

# A Critical Review of the Fluoroquinolones

## Focus on Respiratory Tract Infections

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## Abstract

The new fluoroquinolones (clinafloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sitafloxacin, sparfloxacin and trovafloxacin) offer excellent activity against Gram-negative bacilli and improved Gram-positive activity (e.g. against *Streptococcus pneumoniae* and *Staphylococcus aureus*) over ciprofloxacin. Ciprofloxacin still maintains the best *in vitro* activity against *Pseudomonas aeruginosa*. Clinafloxacin, gatifloxacin, moxifloxacin, sitafloxacin, sparfloxacin and trovafloxacin display improved activity against anaerobes (e.g. *Bacteroides fragilis*) versus ciprofloxacin. All of the new fluoroquinolones display excellent bioavailability and have longer serum half-lives than ciprofloxacin allowing for once daily dose administration.

Clinical trials comparing the new fluoroquinolones to each other or to standard therapy have demonstrated good efficacy in a variety of community-acquired respiratory infections (e.g. pneumonia, acute exacerbations of chronic bronchitis and acute sinusitis). Limited data suggest that the new fluoroquinolones as a class may lead to better outcomes in community-acquired pneumonia and acute exacerbations of chronic bronchitis versus comparators. Several of these agents have either been withdrawn from the market, had their use severely restricted because of adverse effects (clinafloxacin because of phototoxicity and hypoglycaemia; grepafloxacin because of prolongation of the QTc and resultant torsades de pointes; sparfloxacin because of phototoxicity; and trovafloxacin because of hepatotoxicity), or were discontinued during developmental phases. The remaining fluoroquinolones such as gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin have adverse effect profiles similar to ciprofloxacin. Extensive post-marketing safety surveillance data (as are available with ciprofloxacin and levofloxacin) are required for all new fluoroquinolones before safety can be definitively established. Drug interactions are limited; however, all fluoroquinolones interact with metal ion containing drugs (eg. antacids).

The new fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin) offer several advantages over ciprofloxacin and are emerging as important therapeutic agents in the treatment of community-acquired respiratory infections. Their broad spectrum of activity which includes respiratory pathogens such as penicillin and macrolide resistant *S. pneumoniae*, favourable pharmacokinetic parameters, good bacteriological and clinical efficacy will lead to growing use of these agents in the treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute sinusitis. These agents may result in cost savings especially in situations where, because of their potent broad-spectrum activity and excellent bioavailability, they may be used orally in place of intravenous antibacterials. Prudent use of the new fluoroquinolones will be required to minimise the development of resistance to these agents.

The emergence of a new class of antibacterial agents began with the synthesis of nalidixic acid by Leshner et al. in 1962.<sup>[1]</sup> Although it was introduced into clinical use in the mid 1960s, the use of nalidixic acid was limited to the treatment of urinary tract infections caused by Gram-negative organisms because of its inherent properties.<sup>[2-4]</sup> The shortcomings of nalidixic acid included a lack of

activity against *Pseudomonas* spp., poor inhibition of Gram-positive organisms, failure to attain adequate serum concentrations, and a high incidence of adverse effects.<sup>[3,5]</sup> However, what is more important is that the discovery of this compound sparked the ensuing fluoroquinolone era and development of this new class of agents.<sup>[6]</sup>

Modification of the nalidixic acid structure led

to the synthesis of the first fluoroquinolone; norfloxacin, which exhibited enhanced activity for Gram-negative organisms, including *Pseudomonas aeruginosa*.<sup>[7]</sup> However, because adequate serum concentrations were difficult to attain, indications for norfloxacin were still limited to the treatment of infections of the urinary tract.<sup>[4]</sup> Further substitutions of the fluoroquinolone molecule resulted in the development of ciprofloxacin in the 1980s,<sup>[8]</sup> the first fluoroquinolone indicated for infections outside the urinary tract.<sup>[9]</sup> Ciprofloxacin possesses a broad spectrum of antimicrobial action, maintaining the potent Gram-negative activity of previous compounds, but with improved activity against Gram-positive organisms. It also portrays favourable pharmacokinetics, which allow for twice-daily dose administration, and a low potential for adverse effects.<sup>[8]</sup> Unfortunately, ciprofloxacin demonstrated poor activity against *Streptococcus pneumoniae* limiting its use in respiratory infections.<sup>[10,11]</sup>

Several attempts have been made to further modify the fluoroquinolone molecule to overcome the limitations of ciprofloxacin and develop new fluoroquinolones with extended antimicrobial activities.<sup>[12]</sup> Numerous manipulations of the fluoroquinolone structure have been attempted in order to synthesise a group of new fluoroquinolones with important advantages over their predecessors, namely expanded antimicrobial activity against Gram-positive cocci (e.g. *S. pneumoniae*) and anaerobes, improved pharmacokinetic profiles, decreased selection of resistant mutants, decreased occurrence of adverse effects, and improved *in vivo* efficacy.<sup>[6,13-15]</sup> However, these enhancements have come at the price of reduced activity against *P. aeruginosa*. In addition, it should be mentioned that neither ciprofloxacin nor the new fluoroquinolones are presently indicated for use in paediatrics because of potential safety concerns (adverse cartilaginous effects).

We previously published an extensive review that described the characteristics of the fluoroquinolones resulting from these modifications, including clinafloxacin, gatifloxacin, grepafloxacin,

**Table I.** Current status of fluoroquinolones used for respiratory infections

| Fluoroquinolone | Current market status (no. prescriptions dispensed) |
|-----------------|-----------------------------------------------------|
| Ciprofloxacin   | Marketed (> 150 million)                            |
| Clinafloxacin   | Withdrawn because of adverse effects                |
| Gatifloxacin    | Marketed (>4 million)                               |
| Gemifloxacin    | Awaiting regulatory approval                        |
| Grepafloxacin   | Withdrawn because of adverse effects                |
| Levofloxacin    | Marketed (>150 million)                             |
| Moxifloxacin    | Marketed (>6 million)                               |
| Sitafoxacin     | Phase III                                           |
| Sparfloxacin    | Withdrawn because of adverse effects                |
| Trovafloxacin   | Use restricted because of adverse effects           |

levofloxacin, moxifloxacin, sparfloxacin, and trovafloxacin.<sup>[16]</sup> This article serves as an update of the information provided in the previous review as it includes the extensive clinical development of the newer fluoroquinolones since that time. It also includes two newly introduced fluoroquinolones, gemifloxacin and sitafloxacin. The focus of this article is on the use of new fluoroquinolones in community-acquired respiratory tract infections such as community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis. High rates of penicillin-resistant and multidrug-resistant *S. pneumoniae*,<sup>[17]</sup> as well as reports of resistance with *Haemophilus influenzae* and *Moraxella catarrhalis*<sup>[18]</sup> are influencing the empirical treatment of community-acquired respiratory infections and resulting in the new fluoroquinolones serving as important treatment alternatives.<sup>[19]</sup> This review fully describes the chemistry, mechanism of action, mechanisms of resistance, *in vitro* activity, pharmacokinetics, pharmacodynamics, *in vivo* activity, adverse effects, drug interactions, and pharmacoeconomic formulary considerations of the new fluoroquinolones. All of the nine agents listed above and ciprofloxacin will be discussed in the chemistry, *in vitro* activity, and pharmacokinetic sections for comparison and explanation purposes (table I). In the other sections, ciprofloxacin

and the fluoroquinolones that have been withdrawn or had their use severely restricted since our previous review because of their safety profiles, namely clinafloxacin, grepafloxacin, sparfloxacin, and trovafloxacin, will not be fully evaluated. They will simply serve as points of reference in some sections against which the upcoming and currently available fluoroquinolones can be compared. Numbered compounds such as BMS-284756 or ABT-492 will not be discussed because, although microbiological data are available, there is only limited clinical data.

## 1. Chemistry

After the discovery of nalidixic acid and subsequent synthesis of ciprofloxacin, the basic quinolone molecular structure marked the starting point for the creation of novel fluoroquinolones with important advantages over their predecessors. The quinolone nucleus serves as the basic molecular structure for all of the new fluoroquinolones except for trovafloxacin and gemifloxacin, which are both analogues of the basic naphthyridine ring structure (figure 1).<sup>[5]</sup> The common features of all of the new fluoroquinolones include retention of the nitrogen at N-1, the carboxylic acid at C-3, the ketone at C-4, and the fluorine atom at C-6 (figure 1), all of which have demonstrated importance for the maintenance of potent antibacterial activity.<sup>[20]</sup> The chemical structures of the basic quinolone and naphthyridine molecules, ciprofloxacin, and the new fluoroquinolones are presented in figure 1.<sup>[21-29]</sup> Included is the structure of the intravenous prodrug of trovafloxacin, alatrofloxacin.

Numerous modifications of the substituents at positions 1, 5, 7, and 8 (figure 1) have sparked the development of the new fluoroquinolones, which exhibit varied antibacterial potencies and characteristics.<sup>[21]</sup> Figure 2 summarises the structure activity relationships that have been proposed for the fluoroquinolones.<sup>[15]</sup> Substituents placed on the N-1 nitrogen atom are essential for the activity of fluoroquinolones<sup>[5]</sup> and effectively influence the overall antimicrobial potency of the molecule. N-1 cyclopropyl substitution, as is present in all of the

new fluoroquinolones except levofloxacin and trovafloxacin (figure 1), is considered optimal and exhibits particularly potent antibacterial activity.<sup>[5,15,30]</sup> Antibacterial activity appears to be due not only to the steric bulk of the substituent at the N-1 position, but also to other spatial effects that influence the molecule's interaction with DNA gyrase.<sup>[5]</sup> The substitution of levofloxacin (figure 1) at N-1 is characterised by a third ring that links the N-1 and C-8 positions, thus classifying it as a 1,8-cyclo compound.<sup>[4]</sup>

The 3-carboxyl group and the ketone moiety at position 4 are possessed by all of the new fluoroquinolones (figure 1). These substituents are essential for fluoroquinolone antimicrobial activity because they are involved in the binding of the molecule to its target DNA/DNA-gyrase complex and facilitate its penetration into the bacterial cell through chelating effects.<sup>[5,15,20]</sup> Since this is the region responsible for the observed fluoroquinolone chelation with polyvalent cations ( $\text{Al}^{3+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Mg}^{2+}$ ), this drug interaction is common to all of the fluoroquinolone agents.<sup>[15]</sup> As a consequence of its proximity to the binding region of the molecule, position C-2 has limited substitution alternatives and optimally remains unsubstituted,<sup>[15,20,21]</sup> as is evidenced by the structures of all of the new fluoroquinolones (figure 1).

Substitution at the C-5 position of the molecule effects *in vitro* activity, especially against Gram-positive organisms,<sup>[15]</sup> primarily because of steric influences.<sup>[20]</sup> The position can remain unsubstituted or have relatively small substituents, such as amine or methyl groups,<sup>[15,21]</sup> but the antimicrobial potency is dramatically decreased with larger groups.<sup>[15]</sup>

The addition of a fluorine atom at the C-6 position is essential for potent antimicrobial activity,<sup>[5,15,21]</sup> as it enhances the inhibition of DNA gyrase and the penetration of the molecule into the cell.<sup>[20]</sup> The importance of this substituent is evident as it serves as the basis for the class name and is present in all of the new fluoroquinolone structures (figure 1).

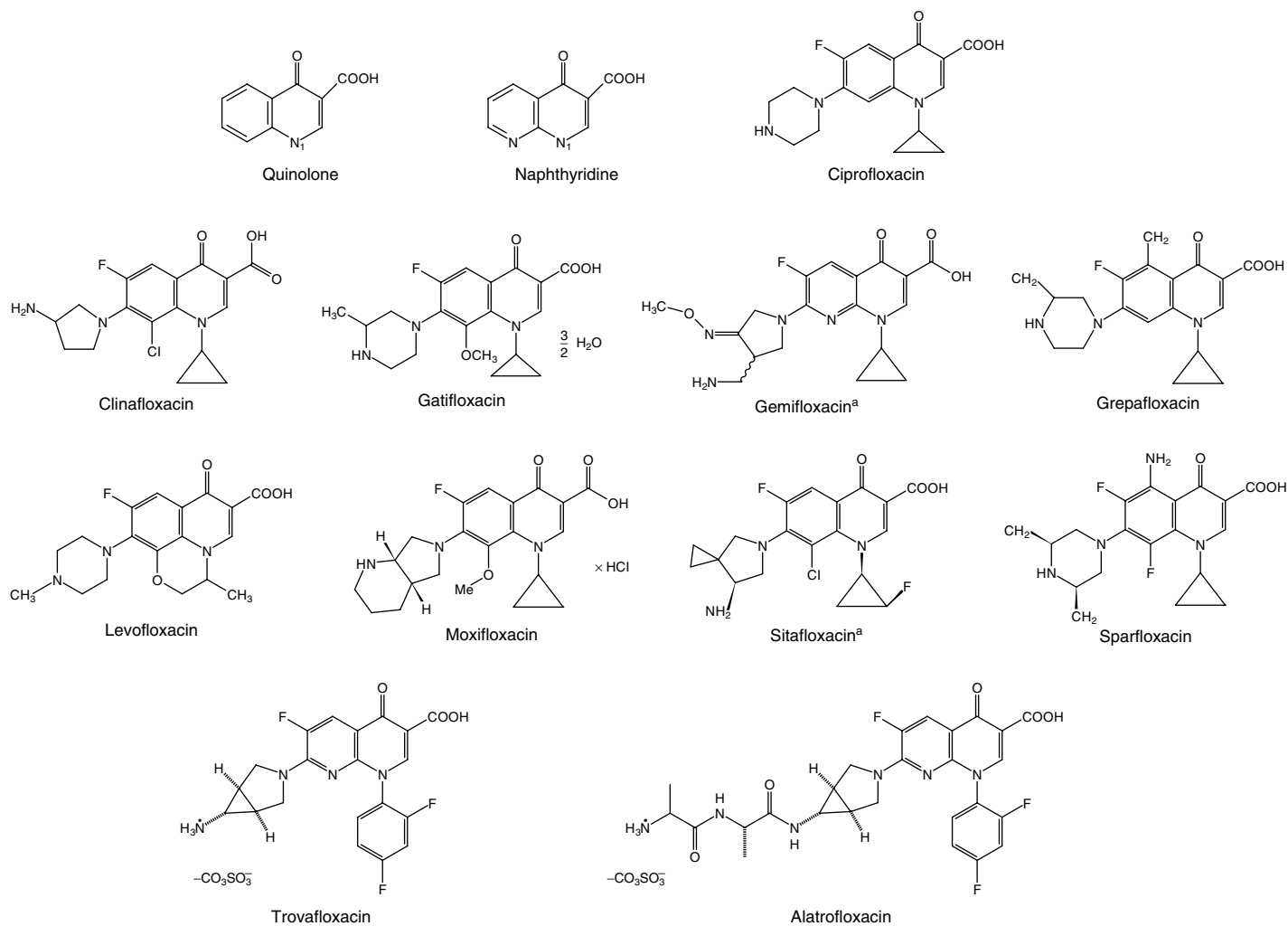


**Fig. 1.** Chemical structures of quinolone, naphthyridine and the fluoroquinolones.  
a Not yet licensed or marketed in any country.

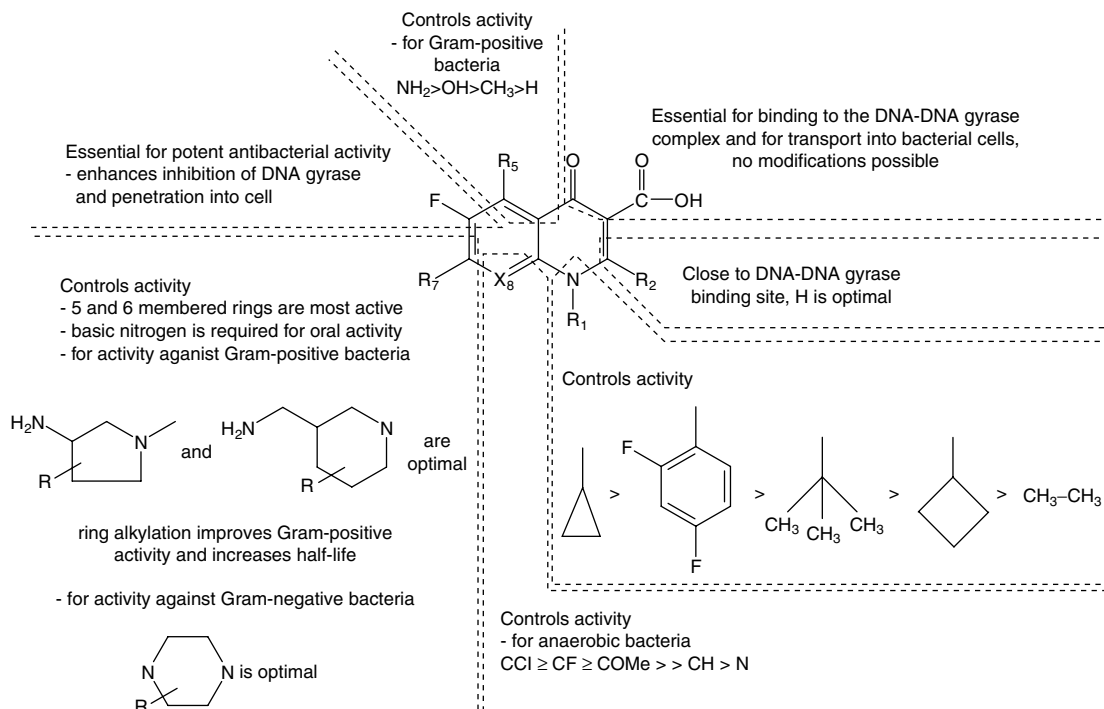


**Fig. 2.** Structure activity relationships of fluoroquinolones.

C-7 substitution enhances antibacterial activity, probably through interactions with bacterial enzymes, and influences on cell penetration.<sup>[20]</sup> A basic group is necessary for activity<sup>[20]</sup> and the optimal substituents have proven to be 5- and 6-membered nitrogen heterocycles that contain peripheral nitrogens.<sup>[15]</sup> A substituted pyrrolidine ring at this position (eg, clinafloxacin, gemifloxacin, moxifloxacin, sitafloxacin, and trovafloxacin) shows enhanced activity for Gram-positive organisms, whereas a piperazine substituent (eg, ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, and sparfloxacin) displays increased action against Gram-negative bacteria.<sup>[15]</sup> Further alkyl substitution of either type of ring improves the activity against Gram-positive organisms,<sup>[15]</sup> prolongs the half-life, and enhances water solubility of the molecule, minimising the risk of crystalluria.<sup>[15,20]</sup> Similarly, azabicyclo-substitution at C-7 in moxifloxacin has been associated with substantially im-

proved Gram-positive activity.<sup>[31]</sup> The potential for CNS adverse effects and drug interactions with theophylline and nonsteroidal anti-inflammatories (NSAIDs) is heavily influenced by the C-7 substitution. Theoretically, fluoroquinolones with bulky (alkylated) pyrrolidine or piperazine rings have minimal interactions with theophylline and less risk of adverse CNS effects compared with the non-alkylated structures (eg, ciprofloxacin and clinafloxacin).<sup>[15,20]</sup> Bulky C-7 substituents, including pyrrolidines and alkylated piperazines also result in agents with a decreased risk of interaction with NSAIDs compared with their unsubstituted piperazine counterparts (eg, ciprofloxacin).<sup>[15,20]</sup>

