Bozkurt, M. M. Yildiz, and A. Akin, "Antimicrobial resistance of urinary *Escherichia coli* isolates," *Tropical Journal of Pharmaceutical Research*, vol. 9, no. 2, pp. 205–209, 2010.
- [487] Z. Daoud and C. Afif, "*Escherichia coli* isolated from urinary tract infections of Lebanese patients between 2000 and 2009; epidemiology and profiles of resistance," *Chemotherapy Research and Practice*, vol. 2011, Article ID 218431, 6 pages, 2011.
- [488] M. Akram, M. Shahid, and A. U. Khan, "Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in J N M C Hospital Aligarh, India," *Annals of Clinical Microbiology and Antimicrobials*, vol. 6, article 4, 2007.
- [489] A. Kothari and V. Sagar, "Antibiotic resistance in pathogens causing community-acquired urinary tract infections in India: a multicenter study," *Journal of Infection in Developing Countries*, vol. 2, no. 5, pp. 354–358, 2008.
- [490] S. Mohanty, A. Kapil, B. K. Das, and B. Dhawan, "Antimicrobial resistance profile of nosocomial uropathogens in a tertiary care hospital," *Indian Journal of Medical Sciences*, vol. 57, no. 4, pp. 148–154, 2003.
- [491] S. Mathavi, G. Sasikala, A. Kavitha, K. R. Rajesh, and I. Priyadharsini, "Antibiotic susceptibility pattern of urinary isolates with special reference to ciprofloxacin resistance in a tertiary care hospital," *Journal of Pharmaceutical and Biomedical Sciences*, vol. 12, no. 13, 2011.
- [492] K. R. Rajesh, S. Mathavi, and R. I. Priyadarsini, "Prevalence of antimicrobial resistance in uropathogens and determining empirical therapy for urinary tract infections," *International Journal Of Basic Medical Sciences*, vol. 1, no. 1, pp. 1–9.
- [493] F. Ullah, S. A. Malik, and J. Ahmed, "Antibiotic susceptibility pattern and ESBL prevalence in nosocomial *Escherichia coli* from urinary tract infections in Pakistan," *African Journal of Biotechnology*, vol. 8, no. 16, pp. 3921–3926, 2009.
- [494] M. T. Mehr, H. Khan, T. M. Khan, N. Ul Iman, S. Iqbal, and S. Adnan, "*E. Coli* urine super bug and its antibiotic sensitivity—A prospective study," *Journal of Medical Sciences*, vol. 18, no. 2, pp. 110–113, 2010.
- [495] A. Behrooz, M. Rahbar, and J. V. Yousefi, "A survey on epidemiology of urinary tract infections and resistance pattern of uropathogens in an Iranian 1000-bed tertiary care hospital," *African Journal of Microbiology Research*, vol. 4, no. 9, pp. 753–756, 2010.
- [496] D. S. Lee, C. B. Lee, and S. J. Lee, "Prevalence and risk factors for extended spectrum beta-lactamase-producing uropathogens in patients with urinary tract infection," *Korean Journal of Urology*, vol. 51, no. 7, pp. 492–497, 2010.
- [497] S.-J. Lee, D. S. Lee, H. S. Choe et al., "Antimicrobial resistance in community-acquired urinary tract infections: results from the Korean Antimicrobial Resistance Monitoring System," *Journal of Infection and Chemotherapy*, vol. 17, no. 3, pp. 440–446, 2011.

- [498] S.-K. Lim, I. W. Park, W. G. Lee, H. K. Kim, and Y. H. Choi, "Change of antimicrobial susceptibility among *Escherichia coli* strains isolated from female patients with community-onset acute pyelonephritis," *Yonsei Medical Journal*, vol. 53, no. 1, pp. 164–171, 2012.
- [499] P. L. Ho, K. S. Yip, K. H. Chow, J. Y. C. Lo, T. L. Que, and K. Y. Yuen, "Antimicrobial resistance among uropathogens that cause acute uncomplicated cystitis in women in Hong Kong: a prospective multicenter study in 2006 to 2008," *Diagnostic Microbiology and Infectious Disease*, vol. 66, no. 1, pp. 87–93, 2010.
- [500] T. M. Habte, S. Dube, N. Ismail, and A. A. Hoosen, "Hospital and community isolates of uropathogens at a tertiary hospital in South Africa," *South African Medical Journal*, vol. 99, no. 8, pp. 584–587, 2009.
- [501] B. Lobel, A. Valot, V. Cattoir, O. Lemenand, and O. Gaillet, "Comparison of antimicrobial susceptibility of 1 217 *Escherichia coli* isolates from women with hospital and community-acquired urinary tract infections," *Presse Medicale*, vol. 37, no. 5, pp. 746–750, 2008.
- [502] M. I. García García, J. Á. Muñoz Bellido, and J. Á. García Rodríguez, "In vitro susceptibility of community-acquired urinary tract pathogens to commonly used antimicrobial agents in Spain: a comparative multicenter study (2002–2004)," *Journal of Chemotherapy*, vol. 19, no. 3, pp. 263–270, 2007.
- [503] M. Gobernado, L. Valdés, J. I. Alós, C. García-Rey, R. Dal-Ré, and J. García-de-Lomas, "Antimicrobial susceptibility of clinical *Escherichia coli* isolates from uncomplicated cystitis in women over a 1-year period in Spain," *Revista Espanola de Quimioterapia*, vol. 20, no. 1, pp. 68–76, 2007.
- [504] L. S. Stratchounski and V. V. Rafalski, "Antimicrobial susceptibility of pathogens isolated from adult patients with uncomplicated community-acquired urinary tract infections in the Russian Federation: two multicentre studies, UTIAP-1 and UTIAP-2," *International Journal of Antimicrobial Agents*, vol. 28, supplement 1, pp. 4–9, 2006.
- [505] D. J. Farrell, I. Morrissey, D. de Rubeis, M. Robbins, and D. Felmingham, "A UK multicentre study of the antimicrobial susceptibility of bacterial pathogens causing urinary tract infection," *Journal of Infection*, vol. 46, no. 2, pp. 94–100, 2003.
- [506] R. Colodner, Y. Keness, B. Chazan, and R. Raz, "Antimicrobial susceptibility of community-acquired uropathogens in northern Israel," *International Journal of Antimicrobial Agents*, vol. 18, no. 2, pp. 189–192, 2001.
- [507] S. E. Mofett, B. W. Frazee, J. C. Stein et al., "Antimicrobial resistance in uncomplicated urinary tract infections in 3 California EDs," *The American Journal of Emergency Medicine*, vol. 30, no. 6, pp. 942–949, 2012.
- [508] C. D. J. den Heijer, G. A. Donker, J. Maes, and E. E. Stobberingh, "Antibiotic susceptibility of unselected uropathogenic *Escherichia coli* from female Dutch general practice patients: a comparison of two surveys with a 5 year interval," *Journal of Antimicrobial Chemotherapy*, vol. 65, no. 10, Article ID dkq286, pp. 2128–2133, 2010.
- [509] J. Nicoletti, S. P. Kuster, T. Sulser et al., "Risk factors for urinary tract infections due to ciprofloxacin-resistant *Escherichia coli* in a tertiary care urology department in Switzerland," *Swiss medical weekly*, vol. 140, p. w13059, 2010.



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