C-8 substitution primarily effects *in vivo* efficacy, anaerobic activity and adverse reactions.<sup>[15]</sup> This position can remain unsubstituted or contain relatively small substituents, such as a halogen or a methoxy group.<sup>[21]</sup> Although halogenation at the C-8 position (eg., clinafloxacin, sitafloxacin, sparf-

loxacin) is associated with an expanded spectrum for anaerobic bacteria,<sup>[15]</sup> and improved oral absorption and water solubility,<sup>[20]</sup> it is the primary cause of fluoroquinolone-induced phototoxicity.<sup>[15,20]</sup> The C-8 methoxy group seen in gatifloxacin and moxifloxacin (figure 1) retains the advantages of improved water solubility<sup>[20]</sup> and anaerobic activity of halogens, without the same increase in phototoxic potential.<sup>[15,20]</sup> It has also been demonstrated that the presence of a methoxy group at C-8 of the fluoroquinolone structure appears to be associated with more potent activity against resistant DNA gyrase strains and may decrease the rate of resistance development.<sup>[32-34]</sup> The fluoroquinolone/theophylline interaction is also affected by C-8 substitution.<sup>[15,35]</sup> Agents with bulky substituents at position 8, such as fluoro or methoxy groups, are associated with less potential for theophylline interactions than those without an 8-substituent (eg, ciprofloxacin and grepafloxacin).<sup>[15,35]</sup>

## 2. Mechanism of Action

In order to exert their action, it has been proposed that fluoroquinolones bind to a specific target site on bacterial DNA.<sup>[36,37]</sup> Consequently, intracellular accumulation of the fluoroquinolone molecule is essential for its antimicrobial activity and has been shown to occur by simple diffusion across the cell membrane into *Escherichia coli* and *Staphylococcus aureus*,<sup>[38]</sup> with some uptake through the porin pathway in the outer membrane of Gram-negative organisms.<sup>[39]</sup> Once inside the cell, the antimicrobial action of fluoroquinolones is mediated through the inhibition of two type II DNA topoisomerase enzymes, DNA gyrase and topoisomerase IV.<sup>[36,40-42]</sup> As a class, topoisomerases are essential in controlling the topological state of DNA by catalysing supercoiling, relaxing, knotting, and catenation reactions which are vital for DNA replication, transcription, recombination and repair.<sup>[42-45]</sup>

DNA gyrase is a tetrameric protein comprised of two A and two B subunits (A<sub>2</sub>B<sub>2</sub>).<sup>[39]</sup> The A subunits (GyrA), encoded by the *gyrA* gene, cause

strand breaks in the bacterial chromosome and re-seal the chromosome after supercoiling. After the chromosomal strands are resealed, the B subunits (GyrB), encoded by the *gyrB* gene, are responsible for introducing negative supercoils into the DNA strand.<sup>[46,47]</sup> Fluoroquinolones bind to the DNA/DNA-gyrase complex<sup>[21,36]</sup> and inhibit the A subunits of the enzyme, preventing the bacterial chromosome from rejoining.<sup>[39,48]</sup> This interferes with DNA repair, replication processes as well as transcription,<sup>[46]</sup> and ultimately leads to bacterial cell death.<sup>[39,40]</sup>

Topoisomerase IV, conversely, is comprised of two ParC and two ParE subunits (ParC<sub>2</sub>ParE<sub>2</sub>), encoded for by *parC* and *parE* genes, respectively.<sup>[42]</sup> These enzymes play an essential role in partitioning replicated chromosomal DNA during cell division<sup>[42,49]</sup> and in DNA relaxation and decatenation reactions.<sup>[36,42,43]</sup>

A number of studies have demonstrated that the primary target of fluoroquinolones in certain Gram-negative species, such as *E. coli* and *Neisseria gonorrhoeae*, is DNA gyrase, with topoisomerase IV serving as the secondary target.<sup>[36,41,50]</sup> Conversely, studies on *S. aureus* have indicated that the primary target of fluoroquinolone action is topoisomerase IV, rather than DNA gyrase.<sup>[36,43,50,51]</sup> This led to the initial hypothesis that the preferential target of fluoroquinolones may be DNA gyrase in Gram-negative species and topoisomerase IV in Gram-positive organisms.<sup>[21]</sup> However, recent reports have indicated that the molecular structure of the respective fluoroquinolone agent plays a role in differential target selection between DNA gyrase and topoisomerase IV in certain bacteria.

For *S. pneumoniae*, an important respiratory pathogen, the principle target of fluoroquinolone action appears to vary dependent on the chosen antibacterial agent. In *S. pneumoniae* topoisomerase IV has been reported as the preferential target of action for ciprofloxacin,<sup>[52-59]</sup> clinafloxacin,<sup>[52]</sup> grepafloxacin,<sup>[54]</sup> levofloxacin,<sup>[53-55,57-59]</sup> and trovafloxacin.<sup>[54,56]</sup> In comparison, it has been demonstrated that gemifloxacin and sitafloxacin exhibit dual activity against both topoisomerase IV and

DNA gyrase enzymes.<sup>[53-55,58,59]</sup> Moxifloxacin<sup>[60]</sup> and gatifloxacin,<sup>[57]</sup> on the other hand, primarily target the *gyrA* subunit of DNA gyrase in *S. pneumoniae*. On the basis of these findings, and reports of sparflloxacin preferentially targeting DNA gyrase in *S. pneumoniae*,<sup>[57,60,61]</sup> it has been proposed that fluoroquinolones with a free substituent at position C-8 may have enhanced activity for DNA gyrase over topoisomerase IV in Gram-positive organisms.<sup>[60]</sup> However, conflicting reports of sparflloxacin demonstrating preferential inhibition of the topoisomerase IV enzyme<sup>[52,53,55]</sup> mean that this hypothesis still remains to be answered. Al-overa et al.<sup>[62]</sup> have also proposed that modifications of the substituent at the C-7 position of the fluoroquinolone structure can alter the target preference in *S. pneumoniae* from topoisomerase IV to DNA gyrase. Although further study is required in this area, at the present it is clear that in *S. pneumoniae*, the situation appears more complex than in other bacteria, and that both DNA gyrase and topoisomerase IV are important targets of fluoroquinolone action.<sup>[52]</sup>

### 3. Mechanisms of Resistance

Generally, bacteria develop resistance to fluoroquinolones through chromosomal mutation in the target enzymes of fluoroquinolone action, DNA gyrase and topoisomerase IV, and by inhibiting the accumulation of the drug in the bacterial cell.<sup>[14,39,63]</sup> Since one of the major areas of interest in the development of new fluoroquinolone molecules lies in their use in community-acquired respiratory tract infections,<sup>[40]</sup> resistance of respiratory pathogens to fluoroquinolone agents is of great concern. Fluoroquinolone resistance in these organisms has generally remained low,<sup>[64]</sup> but recent reports of fluoroquinolone-resistant *S. pneumoniae*,<sup>[65,66]</sup> coupled with growing incidence of *S. pneumoniae* resistance to other antimicrobial agents,<sup>[17,67,68]</sup> has sparked concern over the further development of fluoroquinolone-resistant *S. pneumoniae* strains. Consequently, this section primarily focuses on the mechanisms of the development of fluoroquinolone resistance in *S. pneumoniae*.

Although widespread resistance to fluoroquinolones is not common in *S. pneumoniae*, Piddock and Jin<sup>[69]</sup> demonstrated that fluoroquinolone-resistant mutations can develop spontaneously in the organism after one exposure to ciprofloxacin *in vitro*. Because of the different preferential targets of various fluoroquinolone molecules, pneumococcal resistance could theoretically be conferred by mutations in either the *gyrA* or *gyrB* genes (encoding DNA gyrase) or in the *parC* or *parE* genes (encoding topoisomerase IV). There have been numerous reports of alterations in *gyrA* or *parC* contributing to fluoroquinolone resistance in *S. pneumoniae*,<sup>[56,70-78]</sup> but the significance of mutations in *gyrB* and *parE* genes is more controversial. Although mutations in these genes have been identified<sup>[71,75,76,79]</sup> and *parE* mutations have been reported to confer fluoroquinolone resistance in *S. pneumoniae*,<sup>[74,80]</sup> conflicting reports have demonstrated that these alterations do not contribute significantly to the emerging fluoroquinolone resistance patterns.<sup>[73,76]</sup> Presently, it appears that even if *gyrB* and *parE* play some role in the development of fluoroquinolone resistance, the resistance is primarily mediated by mutations in *gyrA* and *parC* genes.

Fluoroquinolone resistance in *S. pneumoniae* can be assessed through study of the quinolone resistance-determining region (QRDR) of both *gyrA* and *parC* genes. In a worldwide surveillance study of fluoroquinolone resistance in *S. pneumoniae*, the most frequent mutations that contributed significantly to resistance in *gyrA* and *parC* were Ser-81 Phe or Tyr and Ser-79 Tyr, respectively.<sup>[73]</sup> Broskey et al.<sup>[76]</sup> similarly reported that the main two substitutions that affected the susceptibility of *S. pneumoniae* to fluoroquinolones were Ser-81 Phe in *gyrA* and Ser-79 Phe in *parC*, affirming that these two loci in the respective genes are important regions in the development of resistance. It has been documented that low-level fluoroquinolone resistance can occur through a single mutation in *gyrA* or *parC*, depending on the respective agent, but that high-level resistance requires at least two different sequential muta-

tions.<sup>[55,70,71,75,76,78]</sup> Varon et al.<sup>[78]</sup> demonstrated that the highest levels of pneumococcal resistance occur when there are double mutations in both *parC* and *gyrA* genes.

It has been found that *S. pneumoniae* also exhibits resistance to fluoroquinolone agents through active efflux of the drug.<sup>[78,81-83]</sup> This efflux mechanism is not unique to the export of fluoroquinolones, but instead is probably a multidrug transporter that contributes a degree of intrinsic resistance to *S. pneumoniae*.<sup>[84]</sup> Hydrophilic fluoroquinolones, such as ciprofloxacin and sparfloxacin, appear more prone to efflux than more hydrophobic molecules like gatifloxacin and grepafloxacin in Gram-positive organisms such as *S. pneumoniae*.<sup>[73,81,82]</sup> Beyer et al.<sup>[85]</sup> have also proposed that the more bulk a fluoroquinolone molecule possesses at the C-7 position, the less it will be affected by efflux mechanisms, contributing to the reduced efflux of moxifloxacin from the *S. pneumoniae* cell.

The emerging development of fluoroquinolone-resistant strains of *S. pneumoniae* makes a thorough investigation of the activities of newer fluoroquinolones even more imperative. It has been reported that gemifloxacin retains activity against *S. pneumoniae* strains displaying a variety of topoisomerase mutations and efflux mechanisms.<sup>[76,79]</sup> Jorgensen et al.<sup>[74]</sup> have reported that clinafloxacin appears to be the least affected by the resistance mechanisms of *S. pneumoniae* in comparison to some older fluoroquinolones, which was reiterated by Jones et al.<sup>[73]</sup> who demonstrated that clinafloxacin and sitafloxacin displayed the highest activity against *S. pneumoniae* mutants.

The emergence of fluoroquinolone resistance has generated an interest in mutant prevention concentrations (MPC). MPC is the drug concentration at which the selection of resistant mutants may be inhibited during antibacterial treatment.<sup>[86]</sup> Selection of resistant mutants occurs within a narrow concentration range.<sup>[86]</sup> Below the low end of the concentration range, growth of the majority of drug-susceptible cells is suppressed.<sup>[86]</sup> The upper boundary of the concentration range is the antibac-

terial concentration at which the growth of resistant, single-step mutants is inhibited.<sup>[86]</sup> This is designated the MPC as two simultaneous mutations must occur for cells to grow at this antibacterial concentration. The simultaneous acquisition of multiple mutations is a rare genetic event.<sup>[86]</sup> The mutational frequency of *S. pneumoniae* for fluoroquinolones is  $10^{-7}$  to  $10^{-10}$ .<sup>[87]</sup> On the basis of a mutational frequency of  $10^{-7}$ , an infection of more than  $10^{14}$  *S. pneumoniae* would be required in order for two simultaneous fluoroquinolone-resistant mutations to occur.<sup>[86,87]</sup> Administering antibacterials at the MPC may then prevent mutant selection.<sup>[86]</sup>

It has been shown that many of the newer fluoroquinolones can be safely administered such that the serum and tissue drug concentrations remain above the MPC throughout the course of treatment.<sup>[87]</sup>

Our results suggest that the MPCs for *S. pneumoniae* vary amongst the fluoroquinolones and between different strains.<sup>[88]</sup> We evaluated the MPC in relation to the actual drug concentration and as a function of the fold minimum inhibitory concentration (MIC) increase (MP<sub>MIC</sub>). The MPC demonstrates whether administering the necessary dose is clinically achievable. The MP<sub>MIC</sub> permits a comparison of the antibacterials' intrinsic abilities to prevent the formation of resistant mutants. Whether dose administration at MPC levels will truly prevent the selection of antibacterial-resistant mutants remains to be determined.<sup>[86]</sup> Thus, further MPC studies need to be conducted. The possibility of curtailing the selection of antibacterial-resistant mutants by altering dose administration strategies is a new, important area of study.

Although fluoroquinolone resistance in *H. influenzae* is very rare, probably as a result of the excellent intrinsic activity of fluoroquinolones against this species, resistance has been reported.<sup>[89]</sup> Ongoing surveillance is required to assess whether the incidence of fluoroquinolone-resistant *H. influenzae* will increase over time.

#### 4. In Vitro Activity

The *in vitro* activity of the new fluoroquinolones against clinically important bacteria is summarised in tables II to V.<sup>[10,12,26,90-201]</sup> These tables display the necessary concentration of each agent in order to inhibit 50 and 90% of isolates, MIC<sub>50</sub> and MIC<sub>90</sub>, respectively. The MIC values provided in the tables were gathered from the review and synthesis of the most recently reported values for each drug. An attempt was made to focus primarily on reports from 1998 until the present, but where this span was inadequate for a complete report of the drug's antibacterial activity, earlier studies were reviewed and included where deemed appropriate. Inclusion criteria for studies to be used in this section were not restrictive for either growth conditions (including growth media) or the methodology by which the study was performed.

Concurring with our previous review,<sup>[16]</sup> all of the new fluoroquinolone antibacterial agents exhibit improved activity against Gram-positive bacteria relative to ciprofloxacin (table II).<sup>[10,12,26,90-147]</sup> Gemifloxacin and sitafloxacin are the two fluoroquinolones added to this review that were not reviewed previously. Overall they appear to display the most potent activity versus Gram-positive species. Based only on MIC<sub>90</sub> values, the order of activity of the new fluoroquinolones against *S. aureus* (methicillin sensitive) is approximately gemifloxacin = sitafloxacin > clinafloxacin = trovafloxacin > gatifloxacin = grepafloxacin = moxifloxacin = sparfloxacin > levofloxacin > ciprofloxacin. Displaying a similar rank, the order of activity against *S. pneumoniae* (penicillin sensitive) is approximately gemifloxacin > sitafloxacin > clinafloxacin > grepafloxacin = moxifloxacin = trovafloxacin > gatifloxacin = sparfloxacin > levofloxacin > ciprofloxacin. This approximate order is maintained for both penicillin intermediate and penicillin-resistant strains of *S. pneumoniae*. Against *Enterococcus faecium*, the activity of fluoroquinolones is weak with, clinafloxacin > gatifloxacin = gemifloxacin = moxifloxacin = sparfloxacin = trovafloxacin > ciprofloxacin =

levofloxacin > grepafloxacin (no MIC<sub>90</sub> data are available for sitafloxacin).

The new fluoroquinolones generally maintain the excellent Gram-negative activity displayed by ciprofloxacin (table III).<sup>[12,26,90,91,93,100,102,104,108,109,111,113,119,130,134,135,137]</sup> For *H. influenzae*, an important respiratory pathogen, all of the new fluoroquinolones and ciprofloxacin demonstrate exceptional activity [MIC<sub>90</sub> range 0.004 to 0.03 µg/ml] (table III). The potent activity of all the new fluoroquinolones is maintained against *M. catarrhalis* [MIC<sub>90</sub> range 0.008 to 0.06 µg/ml] (table III). The ranking against *P. aeruginosa* is approximately clinafloxacin > ciprofloxacin = sitafloxacin > gatifloxacin = gemifloxacin = moxifloxacin = sparfloxacin = trovafloxacin > levofloxacin = grepafloxacin. Overall, the MIC<sub>90</sub> values for all of the new fluoroquinolones are generally <1 µg/ml against the majority of Gram-negative bacteria reviewed (except *P. aeruginosa*). Although ciprofloxacin continues to demonstrate potent Gram-negative activity comparable or superior to most of the new fluoroquinolones, clinafloxacin and gemifloxacin also demonstrate equivalent or enhanced activity relative to other fluoroquinolones against the majority of Gram-negative pathogens included in this review.

All of the new fluoroquinolones demonstrate enhanced activity against anaerobes in comparison to ciprofloxacin (table IV).<sup>[91,93-97,100,104,134,135,142,-143,146,147,162,165]</sup> In terms of MIC<sub>90</sub> values, the order of activity of the new fluoroquinolones against *Bacteroides fragilis* is sitafloxacin > trovafloxacin > clinafloxacin = gatifloxacin = moxifloxacin > gemifloxacin = sparfloxacin > levofloxacin > grepafloxacin = ciprofloxacin. Overall, sitafloxacin appears to display the highest activity against anaerobic bacteria, followed closely by clinafloxacin. Gatifloxacin, moxifloxacin and trovafloxacin also demonstrate increased anaerobic activity compared with ciprofloxacin, while sparfloxacin displays a modest improvement in activity in relation to ciprofloxacin. Grepafloxacin and levofloxacin, relatively, only exhibit a minimal improvement in activity relative to ciprofloxacin.

**Table II.** *In vitro* activity of the new fluoroquinolones against Gram-positive aerobes<sup>a, b</sup>

| Bacteria                               | Fluoroquinolone   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |
|----------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                                        | ciprofloxacin     |                   | clinafloxacin     |                   | gatifloxacin      |                   | gemifloxacin      |                   | grepafloxacin     |                   | levofloxacin      |                   | moxifloxacin      |                   | sitafloxacin      |                   | sparfloxacin      |                   | trovafloxacin     |                   |
|                                        | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>Staphylococcus aureus</i> (MS)      | 0.5               | 1                 | 0.03              | 0.06              | 0.12              | 0.12              | 0.015             | 0.03              | 0.06              | 0.12              | 0.12              | 0.5               | 0.06              | 0.12              | 0.015             | 0.03              | 0.06              | 0.12              | 0.03              | 0.06              |
| <i>Staphylococcus aureus</i> (MR)      | 2                 | 32                | 0.5               | 1                 | 0.5               | 4                 | 2                 | 8                 | 8                 | 16                | 4                 | 16                | 2                 | 4                 | 0.25              | 0.5               | 0.12              | 16                | 1                 | 4                 |
| <i>Staphylococcus epidermidis</i> (MS) | 0.25              | 1                 | 0.03              | 0.25              | 0.12              | 2                 | 0.015             | 0.03              | 0.12              | 2                 | 0.25              | 2                 | 0.06              | 1                 | 0.015             | 0.12              | 0.12              | 1                 | 0.03              | 1                 |
| <i>Staphylococcus epidermidis</i> (MR) | 2                 | 16                | 0.25              | 0.5               | 0.5               | 2                 | 0.5               | 2                 | 0.25              | 4                 | 4                 | 8                 | 1                 | 2                 | 0.12              | 0.25              | 0.25              | 8                 | 1                 | 4                 |
| <i>Staphylococcus saprophyticus</i>    | 0.5               | 0.5               | 0.06              | 0.06              | 0.25              | 0.25              | 0.015             | 0.03              | 0.06              | 0.12              | 0.5               | 0.5               | 0.12              | 0.25              | NA                | NA                | 0.25              | 0.25              | 0.06              | 0.12              |
| <i>Streptococcus pyogenes</i>          | 0.5               | 1                 | 0.03              | 0.06              | 0.5               | 0.5               | 0.015             | 0.03              | 0.25              | 0.5               | 0.5               | 0.5               | 0.12              | 0.25              | NA                | NA                | 0.25              | 0.5               | 0.06              | 0.12              |
| <i>Streptococcus agalactiae</i>        | 1                 | 2                 | 0.12              | 0.12              | 0.12              | 0.4               | 0.06              | 0.06              | 0.25              | 0.5               | 0.5               | 1                 | 0.12              | 0.25              | NA                | NA                | 0.25              | 0.25              | 0.25              | 0.25              |
| <i>Streptococcus pneumoniae</i>        | 1                 | 2                 | 0.06              | 0.12              | 0.25              | 0.5               | 0.03              | 0.03              | 0.12              | 0.25              | 1                 | 1                 | 0.12              | 0.25              | 0.03              | 0.06              | 0.25              | 0.5               | 0.12              | 0.12              |
| <i>Streptococcus pneumoniae</i> (PS)   | 1                 | 2                 | 0.06              | 0.12              | 0.25              | 0.5               | 0.03              | 0.03              | 0.12              | 0.25              | 1                 | 1                 | 0.12              | 0.25              | 0.03              | 0.06              | 0.25              | 0.5               | 0.12              | 0.25              |
| <i>Streptococcus pneumoniae</i> (PI)   | 1                 | 2                 | 0.06              | 0.12              | 0.25              | 0.5               | 0.03              | 0.06              | 0.12              | 0.25              | 1                 | 1                 | 0.12              | 0.25              | 0.03              | 0.06              | 0.25              | 0.5               | 0.12              | 0.25              |
| <i>Streptococcus pneumoniae</i> (PR)   | 1                 | 2                 | 0.06              | 0.12              | 0.25              | 0.5               | 0.03              | 0.06              | 0.12              | 0.25              | 1                 | 1                 | 0.12              | 0.25              | 0.03              | 0.06              | 0.25              | 0.5               | 0.12              | 0.25              |
| <i>Enterococcus faecalis</i>           | 1                 | 16                | 0.12              | 1                 | 0.5               | 2                 | 0.06              | 2                 | 0.25              | 4                 | 1                 | 4                 | 0.25              | 4                 | NA                | NA                | 0.5               | 2                 | 0.25              | 4                 |
| <i>Enterococcus faecium</i>            | 2                 | 16                | 0.5               | 1                 | 2                 | 8                 | 2                 | 8                 | 4                 | >16               | 2                 | 16                | 2                 | 8                 | 0.5               | NA                | 2                 | 8                 | 1                 | 8                 |
| <i>Listeria monocytogenes</i>          | 1                 | 2                 | 0.25              | 0.25              | 0.5               | 0.5               | 0.125             | 0.125             | NA                | NA                | 1                 | 2                 | 0.5               | 0.5               | NA                | NA                | 1                 | 2                 | 0.12              | 0.25              |

a Adapted from references: ciprofloxacin;<sup>[10,12,26,90-137]</sup> clinafloxacin;<sup>[94,97,104,109,116,123,134,135]</sup> gatifloxacin;<sup>[91,93,102,104,105,117,121,123,128,133,138]</sup> gemifloxacin;<sup>[26,96-98,118,119,124,132,139]</sup> grepafloxacin;<sup>[26,97,98,118,119,122,124,126,132]</sup> levofloxacin;<sup>[10,26,91,92,94,96,98,100,102-105,107-111,115,117-123,126-129,133,134,136-138,140,141]</sup> moxifloxacin;<sup>[10,94,97,99,104,106,108-110,114,121,122,124,125,131,132,142,143]</sup> sitafloxacin;<sup>[104,128,130,141]</sup> sparfloxacin;<sup>[90,91,94,95,101,102,105,109,113,116-118,121-124,126,128,129,132,136,138,141,144,145]</sup> trovafloxacin.<sup>[10,12,26,90,94-100,102,104,105,107,109,110,114,116-119,121,123,128,131,132,134,140-142,146,147]</sup>

b National Committee for Clinical Laboratory Standards Approved and tentative Breakpoints:<sup>[202]</sup> (i) *Staphylococcus* spp: ciprofloxacin = 4 µg/ml is resistant, grepafloxacin = 4 µg/ml is resistant, levofloxacin = 8 µg/ml is resistant, sparfloxacin = 2 µg/ml is resistant, and no data are available for others; (ii) *Streptococcus pneumoniae*: grepafloxacin = 2 µg/ml is resistant, levofloxacin = 8 µg/ml is resistant, sparfloxacin = 2 µg/ml is resistant, trovafloxacin = 4 µg/ml is resistant. Gatifloxacin and moxifloxacin = 4 µg/ml resistant (Food and Drug Administration FDA approved breakpoints); (iii) *Streptococcus* spp. other than *S. pneumoniae*: grepafloxacin = 2 µg/ml is resistant, levofloxacin = 8 µg/ml is resistant, trovafloxacin = 4 µg/ml is resistant, and no data are available for others; (iv) *Enterococcus* spp.: ciprofloxacin = 4 µg/ml is resistant, levofloxacin = 8 µg/ml is resistant, and no data are available for others.

MIC<sub>50</sub> = minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> = minimum inhibitory concentration of 90% of isolates; NA = information not available; MS = methicillin sensitive; MR = methicillin resistant; PS = penicillin susceptible (MIC ≥0.06 µg/ml); PI = penicillin intermediate (MIC 0.12-1 µg/ml); PR = penicillin resistant (penicillin MIC ≥2.0 µg/ml).

**Table III.** *In vitro* activity of the new fluoroquinolones against Gram-negative aerobes<sup>a, b</sup>

| Bacteria                             | Fluoroquinolone   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |
|--------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                                      | ciprofloxacin     |                   | clinafloxacin     |                   | gatifloxacin      |                   | gemifloxacin      |                   | grepafloxacin     |                   | levofloxacin      |                   | moxifloxacin      |                   | sitafloxacin      |                   | sparfloxacin      |                   | trovafloxacin     |                   |
|                                      | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>Acinetobacter</i> spp.            | 0.25              | 2                 | 0.06              | 0.25              | 0.12              | 0.5               | 0.016             | 0.5               | 0.03              | 4                 | 0.25              | 0.5               | 0.12              | 4                 | 1                 | 2                 | 0.06              | 0.25              | 0.03              | 8                 |
| <i>Citrobacter freundii</i>          | 0.015             | 0.25              | 0.03              | 0.25              | 0.06              | 1                 | 0.03              | 1                 | 0.06              | 0.5               | 0.06              | 0.5               | 0.12              | 1                 | 0.03              | 0.5               | 0.06              | 0.25              | 0.06              | 4                 |
| <i>Enterobacter aerogenes</i>        | 0.015             | 0.12              | 0.03              | 0.25              | 0.03              | 0.12              | 0.015             | 0.12              | 0.03              | 0.5               | 0.06              | 0.12              | 0.12              | 0.5               | 0.03              | 1                 | 0.06              | 0.12              | 0.03              | 0.25              |
| <i>Enterobacter cloacae</i>          | 0.015             | 0.5               | 0.015             | 0.03              | 0.06              | 0.12              | 0.03              | 0.5               | 0.03              | 0.25              | 0.06              | 0.12              | 0.12              | 0.5               | 0.015             | 0.25              | 0.015             | 0.5               | 0.03              | 1                 |
| <i>Escherichia coli</i>              | 0.015             | 0.25              | 0.008             | 0.06              | 0.02              | 0.1               | 0.015             | 0.015             | 0.015             | 0.06              | 0.03              | 0.12              | 0.06              | 0.5               | 0.008             | 0.5               | 0.03              | 0.12              | 0.016             | 0.12              |
| <i>Haemophilus influenzae</i>        | 0.004             | 0.008             | 0.002             | 0.004             | 0.008             | 0.015             | 0.004             | 0.008             | 0.008             | 0.015             | 0.015             | 0.03              | 0.03              | 0.03              | 0.008             | 0.008             | 0.008             | 0.015             | 0.008             | 0.015             |
| <i>Haemophilus influenzae</i> (BLP)  | 0.004             | 0.008             | 0.002             | 0.004             | 0.008             | 0.015             | 0.008             | 0.015             | 0.008             | 0.008             | 0.015             | 0.015             | 0.03              | 0.03              | NA                | NA                | 0.008             | 0.008             | 0.008             | 0.008             |
| <i>Klebsiella pneumoniae</i>         | 0.03              | 0.06              | 0.015             | 0.12              | 0.06              | 0.12              | 0.03              | 0.12              | 0.03              | 0.12              | 0.06              | 0.12              | 0.12              | 0.5               | 0.015             | 0.12              | 0.06              | 0.25              | 0.06              | 0.5               |
| <i>Klebsiella</i> spp.               | 0.03              | 0.03              | 0.03              | 0.06              | 0.12              | 0.5               | 0.06              | 0.25              | 0.03              | 0.12              | 0.03              | 0.06              | 0.12              | 0.25              | NA                | NA                | 0.03              | 0.25              | 0.06              | 1                 |
| <i>Moraxella catarrhalis</i>         | 0.03              | 0.03              | 0.008             | 0.015             | 0.03              | 0.03              | 0.015             | 0.015             | 0.008             | 0.015             | 0.06              | 0.06              | 0.06              | 0.06              | 0.008             | 0.008             | 0.015             | 0.015             | 0.015             | 0.015             |
| <i>Morganella morganii</i>           | 0.015             | 0.06              | 0.015             | 0.03              | 0.06              | 0.25              | 0.06              | 0.12              | 0.12              | 0.25              | 0.06              | 0.12              | 0.12              | 1                 | 0.015             | 0.25              | 0.12              | 1                 | 0.25              | 0.5               |
| <i>Neisseria gonorrhoeae</i> (PS,PR) | 0.004             | 0.004             | 0.002             | 0.002             | 0.004             | 0.015             | 0.002             | 0.002             | 0.008             | 0.015             | 0.008             | 0.015             | 0.008             | 0.015             | 0.008             | 0.008             | 0.004             | 0.008             | 0.004             | 0.008             |
| <i>Neisseria meningitidis</i>        | 0.004             | 0.008             | 0.008             | 0.008             | 0.008             | 0.008             | 0.001             | 0.002             | NA                | NA                | 0.008             | 0.015             | 0.008             | 0.008             | 0.008             | 0.008             | 0.004             | 0.008             | 0.004             | 0.008             |
| <i>Proteus mirabilis</i>             | 0.03              | 0.12              | 0.03              | 0.06              | 0.25              | 0.5               | 0.06              | 0.12              | 0.12              | 0.5               | 0.06              | 0.12              | 0.25              | 0.5               | 0.03              | 0.5               | 0.25              | 0.5               | 0.25              | 0.5               |
| <i>Proteus vulgaris</i>              | 0.03              | 0.03              | 0.015             | 0.03              | 0.25              | 0.5               | 0.06              | 0.12              | 0.12              | 0.5               | 0.03              | 0.06              | 0.25              | 0.5               | 0.03              | 0.12              | 0.25              | 0.5               | 0.12              | 0.25              |
| <i>Providencia rettgeri</i>          | 0.06              | 1                 | 0.03              | 0.03              | 1                 | 4                 | 0.06              | 8                 | 0.12              | 4                 | 0.25              | 4                 | 1                 | 4                 | NA                | NA                | 0.25              | 2                 | 0.25              | 1                 |
| <i>Providencia stuartii</i>          | 0.25              | 2                 | 0.03              | 0.25              | 0.25              | 1                 | 0.12              | 0.25              | 0.12              | 4                 | 0.015             | 1                 | 1                 | 4                 | NA                | NA                | 1                 | 2                 | 0.5               | 4                 |
| <i>Pseudomonas aeruginosa</i>        | 0.25              | 4                 | 0.12              | 1                 | 2                 | 8                 | 0.25              | 8                 | 0.5               | 16                | 0.5               | 16                | 2                 | 8                 | 0.12              | 4                 | 1                 | 8                 | 0.5               | 8                 |
| <i>Burkholderia cepacia</i>          | 4                 | 32                | 1                 | 8                 | 2                 | 16                | 2                 | 16                | NA                | NA                | 4                 | 16                | 2                 | 16                | 0.25              | 4                 | 4                 | 32                | 2                 | 32                |
| <i>Salmonella</i> spp.               | 0.015             | 0.03              | 0.008             | 0.015             | 0.06              | 0.12              | 0.03              | 0.06              | 0.015             | 0.06              | 0.06              | 0.06              | 0.06              | 0.12              | NA                | NA                | 0.03              | 0.06              | 0.06              | 0.12              |
| <i>Serratia marcescens</i>           | 0.12              | 2                 | 0.06              | 0.25              | 0.25              | 2                 | 0.25              | 0.25              | 0.12              | >4                | 0.25              | 2                 | 0.5               | 2                 | 0.06              | 0.5               | 1                 | 4                 | 0.5               | 2                 |
| <i>Shigella</i> spp.                 | 0.015             | 0.03              | 0.008             | 0.008             | 0.03              | 0.03              | 0.004             | 0.008             | 0.008             | 0.03              | 0.03              | 0.03              | 0.03              | 0.06              | 0.008             | 0.015             | 0.03              | 0.03              | 0.015             | 0.03              |
| <i>Stenotrophomonas maltophilia</i>  | 2                 | 16                | 0.12              | 1                 | 1                 | 4                 | 0.5               | 4                 | 0.5               | 4                 | 1                 | 4                 | 0.5               | 2                 | 0.12              | 0.25              | 0.5               | 2                 | 0.5               | 2                 |
| <i>Yersinia enterocolitica</i>       | 0.015             | 0.03              | 0.008             | 0.015             | 0.015             | 0.06              | 0.008             | 0.015             | 0.015             | 0.03              | 0.03              | 0.06              | 0.03              | 0.06              | 0.008             | 0.015             | 0.03              | 0.12              | 0.015             | 0.06              |

a Adapted from references: ciprofloxacin;<sup>[12,26,90,91,93,95-97,100,102,104,108,109,111,113,119,125-128,130,134,135,137,142,145,148-167]</sup> clinafloxacin;<sup>[97,104,109,134,135,156,167]</sup>

gatifloxacin;<sup>[91,93,102,104,128,151,153,155,156,158,161,162,164]</sup> gemifloxacin;<sup>[26,96,97,119,163,165,168,169]</sup> grepafloxacin;<sup>[26,97,119,126,150,162,163,170-172]</sup>

levofloxacin;<sup>[26,91,96,100,102,104,108,109,111,119,126-128,134,137,144,145,149,151-157,159-165,167]</sup> moxifloxacin;<sup>[97,104,108,109,125,142,143,150,156]</sup> sitafloxacin;<sup>[104,128,130]</sup>

sparfloxacin;<sup>[90,91,95,102,109,113,126,128,144,145,150,151,153,156,157,159,161-165,167,173]</sup> trovafloxacin.<sup>[12,26,90,95-97,100,102,104,109,119,128,134,142,144-147,149-151,153,154,156,161-165,167]</sup>

b National Committee for Clinical Laboratory Standards Approved and tentative Breakpoints :<sup>[202]</sup> (i) *Enterobacteriaceae*: ciprofloxacin  $\geq 4$   $\mu\text{g/ml}$  is resistant, grepafloxacin  $\geq 4$   $\mu\text{g/ml}$  is resistant, levofloxacin  $\geq 8$   $\mu\text{g/ml}$  is resistant, and no data are available for others; (ii) *Neisseria gonorrhoeae*: ciprofloxacin  $\geq 1$   $\mu\text{g/ml}$  is resistant, grepafloxacin  $\geq 1$   $\mu\text{g/ml}$  is resistant, and no data are available for others; (iii) *Pseudomonas aeruginosa* and other non-*Enterobacteriaceae*: ciprofloxacin  $\geq 4$   $\mu\text{g/ml}$  is resistant, levofloxacin  $\geq 8$   $\mu\text{g/ml}$  is resistant, and no data are available for others.

MIC<sub>50</sub> = minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> = minimum inhibitory concentration of 90% of isolates; NA = information not available; BLP =  $\beta$ -lactamase positive; PS = penicillin susceptible; PR = penicillin resistant.

The activity of the new fluoroquinolones against *Chlamydia pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Ureaplasma urealyticum* are presented in table V.<sup>[93,100,144,147]</sup> The new fluoroquinolones all display good activity against atypical pathogens with MIC<sub>90</sub> values ≤1.0 µg/ml versus *C. pneumoniae*, 0.03 µg/ml versus *L. pneumophila*, 0.5 µg/ml versus *M. pneumoniae*, and 1.0 µg/ml versus *U. urealyticum*.

Table IV to go here

5. Pharmacokinetics

The pharmacokinetic parameters of the new fluoroquinolones after a single oral dose are summarised in table VI.<sup>[8,203-261]</sup>

5.1 Absorption

All of the new fluoroquinolones are well absorbed after oral administration, with bioavailability ranging from approximately 70% for grepafloxacin to 99% for levofloxacin (table VI). The majority of the new fluoroquinolones are absorbed quickly, attaining their maximum concentration in plasma (C<sub>max</sub>) within approximately 1 to 2 hours after oral administration (table VI). A number of investigations into the effect of food on the pharmacokinetics of the new fluoroquinolones have demonstrated that although food intake can slow absorption, it does not cause clinically significant alterations in the extent of absorption [area under the plasma concentration time curve (AUC)] or overall bioavailability of gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sitafloxacin, sparfloxacin, and trovafloxacin.<sup>[31,212,219,229,232,240,243,253,262]</sup> Therefore, all of these new fluoroquinolones can be given orally without regard to food intake.

5.2 Distribution

The new fluoroquinolones have volumes of distribution, ranging from 1.1 to 7.7 L/kg and protein binding ranging from 5 to 73% (table VI). Their distribution into selected fluids and tissues is summarised in table VII.<sup>[204,206,208,212,213,225,232,237,241,243,257,263-281]</sup> The limited data on the pene-

**Table IV.** *In vitro* activity of the new fluoroquinolones against anaerobes<sup>a</sup>

| Bacteria                          | Fluoroquinolone   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |
|-----------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                                   | ciprofloxacin     |                   | clinafloxacin     |                   | gatifloxacin      |                   | gemifloxacin      |                   | grepafloxacin     |                   | levofloxacin      |                   | moxifloxacin      |                   | sitafloxacin      |                   | sparfloxacin      |                   | trovafloxacin     |                   |
|                                   | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>Bacteroides fragilis</i>       | 4                 | 16                | 0.25              | 1                 | 0.5               | 1                 | 0.5               | 2                 | 2                 | 16                | 2                 | 8                 | 0.25              | 1                 | 0.06              | 0.25              | 1                 | 2                 | 0.25              | 0.5               |
| <i>Bacteroides fragilis</i> group | 8                 | 32                | 0.12              | 0.25              | 1                 | 4                 | 1                 | 4                 | 2                 | 4                 | 2                 | 16                | 0.5               | 1                 | 0.12              | 1                 | 2                 | 4                 | 0.5               | 1                 |
| <i>Clostridium difficile</i>      | 8                 | 16                | 0.25              | 1                 | 1                 | 2                 | 1                 | 8                 | 16                | 32                | 4                 | 8                 | 1                 | 2                 | 0.25              | 0.5               | 4                 | 8                 | 1                 | 8                 |
| <i>Clostridium perfringens</i>    | 0.5               | 1                 | 0.12              | 0.12              | 0.5               | 0.5               | 0.06              | 0.12              | 0.25              | 0.5               | 0.5               | 1                 | 0.5               | 0.5               | 0.06              | 0.06              | 0.25              | 0.5               | 0.25              | 0.25              |
| <i>Fusobacterium</i> spp.         | 2                 | 8                 | 0.06              | 0.25              | 1                 | 1                 | 0.25              | 2                 | 2                 | 8                 | 0.5               | 4                 | 0.12              | 0.5               | 0.25              | 0.5               | 2                 | 4                 | 0.5               | 4                 |
| <i>Peptostreptococcus</i> spp.    | 1                 | 4                 | 0.12              | 0.25              | 0.25              | 1                 | 0.12              | 0.12              | 0.5               | 1                 | 0.5               | 2                 | 0.25              | 0.5               | 0.03              | 0.12              | 0.5               | 1                 | 0.25              | 1                 |

a Adapted from references: ciprofloxacin;<sup>[91,93,95-97,100,104,142,162,174-178]</sup> clinafloxacin;<sup>[94,97,104,134,135]</sup> gatifloxacin;<sup>[91,93,104,162,175-177]</sup> gemifloxacin;<sup>[96,97,165,179,180]</sup> grepafloxacin;<sup>[97,162,179]</sup> levofloxacin;<sup>[91,96,100,104,162,174,175,178,179,181]</sup> moxifloxacin;<sup>[94,97,104,142,143,175,181-183]</sup> sitafloxacin;<sup>[104,179,184,185]</sup> sparfloxacin;<sup>[91,94,95,162,177,179]</sup> trovafloxacin.<sup>[94-97,100,104,134,146,147,162,175-180,182,186]</sup>

MIC<sub>50</sub> = minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> = minimum inhibitory concentration of 90% of isolates.

Table V to go here

tration of the new fluoroquinolones into cerebrospinal fluid suggests that it is not as extensive as that of ciprofloxacin (table VII). Overall, the new fluoroquinolones display good penetration into alveolar macrophages, bronchial mucosa, epithelial lining fluid, and saliva. Specifically, grepafloxacin, moxifloxacin and sparfloxacin display superior penetration into alveolar macrophages and epithelial lining fluid in comparison to ciprofloxacin (table VII). In regard to inflammatory fluid penetration, the new fluoroquinolones all demonstrate fluid to serum ratios in the range of 0.9 to 1.3 (table VII). Limited data on gemifloxacin suggests that it is well distributed into inflammatory fluid, prostatic fluid and saliva similar to other fluoroquinolones (table VII). This is not surprising as gemifloxacin demonstrates a large volume of distribution (3.5 L/kg) (table VI).

### 5.3 Elimination

All of the new fluoroquinolones exhibit longer half-lives than that of ciprofloxacin, ranging from 4.7 hours for sitafloxacin to 18.7 hours for sparfloxacin (table VI). Clinafloxacin, gatifloxacin, levofloxacin, and sitafloxacin are excreted in the urine as the parent compound (>50%), indicating that these agents primarily undergo renal elimination (table VI). Conversely, gemifloxacin, grepafloxacin, moxifloxacin, sparfloxacin, and trovafloxacin are all eliminated predominantly by nonrenal pathways (table VI). In patients with renal impairment, the dosages of clinafloxacin, gatifloxacin and levofloxacin all require dosage adjustments.<sup>[210,232,279]</sup> Dosage adjustment is also required for gemifloxacin and sparfloxacin in patients with renal impairment, even though these two agents display predominantly nonrenal elimination (table VI). Allen et al.<sup>[223]</sup> demonstrated that in severely renally impaired patients [creatinine clearance (CrCl) 10 to 29 ml/min], the total plasma clearance of gemifloxacin overall is reduced by approximately 50% and the half-life is prolonged to approximately double that compared with individuals with normal renal function. On the basis of these findings, it is recommended to reduce the

**Table V.** *In vitro* activity of the new fluoroquinolones against other clinically important bacteria<sup>a</sup>

| Bacteria                      | Fluoroquinolone   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                               | ciprofloxacin     |                   | clinafloxacin     |                   | gatifloxacin      |                   | gemifloxacin      |                   | grepafloxacin     |                   | levofloxacin      |                   | moxifloxacin      |                   | sitafloxacin      |                   | sparfloxacin      |                   | trovafloxacin     |                   |
|                               | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>Chlamydia pneumoniae</i>   | 1                 | 2                 | NA                | NA                | 0.12              | 0.25              | 0.25              | 0.25              | NA                | 0.12              | 0.5               | 1                 | 0.5               | 1                 | NA                | NA                | 0.06              | 0.06              | 0.5               | 1                 |
| <i>Legionella pneumophila</i> | 0.03              | 0.03              | 0.008             | 0.015             | 0.015             | 0.015             | 0.015             | 0.03              | 0.008             | 0.015             | 0.008             | 0.015             | 0.015             | 0.015             | NA                | NA                | 0.004             | 0.015             | 0.004             | 0.008             |
| <i>Mycoplasma pneumoniae</i>  | 1                 | 2                 | 0.06              | 0.06              | 0.06              | 0.12              | 0.06              | 0.12              | 0.12              | 0.25              | 0.5               | 0.5               | 0.12              | 0.12              | NA                | NA                | 0.12              | 0.12              | 0.12              | 0.25              |
| <i>Ureaplasma urealyticum</i> | 4                 | 8                 | 0.25              | 0.5               | 0.5               | 1                 | 0.12              | 0.25              | 0.5               | 1                 | 0.5               | 1                 | 0.25              | 0.25              | NA                | NA                | 0.25              | 0.5               | 0.06              | 0.25              |

a Adapted from references: ciprofloxacin;<sup>[93,100,144,187-193]</sup> clinafloxacin;<sup>[193]</sup> gatifloxacin;<sup>[93,190,192,194]</sup> gemifloxacin;<sup>[191,195,196]</sup> grepafloxacin;<sup>[189,191,196,197]</sup> levofloxacin;<sup>[100,144,187,191,192,195,196]</sup> moxifloxacin;<sup>[191,195,198-200]</sup> sparfloxacin;<sup>[144,189,192,200]</sup> trovafloxacin.<sup>[144,147,191,195,196,201]</sup>

MIC<sub>50</sub> = minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> = minimum inhibitory concentration of 90% of isolates; NA = information not available.

**Table VI.** Pharmacokinetic parameters of the new fluoroquinolones after a single oral dose

| Drug          | Dose <sup>a</sup><br>(mg) | F<br>(%) | C <sub>max</sub><br>(µg/ml) | t <sub>max</sub><br>(h) | AUC<br>(mg /Lh) | t <sub>1/2</sub><br>(h) | Vd/F<br>(L/kg) | Protein<br>binding<br>(%) | Excreted<br>unchanged<br>(%) | Dose adjustment <sup>b</sup> |         | References                |
|---------------|---------------------------|----------|-----------------------------|-------------------------|-----------------|-------------------------|----------------|---------------------------|------------------------------|------------------------------|---------|---------------------------|
|               |                           |          |                             |                         |                 |                         |                |                           |                              | renal                        | hepatic |                           |
| Ciprofloxacin | 500                       | 70       | 2.30                        | 1.2                     | 10.1            | 3.5                     | 3.5            | 30                        | 34                           | Yes                          | No      | 8, 203-206                |
|               | 750                       | 70       | 3.00                        | 1.2                     | 14.0            | 3.5                     | 3.5            | 30                        | 34                           | Yes                          | No      |                           |
| Clinafloxacin | 200                       | 90       | 2.10                        | 1.2                     | 10.0            | 5.9                     | 2.3            | 5                         | 50                           | Yes                          | ND      | 207-211                   |
| Gatifloxacin  | 400                       | 96       | 3.86                        | 1.5                     | 33.8            | 8.0                     | 1.8            | 20                        | 76                           | Yes                          | No      | 212-218, 259              |
| Gemifloxacin  | 320                       | ND       | 1.19                        | 1.2                     | 7.3             | 8.0                     | 3.5            | 60                        | 27                           | Yes <sup>c</sup>             | No      | 219-223                   |
|               | 640                       | ND       | 2.29                        | 1.2                     | 15.9            | 8.0                     | 3.5            | 60                        | 27                           | Yes                          | No      |                           |
| Grepafloxacin | 200                       | 72       | 0.64                        | 2.3                     | 6.6             | 11.1                    | 7.7            | 50                        | 8                            | No                           | Yes     | 224-229                   |
|               | 400                       | 72       | 1.24                        | 2.3                     | 12.7            | 11.1                    | 7.7            | 50                        | 8                            | No                           | Yes     |                           |
|               | 600                       | 72       | 1.58                        | 2.3                     | 22.6            | 11.1                    | 7.7            | 50                        | 8                            | No                           | Yes     |                           |
| Levofloxacin  | 500                       | 99       | 5.08                        | 1.7                     | 48.0            | 6.9                     | 1.1            | 31                        | 83                           | Yes                          | ND      | 205, 230-233,<br>260, 261 |
|               | 750                       | 99       | 7.13                        | 1.7                     | 82.0            | 6.9                     | 1.1            | 31                        | 83                           | Yes                          | ND      |                           |
| Moxifloxacin  | 200                       | 86       | 1.16                        | 1.7                     | 15.4            | 12.1                    | 3.3            | 47                        | 19                           | No                           | No      | 217,234-239               |
|               | 400                       | 86       | 3.34                        | 1.7                     | 33.8            | 12.1                    | 3.3            | 47                        | 19                           | No                           | No      |                           |
| Sitafloxacin  | 25                        | >70      | 0.29                        | 1.2                     | 1.5             | 4.7                     | 1.7            | 50                        | 72                           | ND                           | ND      | 240                       |
|               | 50                        | >70      | 0.51                        | 1.2                     | 2.6             | 4.7                     | 1.7            | 50                        | 72                           | ND                           | ND      |                           |
|               | 100                       | >70      | 1.00                        | 1.2                     | 5.6             | 4.7                     | 1.7            | 50                        | 72                           | ND                           | ND      |                           |
|               | 200                       | >70      | 1.86                        | 1.2                     | 12.0            | 4.7                     | 1.7            | 50                        | 72                           | ND                           | ND      |                           |
| Sparfloxacin  | 200                       | 90       | 0.77                        | 4.4                     | 20.8            | 18.7                    | 4.7            | 56                        | 9                            | Yes                          | No      | 204, 241-250              |
|               | 400                       | 90       | 1.17                        | 4.4                     | 33.5            | 18.7                    | 4.7            | 56                        | 9                            | Yes                          | No      |                           |
| Trovafoxacin  | 100                       | 88       | 1.17                        | 1.7                     | 10.1            | 11.0                    | 1.3            | 73                        | 6                            | No                           | No      | 251-257                   |
|               | 200                       | 88       | 2.48                        | 1.7                     | 26.2            | 11.0                    | 1.3            | 73                        | 6                            | No                           | No      |                           |

a Dose only applies to C<sub>max</sub> and AUC, the other parameters represent an average of the values available in the literature irrespective of dosage, the dosages reported are based on the dosages commonly used in clinical trials for these drugs.

b Dose adjustment refers to whether or not the fluoroquinolone requires any dosage adjustments in patients with impaired renal or hepatic function.

c Only adjust in severe renal impairment (creatinine clearance ≤29 ml/min).

**AUC** = area under the concentration time curve; **C<sub>max</sub>** = peak concentration reached in the plasma/serum; **F** = bioavailability; **ND** = no data; **t<sub>max</sub>** = time to reach C<sub>max</sub>; **t<sub>1/2</sub>** = half-life; **Vd** = volume of distribution.

**Table VII.** Penetration of the new fluoroquinolones into selected fluids and tissues<sup>a</sup>

| Site                         | Tissue/serum or fluid/serum ratio [reference] |                                     |                                    |                                     |                                    |                                     |                                    |                                     |                       |
|------------------------------|-----------------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|-----------------------|
|                              | ciprofloxacin<br>(1-6) <sup>b</sup>           | clinafloxacin<br>(1-5) <sup>b</sup> | gatifloxacin<br>(2-3) <sup>b</sup> | grepafloxacin<br>(2-5) <sup>b</sup> | levofloxacin<br>(1-6) <sup>b</sup> | moxifloxacin<br>(1-24) <sup>b</sup> | sparfloxacin<br>(2-6) <sup>b</sup> | trovafloxacin<br>(2-6) <sup>b</sup> | gemifloxacin          |
| Aqueous humour               | 0.13 <sup>[263]</sup>                         | ND                                  | ND                                 | ND                                  | 0.23 <sup>[232]c</sup>             | ND                                  | 0.22 <sup>[243]</sup>              | ND                                  | ND                    |
| Cerebrospinal fluid          | 0.37 <sup>[206]d</sup>                        | ND                                  | ND                                 | ND                                  | 0.16 <sup>[232]</sup>              | ND                                  | 0.30 <sup>[243]</sup>              | 0.20 <sup>[275]e</sup>              | ND                    |
| Gall bladder                 |                                               |                                     |                                    |                                     |                                    |                                     |                                    |                                     |                       |
| tissue                       | ND                                            | ND                                  | ND                                 | 6.22 <sup>[266]d</sup>              | 1.53 <sup>[232,270]</sup>          | ND                                  | 7.1 <sup>[243]d,f</sup>            | ND                                  | ND                    |
| bile                         | 5.08 <sup>[263]</sup>                         | ND                                  | ND                                 | 56.4 <sup>[266]d</sup>              | 1.28 <sup>[232,270]</sup>          | 12-27% <sup>[281]</sup>             | 9.6 <sup>[243]d,f</sup>            | ND                                  | ND                    |
| Inflammatory (blister) fluid | 1.17 <sup>[241]</sup>                         | 0.93 <sup>[208]</sup>               | 1.17 <sup>[213]</sup>              | 1.33 <sup>[225]</sup>               | 0.96 <sup>[271]d</sup>             | 0.84 <sup>[237,272]</sup>           | 1.17 <sup>[241]</sup>              | 0.62 <sup>[257]</sup>               | 0.61 <sup>[282]</sup> |
| Male genital tissues         |                                               |                                     |                                    |                                     |                                    |                                     |                                    |                                     |                       |
| epididymis                   | ND                                            | ND                                  | ND                                 | 4.88 <sup>[267]</sup>               | 1.22 <sup>[232]</sup>              | ND                                  | ND                                 | ND                                  | ND                    |
| testis                       | ND                                            | ND                                  | ND                                 | 4.95 <sup>[267]</sup>               | 1.63 <sup>[232]</sup>              | ND                                  | ND                                 | ND                                  | ND                    |
| Prostate                     |                                               |                                     |                                    |                                     |                                    |                                     |                                    |                                     |                       |
| prostatic fluid              | 2.26 <sup>[206]</sup>                         | ND                                  | ND                                 | 1.23 <sup>[268]</sup>               | ND                                 | ND                                  | 1.5 <sup>[243]</sup>               | ND                                  | 0.70 <sup>[283]</sup> |
| tissue                       | 1.86 <sup>[263]</sup>                         | ND                                  | ND                                 | 3.60 <sup>[267]</sup>               | 1.28 <sup>[232]</sup>              | ND                                  | 1.4 <sup>[243]g</sup>              | 0.96 <sup>[276]d</sup>              | ND                    |
| Respiratory tract            |                                               |                                     |                                    |                                     |                                    |                                     |                                    |                                     |                       |
| alveolar macrophages         | 10.6 <sup>[204]</sup>                         | 10.13 <sup>[265]</sup>              | 26.5                               | 194.52 <sup>[269]d</sup>            | 18.5 <sup>[260]</sup>              | 24.5 <sup>[273,274]</sup>           | 65.5 <sup>[204,264]e</sup>         | 13.32 <sup>[277]</sup>              | ND                    |
| bronchial mucosa             | 1.7 <sup>[264]d,h</sup>                       | 1.72 <sup>[265]</sup>               | 1.65                               | 3.13 <sup>[269]d</sup>              | 1.55 <sup>[281]</sup>              | 2.07 <sup>[273]</sup>               | 3.3 <sup>[264]h</sup>              | 1.07 <sup>[277]</sup>               | ND                    |
| epithelial lining fluid      | 1.9 <sup>[264]</sup>                          | 1.76 <sup>[265]</sup>               | 1.67                               | 12.21 <sup>[269]d</sup>             | 2.0 <sup>[261]</sup>               | 6.95 <sup>[273,274]</sup>           | 63 <sup>[204,264]e</sup>           | 2.27 <sup>[277]</sup>               | ND                    |
| saliva                       | ND                                            | ND                                  | 0.80 <sup>[212]</sup>              | ND                                  | 0.73 <sup>[232]</sup>              | 0.83 <sup>[272]</sup>               | 0.68 <sup>[243]g</sup>             | ND                                  | 0.4 <sup>[284]</sup>  |
| sputum                       | 0.58 <sup>[206]h</sup>                        | ND                                  | 1.27                               | ND                                  | 1.37 <sup>[232]</sup>              | ND                                  | 1.4 <sup>[243]g</sup>              | 0.79 <sup>[278]d</sup>              | ND                    |
| Skin                         | 1.9 <sup>[263]</sup>                          | ND                                  | ND                                 | ND                                  | 1.44 <sup>[232]</sup>              | ND                                  | 1.2 <sup>[243]</sup>               | ND                                  | ND                    |

a Specific dosages and sampling times for all of the above data were not provided because of lack of space – see appropriate reference for further details (found in brackets beside values). No data were available for sitafloxacin, hence it were excluded from this table. Inflammatory fluid to serum ratio was determined by taking the ratio of the AUC values (sampling time not applicable). All others were determined by taking the ratio of tissue concentration to serum concentration (or the ratio of the mean tissue concentration to the mean serum concentration).

b Sampling time (number of hours post dose).

c Sampling time of 2 to 9 hours post dose.

d Multiple doses of the fluoroquinolone were administered to patients before sample was taken, all other data was collected after a single administration of the study drug.

e Sampling time of 1 to 24 hours post dose.

f Sampling time of 18 hours post dose.

g Sample taken at C<sub>max</sub> (time not specified in reference).

h Sampling time not specified.

ND = no data.

dose of gemifloxacin by half when administering it to patients with severe renal impairment.<sup>[223]</sup> Trovafloxacin should be avoided in patients with pre-existing abnormal liver function tests as it may cause hepatotoxicity. No data are available as to whether a dosage adjustment is required for sitafloxacin in patients displaying either renal or hepatic impairment.

A number of investigators have studied the pharmacokinetics of the new fluoroquinolones in special populations. In the elderly, it has been demonstrated that the pharmacokinetics and bio-availability of levofloxacin, gatifloxacin, moxifloxacin, and sparfloxacin are not appreciably affected;<sup>[31,215,231,243]</sup> however, grepafloxacin displays delayed absorption, a 31% increase in the peak plasma concentration, and a 48% increase in AUC in the elderly.<sup>[227]</sup> The pharmacokinetics of trovafloxacin remain unchanged both on administration to infants and children,<sup>[280]</sup> and in patients with AIDS compared with healthy adults.<sup>[285]</sup> Levofloxacin also displays similar pharmacokinetics in asymptomatic HIV-infected individuals compared with healthy individuals.<sup>[286]</sup>

## 6. Pharmacodynamics

The pharmacodynamic parameters of drug molecules describe the relationship between the drug's serum concentration and its corresponding pharmacological and toxicological effects.<sup>[287]</sup> The goal of therapy is to consider and synthesise all of the available data from animal models, *in vitro* pharmacodynamic studies and clinical trials and correlate it to an optimal antibacterial regimen that maximises clinical efficacy and minimises toxicity.<sup>[288]</sup> Evaluation of the *in vitro* activity of fluoroquinolones and other antibacterials is usually performed through measurement of MIC values, and less frequently minimum bactericidal concentration (MBC).<sup>[287,289]</sup> MIC measures the net drug effect when a standard bacterial inoculum is exposed to a fixed and constant drug concentration for 18 to 24 hours.<sup>[290]</sup> Although these important parameters reveal useful information on the inhibition or killing of a pathogen at the measured endpoint,

they are static measurements that do not provide data on the time course of antibacterial action, including the duration of drug exposure necessary for bacterial eradication, the rate of bactericidal activity or persistent effects of antibacterial agents.<sup>[287,289]</sup> Similarly, pharmacokinetic parameters considered alone provide some clues to the clinical outcome, but do not sufficiently predict the true clinical response.<sup>[31]</sup> Assessment of pharmacodynamic activity of antibacterial agents based on the integration of microbiologic activity, pharmacokinetics, and achievable serum and tissue concentrations is necessary for the best prediction of *in vivo* potency and efficacy.<sup>[13,291]</sup>

Inherent in a drug's antibacterial activity is binding or interacting with specific targets in the respective pathogen and occupying the necessary number of critical binding sites for a minimum period of time. As such, the mathematical description of bacterial killing can be described as a function of the relationship between  $C_{\max}$  and time of exposure, expressed as the AUC.<sup>[288]</sup> Pharmacodynamic properties can be used to predict the therapeutic response of micro-organisms to antimicrobials by correlating measures of drug exposure ( $C_{\max}$ , or AUC over 24 hours of dose administration [AUC<sub>24</sub>]) to measures of drug potency (MIC), or by evaluating the time the drug concentration remains above the MIC.<sup>[31]</sup> Thus, the pharmacokinetic/pharmacodynamic parameters of interest in predicting clinical outcomes are the  $C_{\max}/\text{MIC}$ , the AUC<sub>24</sub>/MIC [also sometimes referred to as the area under the inhibitory plasma concentration-time curve (AUC)], and the time above the MIC (T/MIC).<sup>[287]</sup>

It has been clearly documented that antibacterials display two types of antibacterial activity, either concentration-dependent killing or time-dependent killing.<sup>[290]</sup> In time-dependent, (or concentration-independent) killing, once the antibacterial concentration exceeds two to five times the MIC for a particular organism, the rate of killing becomes saturated and further increases in concentration do not increase the speed or extent of microbial death.<sup>[287,288]</sup> The extent of bacterial killing for antibiotics in this group ( $\beta$ -lactams, vanco-

mycin, clindamycin, and the macrolides) correlates poorly with the peak serum concentration and instead the best predictor of clinical success is the duration that serum antibiotic concentrations exceed the MIC of the micro-organism.<sup>[287,288]</sup> Since the primary parameter influencing *in vivo* success of these agents is T/MIC,<sup>[287]</sup> small frequent doses will optimise clinical success.<sup>[31]</sup> Conversely, for antibacterial agents that kill bacteria in a concentration-dependent manner, the rate and extent of bactericidal activity increases proportionately as the drug concentrations are increased, even at concentrations substantially above the MIC of the targeted organism.<sup>[287,288]</sup> Aminoglycosides display concentration-dependent killing and fluoroquinolones are also considered to act in a concentration-dependent manner.<sup>[287,288,291-294]</sup> However, although this theory was proven for Gram-negative pathogens, Dalhoff<sup>[289]</sup> has demonstrated that sparflaxacin and ciprofloxacin exhibit concentration-independent effects on Gram-positive isolates, while retaining concentration-dependent killing for Gram-negative bacteria. In contrast, moxifloxacin displayed concentration-dependent activity for both Gram-positive and -negative organisms, a possible indication of higher intrinsic activity for Gram-positive species or modified target specificity over some of the older agents.<sup>[289]</sup>

Despite the above findings, overall fluoroquinolones are still considered to possess concentration-dependent activity and the AUC<sub>24</sub>/MIC and C<sub>max</sub>/MIC ratios have correspondingly shown to be the major parameters predictive of bacteriological eradication and clinical efficacy.<sup>[295]</sup> In order to optimise clinical outcomes in bacterial infections treated with fluoroquinolones, a number of investigators have studied which of these pharmacodynamic ratios display higher correlation with therapeutic success and the optimal target ratios to maximise bacterial eradication.

*In vitro* models have provided conflicting reports, some indicating that the AUC<sub>24</sub>/MIC provides the best correlation with bacteriological eradication,<sup>[296,297]</sup> whereas others suggest that C<sub>max</sub>/MIC is more predictive of eradication.<sup>[298]</sup> The

characterisation of whether one parameter provides greater predictive correlation with bacteriological and/or clinical cure than the other is difficult as interrelation of the variables is inevitable and neither stands alone as the sole determinant of antibacterial effects.<sup>[296,299]</sup> Further increasing the complexity of the results, *in vitro* studies evaluating the activity of ciprofloxacin, clinafloxacin, gatifloxacin, levofloxacin, sparfloxacin and trovafloxacin against strains of *S. pneumoniae* have shown that the AUC<sub>24</sub>/MIC and the T/MIC may better predict bacteriological eradication than C<sub>max</sub>/MIC,<sup>[300]</sup> potentially because of time-dependent bactericidal activity of some fluoroquinolones for Gram-positive species, as discussed in the previous paragraph. Hoang et al.<sup>[301]</sup> have reported concentration-independent killing of levofloxacin versus *S. pneumoniae*.

Data from human studies exhibit similar controversies. In the treatment of infections with levofloxacin, the C<sub>max</sub>/MIC predicted clinical outcomes and microbiological eradication better than the AUC<sub>24</sub>/MIC, although the two parameters were highly correlated.<sup>[302]</sup> Clinical trials of intravenous ciprofloxacin and oral grepafloxacin in the treatment of respiratory tract infections have demonstrated that the AUC<sub>24</sub>/MIC appears to be the most important parameter predicting the probability of both clinical and bacteriological cures, and the time to bacterial eradication.<sup>[303-305]</sup> However, these trials also showed that a high C<sub>max</sub>/MIC helps prevent selection of resistant bacterial strains, and thus may be the more important parameter if there is a significant risk of emergence of resistant subpopulations.<sup>[305]</sup> Recent explanations suggest that if the C<sub>max</sub>/MIC ratio is greater than 10 : 1 it will be the most important parameter in determining outcomes, whereas at C<sub>max</sub>/MIC ratios of <10 : 1, the AUC<sub>24</sub>/MIC ratio will better predict therapeutic results.<sup>[296,302]</sup>

In terms of optimal target ratios, it has been shown that attainment of C<sub>max</sub> to MIC ratios of >10:1 for fluoroquinolones increases the probability of successful clinical and microbiological outcomes and prevents the emergence of resistant

mutants during therapy.<sup>[287,302,303]</sup> A landmark clinical study by Forrest et al.<sup>[303]</sup> reported that the optimal  $AUC_{24}/MIC$  ( $AUC_{24}$ ) with ciprofloxacin of  $\geq 125$  was associated with bacterial eradication in critically ill patients with nosocomial lower respiratory tract infections caused by Gram-negative bacilli (e.g. *P. aeruginosa*). This critical breakpoint represented the minimum necessary ratio for rapid bacterial eradication and prevention of regrowth of resistant subpopulations; lower values resulted in clinical and bacteriological cure rates of  $<50\%$ .<sup>[303]</sup> A further evaluation of optimal  $AUC_{24}/MIC$  ( $AUC_{24}$ ) in the same patient population with nosocomial lower respiratory tract infections demonstrated a breakpoint for preventing resistance on therapy at approximately 100.<sup>[306]</sup> However, in clinical trials in outpatients with community-acquired respiratory infections such as acute exacerbations of chronic bronchitis performed with oral grepafloxacin, bacteriological and clinical cures resulted at optimal  $AUC_{24}/MIC$  ratios of 75 or above,<sup>[304]</sup> a much lower breakpoint than the minimum recommended in nosocomial infection. This is most likely a result of differences in the immunocompetence of patients in the respective in-patient and outpatient settings.<sup>[291]</sup> However, the authors did report that  $AUC_{24}/MIC$  ratios greater than 175 were associated with more rapid bacterial killing.<sup>[304]</sup>

*In vitro* analyses have demonstrated that the minimum  $AUC_{24}/MIC$  ratio can be significantly lower for Gram-positive pathogens, as clinafloxacin, gatifloxacin, levofloxacin, sparfloxacin and trovafloxacin all display bacterial eradication against *S. pneumoniae* and decreased regrowth of the resistant pneumococcus with  $AUC_{24}/MIC \geq 25$ .<sup>[300,307-311]</sup> However, an investigation into the activity of moxifloxacin against *S. aureus* and  $\beta$ -haemolytic streptococci reported optimal antibacterial effects with  $AUC_{24}/MIC$  ratios of 150 to 200.<sup>[312]</sup>

Complicating the determination of optimal target  $AUC_{24}/MIC$  ratios, longer-acting fluoroquinolones have been shown to display comparable antimicrobial effects at much lower ratios, most

likely a result of their longer half-lives.<sup>[313]</sup> *In vitro* models have predicted that the breakpoints of trovafloxacin and gatifloxacin equivalent to  $AUC_{24}/MIC$  ratio for ciprofloxacin of 125 are 71 and 102, respectively.<sup>[313,314]</sup>

*In summary*, clinical data indicate that a  $C_{max}$  to  $MIC$  ratio of 10:1 or greater and  $AUC_{24}/MIC$  ratios in the range of 100 to 125 maximise bacterial eradication and prevent resistance in critically ill patients with nosocomial lower respiratory infections caused by Gram-negative bacilli (eg. *P. aeruginosa*).<sup>[303,306]</sup> However, in outpatients with community-acquired respiratory infections such as acute exacerbations of chronic bronchitis and community-acquired pneumonia caused by *S. pneumoniae*, animal, *in vitro* and clinical data support  $AUC_{24}/MIC$  of  $\geq 25$  as being predictive of bacterial eradication.<sup>[300,302,307-309]</sup> Perhaps these different pharmacodynamic targets reflect the fact that the new fluoroquinolones display concentration-dependent killing against Gram-negative bacilli and concentration-independent killing against Gram-positive cocci. In table VIII the pharmacodynamic parameters of fluoroquinolones versus *S. pneumoniae* are depicted following single oral dose administration. As can be seen, all of the new fluoroquinolones achieve free  $AUC_{24}/MIC$  ratios  $>25$ . With *H. influenzae*, all of the new fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin) as well as ciprofloxacin achieve  $AUC_{24}/MIC$  ratios  $>1000$ .<sup>[291]</sup>

Although both  $C_{max}/MIC$  and  $AUC_{24}/MIC$  have demonstrated important correlations with therapeutic outcomes, recent suggestions advocate the  $AUC_{24}/MIC$  ratio as the parameter to predict bacteriological response.<sup>[306]</sup> This is because of its incorporation of both concentration intensity and exposure over time, and the fact that  $AUC_{24}/MIC$  ratios are additive properties, unlike  $C_{max}/MIC$  ratios, which facilitates the optimisation of two antibacterial agents.<sup>[306]</sup>

A further pharmacodynamic property exhibited by fluoroquinolones is continued suppression of an organism's growth that persists after exposure, known as the post-antibiotic effect (PAE).<sup>[287,290]</sup>

**Table VIII.** Fluoroquinolone pharmacokinetic/pharmacodynamic parameters versus *Streptococcus pneumoniae* [307]

| Fluoroquinolone (single doses simulated) | C <sub>max</sub> (µg/ml) | AUC <sub>24</sub> total (µg/ml•h) | AUC <sub>24</sub> free (µg/ml•h) | MIC (µg/ml) | AUC <sub>24</sub> /MIC total | AUC <sub>24</sub> /MIC free |
|------------------------------------------|--------------------------|-----------------------------------|----------------------------------|-------------|------------------------------|-----------------------------|
| Ciprofloxacin (500mg bid)                | 2.3                      | 20                                | 14                               | 2           | 10                           | 7                           |
| Ciprofloxacin (750mg bid)                | 3.0                      | 28                                | 20                               | 2           | 14                           | 10                          |
| Gatifloxacin (400mg od)                  | 3.9                      | 34                                | 27                               | 0.5         | 68                           | 54                          |
| Gemifloxacin (320mg od)                  | 1.2                      | 10                                | 4                                | 0.03        | 333                          | 133                         |
| Grepafloxacin (600mg od)                 | 1.6                      | 23                                | 12                               | 0.25        | 92                           | 48                          |
| Levofloxacin (500mg od)                  | 5.1                      | 48                                | 34                               | 1           | 48                           | 34                          |
| Moxifloxacin (400mg od)                  | 3.3                      | 34                                | 18                               | 0.25        | 136                          | 72                          |
| Trovafoxacin (200mg od)                  | 2.5                      | 26                                | 7                                | 0.12        | 217                          | 58                          |

**AUC<sub>24</sub>** = area under the plasma concentration time curve over 24 hours; **bid** = twice daily; **C<sub>max</sub>** = maximum plasma concentration; **MIC** = minimum inhibitory concentration; **od** = once daily.

Although all antibacterials produce PAEs *in vitro* on susceptible Gram-positive pathogens, fluoroquinolones also display prolonged PAEs for Gram-negative bacilli.[287,315-317] The PAEs for fluoroquinolones for both Gram-positive and -negative isolates are generally in the range of 1.5 to 2.5 hours.[315-319] This phenomenon of persistent antibacterial activity becomes important when the concentration of the drug falls below the MIC. Closely related to the PAE properties of fluoroquinolones is another pharmacodynamic phenomenon known as the post-antibiotic sub-MIC effect (PA SME), which is similar to the PAE except that subinhibitory concentrations of the antibacterial are present in the environment, in contrast to when the agent is virtually eliminated.[320] This property has been reported for both ciprofloxacin and levofloxacin against *S. pneumoniae*, inhibiting inoculum regrowth during the early, sub-MIC dose administration intervals.[309,321] In addition, sub-MIC effects of fluoroquinolones have been well described.[322] Post-antibiotic leucocyte enhancement (PALE) is also important in the persistence of antibacterial action as it describes the observed characteristic increase in the susceptibility of bacteria to leucocyte phagocytosis that occurs in the post-antibiotic phase. This added bacterial susceptibility to intracellular killing doubles the duration of the PAE of fluoroquinolones for Gram-negative bacilli.[287] Overall, these supplemental pharmacodynamic properties allow infrequent dose administration of large doses of fluoroquinolones because prolonged

PAEs protect against bacterial regrowth during troughs when serum concentrations decline below the MIC value.[287] Since fluoroquinolones exhibit concentration-dependent killing, these large-dose regimens administered once daily (resulting in the achievement of high AUC and C<sub>max</sub> values) contribute to high initial speed of killing, maximal bactericidal effects, optimal eradication times and decreased selection of resistant bacteria.[292,296] In clinical practice, optimisation of these variables by the achievement of high concentrations must then be balanced with the risk of toxicity and potentially serious adverse drug effects.[292]

7. Clinical Trials

As an update of our previous review,[16] this summary of clinical trials focuses on the new fluoroquinolones, including gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin and sitafloxacin. Human clinical trials were identified by searching the Cochrane Library and Medline for English language articles published between the years 1997 and the first quarter of 2000 (tables IX to XIII).[323-351] Abstracts more than two years old without subsequent publication of the data were not included. Grepafloxacin, sparfloxacin and trovafoxacin, which have been withdrawn from the market or restricted on the basis of their toxicity profiles (see section 8), were not included in this review of clinical trials.

This review focuses on the efficacy of the new fluoroquinolones in the treatment of respiratory

tract infections, primarily acute exacerbations of chronic bronchitis, acute sinusitis and community-acquired pneumonia. Of note, preliminary data on the *in vivo* activity of sitafloxacin in various respiratory tract infections were obtained from the manufacturer and are summarised in table IX,<sup>[349]</sup> but a full evaluation for specific respiratory tract infections is not possible until further trials are completed.

7.1 Acute Exacerbations of Chronic Bronchitis

7.1.1 Gatifloxacin

The results from two randomised, double-blind studies and one nonblind study evaluating the efficacy of gatifloxacin in the treatment of acute exacerbations of chronic bronchitis were combined and analysed by Ramirez et al. (table X).<sup>[324]</sup> Gatifloxacin produced a clinical cure (not defined) of 91% versus 88% for levofloxacin and cefuroxime axetil, which were used as comparators. A subset of this analysis, performed by DeAbate et al.,<sup>[323]</sup> demonstrated that oral gatifloxacin at 400mg daily produced significantly higher clinical cure rates than cefuroxime axetil 250mg administered twice daily. In the combined analysis, the overall bacteriological eradication rates were similar, (93% for gatifloxacin and 88% for the comparators), but gatifloxacin displayed superior bacteriological eradication against *S. pneumoniae* (100% for gatifloxacin versus 77% for comparators) and *H. influenzae* (96% versus 86%, respectively).<sup>[324]</sup> Further analysis of this data demonstrated higher

eradication of *S. pneumoniae* by gatifloxacin (100%) than levofloxacin (88%).<sup>[324]</sup> Compared with cefuroxime axetil, gatifloxacin exhibited significantly higher bacteriological kill rates (90% versus 77%).<sup>[323]</sup>

7.1.2 Gemifloxacin

There is limited clinical data available describing the efficacy of gemifloxacin in the treatment of respiratory tract infections. However, its use to treat acute exacerbations of chronic bronchitis was studied by Ball et al.<sup>[331]</sup> and is summarised in table XI. Gemifloxacin demonstrated similar efficacy to trovafloxacin with clinical success rates of 91.5% for gemifloxacin versus 87.6% for trovafloxacin, and bacteriological success of 87% versus 82%, respectively. However, gemifloxacin displayed statistically superior clinical success over trovafloxacin in the intention-to-treat population at follow-up [89% versus 83%, 95% confidence interval (CI) 0.9,11.7] and long term follow-up (80% versus 70%, 95% CI 3.3,16.8). Recent data with gemifloxacin versus clarithromycin in the Gemifloxacin Long-term Outcomes of Bronchitis Exacerbation (GLOBE) study suggests that gemifloxacin produced better eradication than clarithromycin, which resulted in more patients free of reoccurrence at follow-up (26 weeks) and less hospitalisation.<sup>[350,351]</sup>

7.1.3 Levofloxacin

Levofloxacin has been studied in the treatment of acute exacerbations of chronic bronchitis in four trials (table XII).<sup>[335-338]</sup> In a randomised, double-blind study levofloxacin 500mg daily was reported

Table IX. Results from clinical trials of respiratory tract infections involving sitafloxacin

| Reference                           | Design | Regimen                                                                                      | Duration (days) | Diagnosis: results (no. successes/no. pts)                                                                                                                                                                                                                                |
|-------------------------------------|--------|----------------------------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kobayashi <sup>[349]</sup> (poster) | mc     | S: 50 or 100mg oral bid (most commonly), (other regimens = 50 or 100mg once daily, 50mg tid) | 3-15            | Pneumonia: 62/65 (95%) success; <sup>a</sup> chronic airway infections <sup>b</sup> : 94/113 (83%) success; <sup>a</sup> acute URTI: 33/36 (92%) success; <sup>a</sup> others <sup>c</sup> : 8/10 (80%) success; <sup>a</sup> overall: 197/224 (88%) success <sup>a</sup> |

a Efficacy assessed through 'overall evaluation of clinical outcomes, including laboratory findings'; no definition given for success.  
b 63 patients with chronic bronchitis, 38 patients with bronchiectasia, 12 patients with diffuse panbronchiolitis.  
c 5 patients with *Mycoplasma pneumonia* infection, 4 patients with pulmonary suppuration, 1 patient with atypical pneumonia.  
**bid** = twice daily; **duration** = length of treatment; **mc** = multicentre; **S** = sitafloxacin; **tid** = three times daily; **URTI** = upper respiratory tract infections.

**Table X.** Results from clinical trials of respiratory tract infections involving gatifloxacin

| Reference                                               | Design                                                                                                                    | No.                    | Regimen                                                                                                                                                                                                                                                                                                                  | Duration                            | Results: clinical evaluation                                                                         |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------|
| <b>Acute exacerbations of chronic bronchitis (AECB)</b> |                                                                                                                           |                        |                                                                                                                                                                                                                                                                                                                          |                                     |                                                                                                      |
| DeAbate et al. <sup>[323]</sup>                         | p, r, db, dd, mc, c                                                                                                       | 211 (166)              | G: 400mg oral every day<br>CA: 250mg oral bid                                                                                                                                                                                                                                                                            | 7-10 days<br>7-10 days              | G: 76/85 (89%) cure <sup>a</sup><br>CA: 62/81 (77%) cure <sup>a</sup> [95% CI (0.7%, 22%) p < 0.035] |
| Ramirez et al. <sup>[324]</sup>                         | Pooled results of two trials (r, db, mc, c) and one trial (p, nb, nc) [includes data from DeAbate et al. <sup>[323]</sup> | 907 (432) <sup>b</sup> | G: 400mg oral every day<br>L: 500mg oral every day<br>CA: 250mg oral bid                                                                                                                                                                                                                                                 | 7-10 days<br>7-10 days<br>7-10 days | G: 205/225 (91%) cure <sup>c</sup><br>L and CA pooled data: 183/207 (88%) cure <sup>c</sup>          |
| <b>Acute sinusitis</b>                                  |                                                                                                                           |                        |                                                                                                                                                                                                                                                                                                                          |                                     |                                                                                                      |
| Fogarty et al. <sup>[325]</sup>                         | r, db, mc, c                                                                                                              | 421 (277)              | G: 400mg oral every day<br>Clar: 500mg oral bid                                                                                                                                                                                                                                                                          | 10 days<br>14 days                  | G: 124/133 (93%) cure <sup>d</sup><br>Clar: 129/144 (90%) cure <sup>d</sup>                          |
| Lopez-Sisniega et al. <sup>[326]</sup>                  | mc, nb, nc, phase II/III                                                                                                  | 364 (258)              | G: 400mg oral every day                                                                                                                                                                                                                                                                                                  | 10 days                             | G: 245/258 (95%) cure <sup>d</sup>                                                                   |
| Lopez-Sisniega et al. <sup>[327]</sup> (Abstr)          | mc, nb, nc, phase II                                                                                                      | 63 (60)                | G: 400mg oral every day                                                                                                                                                                                                                                                                                                  | 10 days                             | G: 93% cure <sup>c</sup>                                                                             |
| <b>Community-acquired pneumonia (CAP)</b>               |                                                                                                                           |                        |                                                                                                                                                                                                                                                                                                                          |                                     |                                                                                                      |
| Fogarty et al. <sup>[328]</sup>                         | p, r, db, mc, c, phase III (CAP in hospitalised patients)                                                                 | 283 (205)              | G: 400mg IV every day, followed by stepdown to oral G 400mg every day anytime after day 2 at investigator's discretion<br>Cef: 1 or 2g IV every day ± IV erythromycin (0.5 or 1g every 6h) if atypical pathogens suspected, followed by stepdown to oral Clar 500mg bid anytime after day 2 at investigator's discretion | 7-14 days<br>7-14 days              | G: 96/99 (97%) cure <sup>e</sup><br>Cef: 96/106 (91%) cure <sup>e</sup> [95% CI (-2.5%, 17.6%)]      |
| Ramirez et al. <sup>[329]</sup>                         | p, r, db, dd, mc, c                                                                                                       | 431 (372)              | G: 400mg oral every day<br>Clar: 500mg oral bid                                                                                                                                                                                                                                                                          | 7-14 days<br>7-14 days              | G: 95% cure <sup>e</sup><br>Clar: 93% cure <sup>e</sup> [95% CI (-4.2%, 9.1%)]                       |
| Sullivan et al. <sup>[330]</sup>                        | r, db, dd, c (CAP in newly hospitalised patients)                                                                         | 417 (339)              | G: 400mg IV or oral every day<br>L: 500mg IV or oral every day                                                                                                                                                                                                                                                           | 7-14 days<br>7-14 days              | G: 156/163 (96%) cure <sup>e</sup><br>L: 166/176 (94%) cure <sup>e</sup> [95% CI (-4.9%, 8.2%)]      |

a All signs and symptoms present at study entry were resolved at day +7 to day +14, without need for further antibacterials.

b Microbiologically evaluable patients.

c Clinical cure not defined.

d Purulent discharge, sinus pain, and sinus tenderness resolved or improved at day +7 to day +14, without need for further antibacterials and no new symptoms.

e All signs and symptoms of pneumonia resolved or improved at day +5 to day +28, without need for further antibacterials, and an improved or stable chest radiograph.

c = comparative; CA = cefuroxime axetil; Cef = ceftriaxone; CI = confidence interval; Clar = clarithromycin; db = double-blind; dd = double-dummy; duration = length of treatment; G = gatifloxacin; IV = intravenous; L = levofloxacin; mc = multicentre; nb = nonblind; nc = noncomparative; No. = number of patients (number of patients who were 'clinically evaluable' at the end of treatment); p = prospective; r = randomised.

to achieve 68% bacteriological eradication versus 48% for cefuroxime axetil.<sup>[335]</sup> The other three trials reported equivalence, both clinically and bacteriologically, for levofloxacin versus both cefuroxime axetil and cefaclor.<sup>[336-338]</sup> The most commonly isolated pathogens in these studies were *H. in-*

*fluenzae*, *M. catarrhalis*, *Haemophilus parainfluenzae*, and *S. pneumoniae*. DeAbate et al.<sup>[336]</sup> reported advantages in the levofloxacin regimen based on a shorter mean duration of treatment over cefuroxime axetil (7 versus 10 days) and a smaller percentage of resistant isolates. Shah et al.<sup>[338]</sup> sim-

ilarly demonstrated less overall resistance of organisms to levofloxacin (1.8%) than cefuroxime axetil (13%).

7.1.4 Moxifloxacin

Two prospective, randomised, double-blind clinical trials have been performed to evaluate the efficacy of moxifloxacin versus clarithromycin in acute exacerbations of chronic bronchitis (table XIII). Both trials indicated that moxifloxacin demonstrates equivalent clinical efficacy to clarithromycin, immediately post-therapy and at follow-up.<sup>[343,344]</sup> Bacteriological eradication rates were equivalent in one trial,<sup>[343]</sup> but the other showed that moxifloxacin was superior, successfully eradicating 77% of isolates versus 62% for clarithromycin.<sup>[344]</sup> The most common pathogens isolated in both trials were *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*.

7.2 Acute Sinusitis

7.2.1 Gatifloxacin

Currently, there is limited clinical comparative data available assessing the efficacy of gatifloxacin in acute sinusitis (table X). In a randomised, double-blind study, Fogarty et al.<sup>[325]</sup> reported that a 10-day regimen of oral gatifloxacin was equally

effective to 14 days of oral clarithromycin. Two nonblind trials demonstrated clinical cure rates of approximately 95% when gatifloxacin was used in the treatment of acute sinusitis, with up to 97% bacterial eradication.<sup>[326,327]</sup> The main pathogens isolated in these two trials were *S. pneumoniae*, *H. influenzae*, and *S. aureus*.

7.2.2 Gemifloxacin

One study was identified that evaluated the efficacy of gemifloxacin versus trovafloxacin in the treatment of acute sinusitis (table XI).<sup>[332]</sup> Gemifloxacin was clinically and bacteriologically equivalent to trovafloxacin in both the per-protocol and intent-to-treat populations.<sup>[332]</sup>

7.2.3 Levofloxacin

The use of levofloxacin for the treatment of acute sinusitis has been studied in two randomised trials versus clarithromycin (table XII).<sup>[339,340]</sup> Both trials showed that the two agents were equally effective in resolving the infection, with approximately equivalent recurrence rates 1 month post-therapy.<sup>[339,340]</sup> In a nonblind trial, Syndor et al.<sup>[341]</sup> demonstrated that a 500 mg/day regimen of levofloxacin employed for 10 to 14 days resulted in 88% clinical success (58% cured, 30% improved) in 300 clinically evaluable patients. This regimen

Table XI. Results from clinical trials of respiratory tract infections involving gemifloxacin

| Reference                                               | Design        | No.       | Regimen                  | Duration (days) | Results                                                                                              |
|---------------------------------------------------------|---------------|-----------|--------------------------|-----------------|------------------------------------------------------------------------------------------------------|
| <b>Acute exacerbations of chronic bronchitis (AECB)</b> |               |           |                          |                 |                                                                                                      |
| Ball et al. <sup>[331]</sup>                            | p, r, db, dd, | 616 (547) | GM: 320mg oral every day | 5               | GM: 249/272 (91.5%) success <sup>a</sup>                                                             |
|                                                         | pl, mc        |           | T: 200mg oral every day  | 5               | T: 241/275 (87.6%) success <sup>a</sup> [95% CI (-1.2,9.0)]                                          |
| <b>Acute sinusitis</b>                                  |               |           |                          |                 |                                                                                                      |
| Gehanno et al. <sup>[332]</sup>                         | p, r, db, dd, | 401 (340) | GM: 320mg oral every day | 7               | GM: 164/169 (97.0%) success <sup>b</sup>                                                             |
|                                                         | pl, mc, c     |           | T: 200mg oral every day  | 10              | T: 167/171 (97.7%) success <sup>b</sup> [95% CI (-4.0,2.8)]                                          |
| <b>Community-acquired pneumonia (CAP)</b>               |               |           |                          |                 |                                                                                                      |
| File et al. <sup>[333]</sup>                            | p, r, db, dd, | 571 (471) | GM: 320mg oral every day | 7-14            | GM: 228/238 (95.8%) success <sup>b</sup>                                                             |
|                                                         | pl, mc, c     |           | T: 200mg oral every day  | 7-14            | T: 218/233 (93.6%) success <sup>b</sup> (GM regimen is 'as effective' as T regimen for CAP patients) |

a Sufficient improvement or resolution of signs and symptoms such that no additional antibacterials were indicated for treatment, as assessed from days 11 to 22.  
b Sufficient improvement or resolution of signs and symptoms such that no additional antibacterials were indicated for treatment.  
c = comparative; CI = confidence interval; db = double-blind; dd = double-dummy; duration = length of treatment; GM = gemifloxacin; mc = multicentre; No. = number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment); p = prospective; pl = parallel; r = randomised; T = trovafloxacin.

**Table XII.** Results from clinical trials of respiratory tract infections involving levofloxacin<sup>a</sup>

| Reference                                               | Design               | No.       | Regimen                                                                                                                                                                                                                                      | Duration (days)  | Results                                                                                                         |
|---------------------------------------------------------|----------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------|
| <b>Acute exacerbations of bronchiectasis</b>            |                      |           |                                                                                                                                                                                                                                              |                  |                                                                                                                 |
| Tsang et al. <sup>[334]</sup>                           | p, r, pb             | 37 (35)   | L: 300mg oral bid                                                                                                                                                                                                                            | 10               | L: 57% bacterial eradication <sup>b</sup>                                                                       |
|                                                         |                      |           | Ceftaz: 1g iv tid                                                                                                                                                                                                                            | 10               | Ceftaz: 69% bacterial eradication <sup>b</sup>                                                                  |
| <b>Acute exacerbations of chronic bronchitis (AECB)</b> |                      |           |                                                                                                                                                                                                                                              |                  |                                                                                                                 |
| Davies & Maesen <sup>[335]</sup>                        | r, db, dd, c         | 140 (124) | L: 250mg oral every day                                                                                                                                                                                                                      | 7                | L 250 mg: 26/41 (63%) bacterial eradication <sup>b</sup>                                                        |
|                                                         |                      |           | L: 500mg oral every day                                                                                                                                                                                                                      | 7                | L 500 mg: 28/41 (68%) bacterial eradication <sup>b</sup>                                                        |
| DeAbate et al. <sup>[336]</sup>                         | r, nb, mc, c         | 492 (451) | CA: 250mg oral bid                                                                                                                                                                                                                           | 7                | CA: 20/42 (48%) bacterial eradication <sup>b</sup>                                                              |
|                                                         |                      |           | L: 500mg oral every day                                                                                                                                                                                                                      | 5-7              | L: 210/222 (94.6%) success <sup>c</sup>                                                                         |
|                                                         |                      |           | CA: 250mg oral bid                                                                                                                                                                                                                           | 10               | CA: 212/229 (92.6%) success <sup>c</sup><br>[CI not provided]                                                   |
| Habib et al. <sup>[337]</sup>                           | p, r, mc, c, nb      | 373 (309) | L: 500mg oral every day                                                                                                                                                                                                                      | 5-7              | L: 141/154 (92%) success <sup>c</sup>                                                                           |
|                                                         |                      |           | Cef: 250mg oral tid                                                                                                                                                                                                                          | 7-10             | Cef: 142/155 (92%) success <sup>c</sup><br>[95% CI (-6.5, 6.6)]                                                 |
| Shah et al. <sup>[338]</sup>                            | r, db, dd, pl, mc, c | 832 (427) | L: 250mg oral every day                                                                                                                                                                                                                      | 7-10             | L 250 mg: 121/156 (78%) success <sup>d</sup>                                                                    |
|                                                         |                      |           | L: 500mg oral every day                                                                                                                                                                                                                      | 7-10             | L 500 mg: 108/137 (79%) success <sup>d</sup>                                                                    |
|                                                         |                      |           | CA: 250mg oral bid                                                                                                                                                                                                                           | 7-10             | CA: 88/134 (66%) success <sup>d</sup> (Either L regimen is 'at least as effective' as CA regimen)               |
| <b>Acute sinusitis</b>                                  |                      |           |                                                                                                                                                                                                                                              |                  |                                                                                                                 |
| Adelglass et al. <sup>[339]</sup>                       | r, pl, ib, mc, c     | 216 (190) | L: 500mg oral every day                                                                                                                                                                                                                      | 14               | L: 97/101 (96%) success <sup>e</sup>                                                                            |
|                                                         |                      |           | Clar: 500mg oral bid                                                                                                                                                                                                                         | 14               | Clar: 83/89 (93%) success <sup>e</sup><br>[95% CI (-9.2, 3.7)]                                                  |
| Lasko et al. <sup>[340]</sup>                           | r, db, c             | 236 (191) | L: 500mg oral every day                                                                                                                                                                                                                      | 10-14            | L: 92/98 (94%) success <sup>e</sup>                                                                             |
|                                                         |                      |           | Clar: 500mg oral bid                                                                                                                                                                                                                         | 10-14            | Clar: 87/93 (94%) success <sup>e</sup><br>[95% CI (-7.8, 7.1)]                                                  |
| Syndor et al. <sup>[341]</sup>                          | p, nb, mc, nc        | 329 (300) | L: 500mg oral every day                                                                                                                                                                                                                      | 10-14            | L: 265/300 (88%) success <sup>e</sup>                                                                           |
| <b>Community-acquired pneumonia (CAP)</b>               |                      |           |                                                                                                                                                                                                                                              |                  |                                                                                                                 |
| File et al. <sup>[342]</sup>                            | p, r, nb, mc, c      | 590 (456) | L: 500mg iv or oral every day                                                                                                                                                                                                                | 7-14 (mean 11.7) | L: 217/226 (96%) success <sup>c</sup>                                                                           |
|                                                         |                      |           | C: ceftriaxone 1 or 2g iv every day or bid or CA 500mg oral bid, ± erythromycin (500mg to 1g oral or iv every 6 h) or doxycycline if atypical pathogens suspected. Patient was switched from iv to oral therapy at investigator's discretion | 7-14 (mean 11.7) | C: 207/230 (90%) success <sup>c</sup><br>[95% CI (-10.7,-1.3)]<br>(L is 'superior' to the comparator treatment) |

a Does not include comparative CAP study (gatifloxacin vs. levofloxacin) by Sullivan et al.<sup>[330]</sup> reported in table X.

b Measured as eradication of respiratory pathogens from sputum.

c Success defined as cure (resolution of signs and symptoms of acute infection) or improvement of signs and symptoms with no need for further antibacterials as measured on day +5 to day +7.

d Success defined as cure (complete resolution of signs and symptoms of acute infection) or improvement of a least one sign or symptom, with the patient afebrile and no further antibacterials necessary as measured on day +5 to day +14.

e Success defined as cure (resolution of signs and symptoms) or improvement of signs and symptoms with no need for further antibacterials as measured on day +2 to day +5.

**bid** = twice daily; **C** = comparator; **c** = comparative; **CA** = cefuroxime axetil; **Cef** = cefaclor; **Ceftaz** = ceftazidime; **CI** = confidence interval; **Clar** = clarithromycin; **db** = double-blind; **dd** = double-dummy; **duration** = length of treatment; **ib** = investigator-blinded; **iv** = intravenous; **L** = levofloxacin; **mc** = multicentre; **nb** = nonblind; **nc** = noncomparative; **No.** = number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment); **p** = prospective; **pb** = physician-blind; **pl** = parallel; **r** = randomised.

maintained successful outcomes in 92% of patients at a 4 to 6 week follow-up visit.<sup>[341]</sup> The overall bacteriological eradication rate was 92%.<sup>[341]</sup> Of the most commonly isolated pathogens, *H. influenzae*, *S. pneumoniae*, *S. aureus*, and *M. catarrhalis*, the eradication rates were 97%, 100%, 94%, and 93%, respectively.<sup>[341]</sup>

### 7.2.4 Moxifloxacin

Moxifloxacin has been evaluated versus both trovafloxacin and cefuroxime axetil in the treatment of acute sinusitis (table XIII).<sup>[345,346]</sup> In these trials, moxifloxacin was reported to produce equivalent clinical efficacy versus both comparators.<sup>[345,346]</sup> Analysis of a subset of patients with severe infection demonstrated higher clinical resolution rates in those who received moxifloxacin over trovafloxacin (90% vs 81%, respectively).<sup>[345]</sup>

## 7.3 Community-Acquired Pneumonia

### 7.3.1 Gatifloxacin

The efficacy of gatifloxacin in patients with community-acquired pneumonia has been evaluated in three randomised, double-blind trials (table X).<sup>[328-330]</sup> These trials have demonstrated that gatifloxacin produces similar clinical cure rates to that of ceftriaxone (with or without erythromycin), clarithromycin or levofloxacin.<sup>[328-330]</sup> Sullivan et al.<sup>[330]</sup> reported that gatifloxacin produced slightly higher clinical cure rates in patients with severe community-acquired pneumonia versus levofloxacin in this same population (95% versus 91%). Bacteriological eradication by gatifloxacin in all three trials was 97 to 98%, which was similar but slightly higher than that of the comparators (92% for ceftriaxone  $\pm$  erythromycin, 93% for both clarithromycin and levofloxacin).<sup>[328-330]</sup> The most common causative organisms isolated in these trials were *S. pneumoniae*, *S. aureus*, and Gram-negative aerobes,<sup>[328-330]</sup> along with a significant proportion of *M. pneumoniae* (15%) and *C. pneumoniae* (9%) in the trial by Ramirez et al.<sup>[329]</sup> The most substantial difference in bacterial eradication rates was observed with *C. pneumoniae*, where gatifloxacin exhibited 100% eradication versus 76% for clari-

thromycin.<sup>[329]</sup> However, the number of isolates was too small to be statistically significant ( $n = 20$  for gatifloxacin,  $n = 17$  for clarithromycin).

### 7.3.2 Gemifloxacin

The efficacy of gemifloxacin in the treatment of community-acquired pneumonia has been compared with trovafloxacin by File et al., (table XI).<sup>[333]</sup> This evaluation demonstrated similar efficacy, both clinically and microbiologically.<sup>[333]</sup> Bacteriological eradication rates were 88 to 89% for both agents at follow-up (14 to 21 days post-therapy) in the per protocol population.<sup>[333]</sup> *M. pneumoniae*, *S. pneumoniae*, and *C. pneumoniae* were the primary pathogens identified in this trial.<sup>[333]</sup>

### 7.3.3 Levofloxacin

In addition to the trial comparing the efficacy of gatifloxacin versus levofloxacin in the treatment of community-acquired pneumonia reported in section 7.3.1,<sup>[330]</sup> levofloxacin has also been compared with a regimen of ceftriaxone or cefuroxime axetil with or without erythromycin or doxycycline for community-acquired pneumonia (table XII).<sup>[342]</sup> In this trial, the levofloxacin regimen produced a significantly better clinical cure rate versus the comparator treatment, achieving 96% clinical success versus that of 90% for the comparators (95% CI -10.7, -1.3).<sup>[342]</sup> The primary pathogens identified in this study were *H. influenzae*, *S. pneumoniae*, *S. aureus*, and atypical bacteria (*C. pneumoniae*, *M. pneumoniae*, *L. pneumophila*).<sup>[342]</sup> Levofloxacin was reported to demonstrate superior bacteriological eradication in patients with 'typical' respiratory pathogens compared with the ceftriaxone or cefuroxime axetil regimens (98% versus 85%), with 100% bacterial eradication of *H. influenzae* and *S. pneumoniae* isolates.<sup>[342]</sup> Satisfactory clinical responses were achieved in 99% of patients with atypical pneumonia who received the levofloxacin regimen.<sup>[342]</sup>

### 7.3.4 Moxifloxacin

One comparative trial evaluating the efficacy of moxifloxacin versus that of clarithromycin in the treatment of community-acquired pneumonia was

**Table XIII.** Results from clinical trials of respiratory tract infections involving moxifloxacin

| Reference                                               | Design           | No.                    | Regimen                 | Duration (days) | Results                                                                                                                           |
|---------------------------------------------------------|------------------|------------------------|-------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|
| <b>Acute exacerbations of chronic bronchitis (AECB)</b> |                  |                        |                         |                 |                                                                                                                                   |
| Chodosh et al. <sup>[343]</sup>                         | p, r, db, pl, c  | 926 (855) <sup>a</sup> | M: 400mg oral every day | 5               | M 5 day: 274/288 (95%) success <sup>b</sup> 242/270 (90%) overall response <sup>c</sup>                                           |
|                                                         |                  |                        | M: 400mg oral every day | 10              | M 10 day: 266/281 (95%) success <sup>b</sup> 250/273 (92%) overall response <sup>c</sup>                                          |
|                                                         |                  |                        | Clar: 500mg oral bid    | 10              | Clar: 268/286 (94%) success <sup>b</sup> 232/263 (88%) overall response <sup>c</sup>                                              |
| Wilson et al. <sup>[344]</sup>                          | p, r, db, mn, c  | 745 (649)              | M: 400mg oral every day | 5               | M: 287/322 (89%) cure <sup>d</sup> (follow-up: 256/287 (89%) cont'd cure <sup>e</sup> )                                           |
|                                                         |                  |                        | Clar: 500mg oral bid    | 7               | Clar: 289/327 (88%) cure <sup>d</sup> [95% CI (-3.9,5.8)] {follow-up: 257/289 (89%) cont'd cure <sup>e</sup> [95% CI (-3.9,5.4)]} |
| <b>Acute sinusitis</b>                                  |                  |                        |                         |                 |                                                                                                                                   |
| Baz et al. <sup>[345]</sup>                             | p, r, db, mc, c  | 590 (513)              | M: 400mg oral every day | 10              | M: 223/253 (88%) resolution <sup>f</sup>                                                                                          |
|                                                         |                  |                        | T: 200mg oral every day | 10              | T: 232/260 (89%) resolution <sup>f</sup> [95% CI (-6.5,3.9)]                                                                      |
| Burke et al. <sup>[346]</sup> (abstr)                   | p, db, mc, c     | 542 (457)              | M: 400mg oral every day | 10              | M: 89.7% success <sup>g</sup>                                                                                                     |
|                                                         |                  |                        | CA: 250mg oral bid      | 10              | CA: 89.3% success <sup>g</sup> [95% CI (-5.1,6.2)]                                                                                |
| <b>Community-acquired pneumonia (CAP)</b>               |                  |                        |                         |                 |                                                                                                                                   |
| Fogarty et al. <sup>[347]</sup>                         | p, r, db, mc, c  | 474 (382)              | M: 400mg oral every day | 10              | M: 184/194 (95%) overall resolution <sup>h</sup>                                                                                  |
|                                                         |                  |                        | Clar: 500mg oral bid    | 10              | Clar: 178/188 (95%) overall resolution <sup>h</sup> [95% CI (-3.7, 5.3)]                                                          |
| Patel et al. <sup>[348]</sup>                           | p, o, uc, nb, mc | 254 (196)              | M: 400mg oral every day | 10              | M: 182/196 (93%) overall resolution <sup>h</sup> [95% CI (88.1, 95.9)]                                                            |

a Intent-to-treat population. Authors also evaluated an efficacy-valid population (i.e., those with a pretherapy pathogen) of 491 participants - data not included.

b Success defined as cure (resolution of signs and symptoms of acute infection) or sufficient improvement such that no additional or alternate antibacterials were required as measured on day +0 to day +6; results from intent-to-treat analysis.

c Overall response defined as resolution of signs and symptoms or indeterminate response (no clinical assessment) as measured on day +0 to day +6 with continued resolution at follow-up, measured on day +7 to day +17.

d Cure defined as resolution of signs and symptoms of infection, with no need for further antibacterials as measured on day +7.

e Continued cure as measured on day +21 to day +28 of patients cured at day +7.

f Resolution defined as absence or improvement of all signs and symptoms related to the infection with no need for further antibacterials as measured on day +7 to day +21.

g As measured on day +7 to day +21.

h Overall resolution defined as disappearance or sufficient improvement in signs and symptoms that no additional/alternative antibacterials were required as measured at day +0 to day +6 and at day +14 to day +35.

**bid** = twice daily; **c** = comparative; **CA** = cefuroxime axetil; **CI** = confidence interval; **Clar** = clarithromycin; **db** = double-blind; **duration** = length of treatment; **M** = moxifloxacin; **mc** = multicentre; **mn** = multinational; **nb** = nonblind; **No.** = number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment); **p** = prospective; **pl** = parallel; **r** = randomised; **T** = trovafloxacin; **uc** = uncontrolled.

identified and is summarised in table XIII.<sup>[347]</sup> A 10-day regimen of oral moxifloxacin produced equivalent clinical cure rates (95%) as the same duration of clarithromycin treatment.<sup>[347]</sup> Both treatments also achieved equal bacteriological eradication rates (96-97%).<sup>[347]</sup> The most commonly identified pathogens were *C. pneumoniae*,

*M. pneumoniae*, *H. influenzae*, and *S. pneumoniae*, in which moxifloxacin achieved eradication rates of 92%, 96%, 96%, and 100%, respectively.<sup>[347]</sup> In a nonblind assessment of moxifloxacin in the treatment of community-acquired pneumonia, a 10-day regimen demonstrated 93% overall clinical resolution (table XII), with 91% overall bacteriological

response.<sup>[348]</sup> The bacteriological eradication rates achieved against the most commonly isolated pre-therapy pathogens were 89% for *C. pneumoniae*, 93% for *M. pneumoniae*, 93% for *S. pneumoniae*, and 85% for *H. influenzae*.<sup>[348]</sup>

#### 7.4 Overall Evaluation

The above analysis demonstrates that the new fluoroquinolones, specifically gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin, are effective in the treatment of community-acquired respiratory tract infections. *In vivo* efficacy of the new fluoroquinolones demonstrated equivalence to standard therapy in the majority of trials. Evidence of superiority observed in some trials (often not double-blinded), although interesting and encouraging, requires confirmation in well-designed trials. The ease of once daily dose administration and high oral bioavailability are potential advantages over other therapies. The new fluoroquinolones offer effective treatment alternatives to manage respiratory tract infections caused by both typical and atypical bacterial pathogens. Preliminary data on sitafloxacin suggests similar future potential, but more trials must be completed to solidify its place in therapy.

### 8. Adverse Effects

The most common adverse effects associated with the use of fluoroquinolones are gastrointestinal disturbances, nervous system complaints (dizziness, headache), and allergic reactions (skin rashes and pruritus) (table XIV).<sup>[205,323-326,336,337,352]</sup> The incidence of phototoxicity also varies among the quinolones. A comparison of adverse effects among selected quinolones is presented in table XIV. Data were sourced from clinical trials of individual agents and thus represent the approximate frequency of adverse effects. The discussion in this section focuses primarily on a comparison of the newer fluoroquinolones, namely gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin, to those agents that have exhibited serious toxicity. Older agents such as grepafloxacin, trovafloxacin and clinafloxacin were included for comparison in

table XIV. Sitafloxacin is not further discussed, as limited adverse effect data are available.

With the identification of adverse events associated with some fluoroquinolones, newer fluoroquinolones have been scrutinised closely because of class-related adverse effects. Grepafloxacin has been withdrawn from the market on the basis of the propensity to cause prolongation of the QTc interval and potential for torsade de pointes.<sup>[366]</sup> It also results in taste perversion in a large percentage of individuals (table XIV). Sparfloxacin has also been removed as a result of a poor adverse effect profile, which includes a high incidence of phototoxicity and skin toxicities,<sup>[361]</sup> and the potential to prolong the QTc interval.<sup>[367,368]</sup> The use of trovafloxacin for treatment is restricted because of concerns with hepatotoxicity.<sup>[369,370]</sup> Trovafloxacin has also displayed a higher propensity to cause mild to serious neurotoxicity, including a report of uncontrollable muscle tremors and generalised seizures,<sup>[371]</sup> and dizziness<sup>[372]</sup> compared with other fluoroquinolone agents. Clinafloxacin use has been limited because of its relatively high potential to cause phototoxicity and hypoglycaemia.<sup>[354]</sup> These agents were included in table XIV for comparison purposes to gauge the newer fluoroquinolones against, but now have limited roles in the treatment of infections.

#### 8.1 Gastrointestinal

Gatifloxacin and moxifloxacin have been reported to cause nausea in 6 to 10% of patients, a similar rate to that observed with grepafloxacin and trovafloxacin (table XIV). Gemifloxacin and levofloxacin have exhibited slightly lower propensity to cause this adverse effect, but similar incidences of vomiting and diarrhoea as seen with gatifloxacin and moxifloxacin (1 to 5%) (table XIV).

#### 8.2 Central Nervous System

All of the new fluoroquinolone agents have displayed some risk of causing central nervous system adverse effects, primarily headache and dizziness (table XIV). Dizziness has been reported in similar

**Table XIV.** Frequently occurring adverse effects of the new fluoroquinolones and ciprofloxacin (as a comparator)<sup>a</sup>

| Adverse effect                | Fluoroquinolone <sup>b</sup> |               |              |              |               |              |              |             |              |               |
|-------------------------------|------------------------------|---------------|--------------|--------------|---------------|--------------|--------------|-------------|--------------|---------------|
|                               | ciprofloxacin                | clinafloxacin | gatifloxacin | gemifloxacin | grepafloxacin | levofloxacin | moxifloxacin | sitafoxacin | sparfloxacin | trovafloxacin |
| <b>Gastrointestinal</b>       |                              |               |              |              |               |              |              |             |              |               |
| nausea                        |                              |               | ++           |              | ++            |              | ++           | ±           |              | ++            |
| vomiting                      | ±                            | ND            |              |              |               | ±            |              | ±           |              |               |
| diarrhoea                     |                              | ++            |              |              |               |              | ++           |             |              |               |
| <b>Central nervous system</b> |                              |               |              |              |               |              |              |             |              |               |
| dizziness                     | ±                            | ND            |              |              |               | ±            |              | ±           | -            | +++           |
| headache                      | ±                            | ND            |              | ++           |               |              |              |             |              |               |
| <b>Allergic</b>               |                              |               |              |              |               |              |              |             |              |               |
| rash                          |                              |               | ±            |              |               | ±            | ±            |             |              | ±             |
| pruritis                      | ±                            | ND            | -            | ND           |               | -            | ±            | ±           | ±            | ±             |
| Phototoxicity                 | ±                            | ++            | -            | ±            |               | ±            | -            | + / ND      | ++           | ±             |
| Cardiovascular <sup>c</sup>   | ±                            | ±             | ±            |              | ++            |              |              | ±           | ++           | ±             |
| Taste perversion              | ±                            | ND            |              | ±            | +++           | ±            |              | ND          | ±            | ND            |
| Injection site reaction       |                              |               |              | ND           | NA            |              | NA           | ND          | NA           | ±             |
| Vaginitis <sup>d</sup>        | ±                            | ND            | ++           | ND           |               |              |              | ND          | -            |               |

a Adapted from references: 205, 323-326, 328-330, 336, 337, 339-341, 343-349, 352-365

b For clinafloxacin, gemifloxacin, sitafloxacin and trovafloxacin, because these agents have not been extensively studied in clinical trials, if a specific adverse effect was not found to be reported a 'ND' was entered into the table. For ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin and sparfloxacin, because these agents have been extensively studied in clinical trials, if a specific adverse effect was not found to be reported, a '-' was entered into the table.

c QTc prolongation. Percentages of patients experiencing this adverse effect have not been clearly documented. This is considered a class effect and the relative number of '+' symbols here only indicate the relative number of reports of this adverse effect: ± indicates no current published reports; + indicates reported; ++ indicates more frequent reports.

d Percentages of female patients receiving the specified agent.

- indicates adverse effect has not been observed; ± indicates adverse effect occurs in <1% of patients; + indicates adverse effect occurs in 1 to 5% of patients; ++ indicates adverse effect occurs in 6 to 10% of patients; +++ indicates adverse effect occurs in >10% of patients; +/ND indicates adverse effect is expected to occur but has not been documented yet; NA = not applicable (fluoroquinolone is not available in an intravenous formulation); ND = no data.

percentages of patients receiving gatifloxacin, gemifloxacin, levofloxacin or moxifloxacin, at 1 to 5% (table XIV). Confusion, hallucinations and seizures can occur with the use of fluoroquinolones, although they have not yet been reported with gatifloxacin, gemifloxacin, levofloxacin or moxifloxacin. In contrast, data from trovafloxacin clinical trials involving >6000 patients found dizziness occurred in 11% of patients, resulting in warnings regarding the operation of machinery and motor vehicles.<sup>[372]</sup> Avoidance of trovafloxacin has been suggested in patients with underlying seizure or neuropsychiatric disorders because of the excitatory potential of trovafloxacin.<sup>[371]</sup>

### 8.3 Allergic Reactions

Rash and pruritus have been reported to some degree for most of the fluoroquinolone agents. Gatifloxacin, levofloxacin and moxifloxacin have been reported to cause rash in <1% of patients (table XIV), but gemifloxacin has been linked to causing rash in 4.8% of patients.<sup>[355]</sup> Pruritus has not been observed to date with gatifloxacin (table XIV). Cutaneous vasculitis, which has been documented with ciprofloxacin,<sup>[373]</sup> has not yet been reported with gatifloxacin, gemifloxacin, levofloxacin or moxifloxacin.

### 8.4 Phototoxicity

Mild fluoroquinolone-induced photosensitivity generally presents as erythema, oedema, desquamation and hyperpigmentation.<sup>[374]</sup> Painful blistering can occur in more severely affected patients.<sup>[374]</sup> Upon withdrawal of the offending agent resolution occurs quickly with a return to normal within a few weeks.<sup>[375]</sup> This problem appears to be dose-related and is unrelated to patient age. Phototoxicity among fluoroquinolones appears to be influenced by the presence of a halogen at position 8 of the fluoroquinolone molecule. Of the older agents, ciprofloxacin and sparfloxacin are both halogenated at position 8 and have demonstrated significant phototoxicity<sup>[354,361]</sup> that has limited their use, whereas grepafloxacin and trovafloxacin have only displayed mild photosensitising potential ap-

proximately similar to that of ciprofloxacin.<sup>[374,376]</sup> It is thought that a methoxy group or lack of halogen at position 8 in the heterocyclic ring confers low phototoxic potential.<sup>[377]</sup> Of the new fluoroquinolones, phototoxic reactions have not been reported to date with gatifloxacin and moxifloxacin which possess a C-8 methoxy group.

A study to determine the mechanism of fluoroquinolone-induced phototoxicity suggested the production of reactive singlet oxygen species is an important contributor to the phototoxicity of these agents.<sup>[378]</sup> In contrast gatifloxacin did not generate singlet oxygen species.<sup>[378]</sup> In comparison, the phototoxicity of gatifloxacin in clinical studies was similar to placebo,<sup>[362,379]</sup> and less than that observed with ciprofloxacin.<sup>[379]</sup> With respect to moxifloxacin, there were no reports of phototoxicity associated with moxifloxacin during clinical trials nor in a randomised, double-blind study assessing risk of phototoxicity.<sup>[380]</sup> The incidence of phototoxicity with levofloxacin is very low (table XIV). The prevalence of gemifloxacin associated phototoxicity appears low, occurring in 2 of 5249 patients during clinical trials.<sup>[355]</sup> In terms of severity, the phototoxic potential of gemifloxacin is similar to ciprofloxacin.<sup>[381]</sup>

### 8.5 Cardiovascular

The potential for QTc interval prolongation is considered a class effect of all fluoroquinolone agents.<sup>[382]</sup> The severity of this event can vary from mild, asymptomatic, clinically insignificant increases in the QTc to the potential development of torsades de pointes, a polymorphic ventricular tachycardia that can lead to ventricular fibrillation and cause sudden cardiac death.

<sup>[383]</sup> Prolongation of the QTc interval leading to torsades de pointes has been reported in patients receiving sparfloxacin<sup>[367,368]</sup> and grepafloxacin. Analysis of 880 patients who received sparfloxacin revealed a mean QTc interval increase of 3% (11.0 ± 25.0 msec) from baseline and post-marketing surveillance of 750 000 patients who received sparfloxacin revealed seven serious adverse cardiovascular events, including three of polymorphic

ventricular tachycardia.<sup>[367]</sup> These three patients all exhibited underlying cardiac disease and two of them were receiving concomitant amiodarone therapy.<sup>[367]</sup> The magnitude of change in the QTc interval appears to be directly correlated with plasma sparfloxacin concentrations.<sup>[367]</sup> Grepafloxacin use has been linked with seven, possibly associated, sudden cardiac deaths and several cases of torsades de pointes.<sup>[382]</sup> As indicated previously grepafloxacin has since been removed from the market.

Because of the potential class effect of the fluoroquinolones on QTc intervals, labelling has been adjusted for fluoroquinolones such as levofloxacin, although the number of QTc reports appears very low. In an isolated case report, levofloxacin was reported to have caused QTc interval prolongation (127 msec increase) and ventricular tachycardia in an 88 year old female patient with atrial fibrillation.<sup>[384]</sup>

In terms of other agents, in pooled analysis of clinafloxacin (>1500 patients) and gatifloxacin (>3000 patients) prolongation of the QTc interval has not been observed.<sup>[354,362]</sup> In 16 clinical trials, gemifloxacin has been reported to demonstrate small, nonsignificant QTc interval prolongation (3.7 msec) versus comparators. There were no reports of torsade de pointes.<sup>[352,355]</sup> Moxifloxacin has undergone extensive scrutiny and testing with respect to potential cardiac toxicity. There has been one observed case (out of >1 million patients) of possibly related torsades de pointes associated with moxifloxacin therapy occurring in a patient in an intensive care unit with multiple risk factors and concomitant diseases.<sup>[382]</sup>

Currently, fluoroquinolones have been used in significantly large populations at risk for cardiac toxicity, without high proportions of associated ventricular tachycardias or related fatalities.<sup>[382]</sup> Fluoroquinolones should generally be closely monitored or avoided in patients who have significant cardiovascular disease or history of an arrhythmia, or who are receiving other agents that prolong the QTc interval or that inhibit the metabolism of QTc-prolonging drugs.<sup>[382]</sup> Agents that

may lead to QTc interval prolongation may include class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol), erythromycin, cotrimoxazole (trimethoprim/sulfamethoxazole), the antihistamines astemizole and terfenadine, antiprotozoals (e.g. chloroquine, mefloquine, quinine), some psychoactive agents (e.g. haloperidol, lithium, phenothiazines, tricyclic antidepressants), amantadine, and vasopressin.<sup>[383]</sup> Caution must be exercised in elderly patients and in those with electrolyte disturbances.<sup>[382]</sup>

## 8.6 Hepatotoxicity

As mentioned previously, the use of trovafloxacin has been severely restricted because of the rare but severe and sometimes fatal hepatotoxicity associated with its use.<sup>[369,370]</sup> Other fluoroquinolones have not demonstrated the same severe hepatotoxicity, although elevated transaminase liver enzyme levels have been associated with the use of clinafloxacin, sparfloxacin and grepafloxacin in 2 to 16% of patients receiving these agents.<sup>[29,354,361]</sup> Of the newer agents, elevations in liver enzyme levels have not been reported to date with gatifloxacin, levofloxacin or moxifloxacin. Mild and reversible elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have been reported with gemifloxacin (high dose of 640mg) in 3 of 8 volunteers in a pharmacokinetic study.<sup>[385]</sup>

## 8.7 Paediatric Concerns

All fluoroquinolones, to lesser or greater degrees, have been shown to cause arthropathy and cartilage damage in immature animals.<sup>[386,387]</sup> Symptomatic joint damage in these animals generally presented as acute arthritis, with limping and swelling.<sup>[387]</sup> As a consequence, fluoroquinolones are not approved at this time for use in children <18 years old or in pregnant/nursing women.<sup>[386]</sup> However, based on the efficacy of fluoroquinolone agents and rare reports of prolonged toxicity, ciprofloxacin for example has been used in children for compassionate reasons. Paediatric patients with cystic fibrosis with pulmonary exacerbations

have been the most common indication for a fluoroquinolone. Retrospective evaluation of use in this population suggests that fluoroquinolones very rarely cause arthropathy in children.<sup>[387]</sup> In a review of over 1500 children and adolescent patients who received ciprofloxacin, the incidence of adverse effects (gastrointestinal, dermatological and CNS) were similar to that reported with adults.<sup>[388]</sup> Of the more than 1500 patients, 75% of these patients had cystic fibrosis. The incidence of reversible arthralgia in this subgroup was reported to be 3.2%, although there did not appear to be a clear relationship between ciprofloxacin and arthralgia since joint symptoms maybe related to cystic fibrosis. There were no documented incidences of radiological cartilage damage or arthritis reported. In 281 paediatric patients with typhoid fever who received ciprofloxacin, no joint symptoms were reported.<sup>[388]</sup> Although fluoroquinolones are not approved for use in paediatrics and clinical trials in paediatrics are lacking, it is clear that selected use of fluoroquinolones in children for the treatment of severe, life-threatening infections appear to outweigh the risk of arthropathy.<sup>[386]</sup>

### 8.8 Tendinopathy

Fluoroquinolone-induced tendinopathy is rare (approximately 68 patients) and although it has been reported worldwide, most reports are from France. The fluoroquinolones implicated were mostly pefloxacin and ciprofloxacin, although it has been reported with many other fluoroquinolones and is believed to be a class effect.<sup>[389]</sup> The mean age of patients is 58.8 years (range 28 to 92) with the Achilles tendon being involved approximately 90% of the time. Tendinitis almost always occurs, although rupture occurs 40% of the time. Mean duration of onset is 17 days (range 2 hours to 6 months) and time to recovery is 63.9 days (range 1 day to 9 months). Interventions include discontinuation of the fluoroquinolone and rest in 30%, nonsurgical (immobilisation and physiotherapy) in 25% and surgical in 7%. Risk factors include male sex and oral corticosteroids.

### 8.9 Neonatal and *In Utero*

Some studies have been performed to assess the adverse effects of fluoroquinolones with neonatal and *in utero* exposure. A study of the effects of older fluoroquinolones (ciprofloxacin and pefloxacin) on the growth and development of preterm infants found smaller bodyweight and head circumference in neonates who received these agents.<sup>[390]</sup> However, it was not clear from the methods employed whether these effects were a result of fluoroquinolone exposure or the greater severity of illness in the neonates of this group.<sup>[390]</sup> No osteoarticular sequelae were observed and normal development (measured by age of walking and motor, social and language skills) was shown in the children who received fluoroquinolone treatment.<sup>[390]</sup>

In a prospective study of 200 females who received fluoroquinolone treatment during gestation, there were no differences in the rate of major congenital malformations in the fluoroquinolone-treated group (2.2%) versus the control group (2.6%), nor were differences in the rates or measurements of spontaneous abortions, fetal distress, prematurity, and birth weight observed.<sup>[391]</sup> In addition, there were no significant differences in motor development and musculoskeletal dysfunction between the children of both groups.

## 9. Drug Interactions

A number of studies have been published that assess the potential drug interactions between fluoroquinolone agents and various other drugs. The more common and/or potentially serious drug interactions of the new fluoroquinolones are presented in table XV. Ciprofloxacin is included in the table as a reference agent, but clinafloxacin, grepafloxacin, sparfloxacin and trovafloxacin were excluded because of their aforementioned market withdrawals and restrictions. In addition, drug interactions among these fluoroquinolones have been previously reviewed.<sup>[16]</sup>

9.1 Metal Ion-Containing Drugs

Interactions have been observed between all new fluoroquinolone agents on which there are data available and metal-ion containing drugs (table XV). The mechanism of the interaction is considered to be mediated through chelation of metal cations with the fluoroquinolone resulting in formation of insoluble drug-cationic complexes and a corresponding decrease in the absorption and bioavailability of the antibacterial.<sup>[411,412]</sup> Metal-ion containing drugs that have been reported to interact with the new fluoroquinolones include antacids containing aluminium and magnesium, ferrous sulphate and sucralfate, a complex of aluminium hydroxide and sulphated sucrose.<sup>[205,411]</sup>

Administration of metal-ion containing drugs has been observed to reduce the bioavailability of concomitantly administered fluoroquinolones from approximately 35% to 85%.<sup>[218,392,395,397,400,406]</sup> It appears that all of the new fluoroquinolones may be administered at least 2 hours prior to metal-ion containing drugs without significant reductions in bioavailability.<sup>[218,220,397,406,413]</sup> However, the optimal time of administration after ingestion of a metal-ion containing agent depends on the agent itself and varies (3 to 6 hours) for different fluoroquinolones.<sup>[218,220,397,406]</sup> It is currently unclear whether calcium affects the absorption of all of the new fluoroquinolone agents to any significant extent, but studies with gatifloxacin and levofloxacin

**Table XV.** Drug interactions of the new fluoroquinolones and ciprofloxacin <sup>a</sup>

| Interaction with                                             | Fluoroquinolone                                                                                                                                                                                                                   |              |              |              |              |                  |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------|--------------|--------------|------------------|
|                                                              | ciprofloxacin                                                                                                                                                                                                                     | gatifloxacin | gemifloxacin | levofloxacin | moxifloxacin | sitafloxacin     |
| Metal ion containing drugs (e.g. antacids, iron, sucralfate) | Yes                                                                                                                                                                                                                               | Yes          | Yes          | Yes          | Yes          | Yes <sup>b</sup> |
| mechanism                                                    | Chelation resulting in reduced fluoroquinolone bioavailability.                                                                                                                                                                   |              |              |              |              |                  |
| recommendation                                               | Avoid concomitant administration if possible. Otherwise, administer the fluoroquinolone 2 hours before or 3-6 hours after the metal ion-containing drug.                                                                          |              |              |              |              |                  |
| Theophylline                                                 | Yes                                                                                                                                                                                                                               | No           | No           | No           | No           | No               |
| mechanism                                                    | Inhibition of theophylline metabolism, resulting in reduced theophylline clearance.                                                                                                                                               |              |              |              |              |                  |
| recommendation                                               | For ciprofloxacin, monitor theophylline levels and adjust theophylline dosage where necessary. For gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and sitafloxacin, monitor for clinical signs of theophylline toxicity. |              |              |              |              |                  |
| Warfarin                                                     | Yes/No <sup>c</sup>                                                                                                                                                                                                               | ND           | No           | No           | No           | ND               |
| mechanism                                                    | Reduced metabolism of warfarin.                                                                                                                                                                                                   |              |              |              |              |                  |
| recommendation                                               | For ciprofloxacin, monitor prothrombin time or another suitable coagulation parameter.                                                                                                                                            |              |              |              |              |                  |
| Phenytoin                                                    | Yes/No <sup>c</sup>                                                                                                                                                                                                               | ND           | ND           | ND           | ND           | ND               |
| mechanism                                                    | Reduced metabolism of phenytoin.                                                                                                                                                                                                  |              |              |              |              |                  |
| recommendation                                               | For ciprofloxacin, monitor phenytoin levels.                                                                                                                                                                                      |              |              |              |              |                  |
| Probenecid                                                   | Yes                                                                                                                                                                                                                               | Yes          | ND           | Yes          | No           | ND               |
| mechanism                                                    | Blocks proximal tubular secretion of anionic compounds, resulting in decreased clearance and potentially increased half-life and bioavailability of fluoroquinolones that undergo tubular secretion.                              |              |              |              |              |                  |
| recommendation                                               | Interactions unlikely to be clinically significant unless presence of concurrent renal impairment. Monitor for signs of toxicity if this is an issue.                                                                             |              |              |              |              |                  |

a Adapted from references. <sup>[31,205,212,218,220,232,392-410]</sup>

b Theoretical interaction, not yet documented by studies.

c Interaction has been reported rarely.

ND = no data.

have reported no interactions with the concomitant administration of calcium carbonate.<sup>[395,400]</sup>

## 9.2 Theophylline

The fluoroquinolone agents have varying effects on hepatic microsomal enzymes, affecting theophylline and other such agents primarily eliminated via this route. The primary metabolism of theophylline by the cytochrome P450 (CYP) 1A2 isozyme is inhibited by ciprofloxacin, leading to corresponding increases in theophylline concentrations. Concomitant use of ciprofloxacin with theophylline increases in the  $C_{\max}$  and AUC (17% and 22%, respectively) of theophylline.<sup>[394]</sup> Clinically significant changes in theophylline pharmacokinetics have not been observed when co-administered with gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin or sitafloxacin.<sup>[394,396,398,401,407,410]</sup> Nevertheless, patients receiving both agents should still be monitored for signs of theophylline toxicity.

## 9.3 Warfarin

Coadministration of ciprofloxacin with warfarin has resulted in potentiated anticoagulation, primarily in elderly patients, because of decreased warfarin metabolism.<sup>[393]</sup> Administration of gemifloxacin, moxifloxacin and levofloxacin with warfarin have not shown significant alterations in the pharmacokinetics or pharmacodynamic effects of warfarin.<sup>[399,402,409]</sup> Although specific drug interaction studies of gatifloxacin and warfarin were not identified, pooled data from over 3000 patients who received gatifloxacin have not demonstrated interactions with hepatic enzymes.<sup>[362]</sup>

## 9.4 Digoxin

Although no documented interactions have been observed with the use of digoxin and fluoroquinolone agents, because digoxin has such a narrow therapeutic index, it has been studied with most of these new agents for interactions. No significant interactions have been demonstrated between digoxin and gemifloxacin, levofloxacin or

moxifloxacin, and there is no necessity for dosage alterations.<sup>[232,414,415]</sup> Once daily administration of gatifloxacin 40mg for 7 days caused increases in the steady-state  $C_{\max}$  and AUC of digoxin of 12% and 19%, respectively.<sup>[416]</sup> This was not sufficient to cause any adverse effects, meaningful changes in laboratory tests, or warrant recommendations for dosage adjustments when the two agents are used together.<sup>[416]</sup>

## 10. Pharmacoeconomic Considerations

The annual healthcare costs of respiratory tract infections are generally considered enormous, based on the high incidence of these infections and the potential for treatment failures requiring further therapy or hospitalisation. The cost of community-acquired pneumonia is estimated to be \$US8 billion per annum in the US. Currently, there is a complete lack of published pharmacoeconomic studies assessing the new fluoroquinolone agents, namely gatifloxacin, gemifloxacin and moxifloxacin, in respiratory tract infections. For a valid cost-analysis evaluation drug acquisition costs, methods of administration, convenience of administration, laboratory monitoring costs, costs from adverse drug reactions and drug interactions, and cost of treatment failures must all be considered. An analysis of economic outcomes in patients with acute bacterial exacerbations of chronic bronchitis suggests antibacterial efficacy is a major determinant of cost as it relates to the potential reduction in hospitalisation.<sup>[417]</sup> Noncompliance was identified as another important determinant of cost, as it predisposed patients to therapeutic failure, which was associated with high overall costs.<sup>[417]</sup> The acquisition cost of the agent was identified as one of the more minor determinants of overall cost.<sup>[417]</sup> Other factors that may be considered include loss of productivity, quality of life, outpatient resources and out-of-pocket expenses.

The new fluoroquinolones can be administered once daily, which increases the level of compliance associated with their use, and therefore helps minimise the occurrence of treatment failures. The availability of these agents in oral dosage form of-

fers the option of employing outpatient treatment in some situations where patients may have traditionally received inpatient intravenous therapy, and also reduces the risks associated with parenteral therapy. Since hospitalisation is a major contributor to the cost of the management of patients with community-acquired pneumonia, strategies to promote outpatient therapy and decrease the length of hospitalisation would result in significant savings.<sup>[418-420]</sup> The broad spectrum of activity displayed by the new fluoroquinolones and successful *in vivo* efficacy in the treatment of respiratory tract infections has the potential to lower both direct (physician visits) and indirect (loss of work) costs of infection, as well as reduce the incidence of treatment failures. In addition, the availability of agents with a potent spectrum of activity and excellent bioavailability promotes the conversion from intravenous to oral therapy thus promoting early discharge.

Grossman and colleagues<sup>[421]</sup> examined the pharmacoeconomic impact of the use of ciprofloxacin in acute exacerbations (at least four exacerbations per year) of chronic bronchitis compared with traditional therapy. Although not statistically significant there were trends favouring the use of ciprofloxacin over traditional agents with respect to quality of life.

In a study evaluating the impact of a critical pathway with levofloxacin as the main antibacterial compared with hospitals using nonpathway standard therapy, the use of the critical pathway and monotherapy with levofloxacin resulted in significant savings from a institutional, societal and governmental perspective.<sup>[422]</sup> Although further research is required, preliminary data suggests that use of the new fluoroquinolones may be associated with a reduction in mortality.<sup>[423]</sup> It is clear that fluoroquinolones offer potent broad spectrum activity against many respiratory pathogens. As the use of fluoroquinolones increases, data with respect to outcome and mortality will evolve.

## 11. Conclusions

The new fluoroquinolones offer several advantages over ciprofloxacin in the treatment of community-acquired respiratory infections. Their broad spectrum of activity against respiratory pathogens which includes resistant strains, favourable pharmacokinetics, excellent bacteriological and clinical efficacy as well as safety are leading to growing use in the empirical treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute sinusitis. Prudent use of these agents is required to minimise the development of resistance.

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