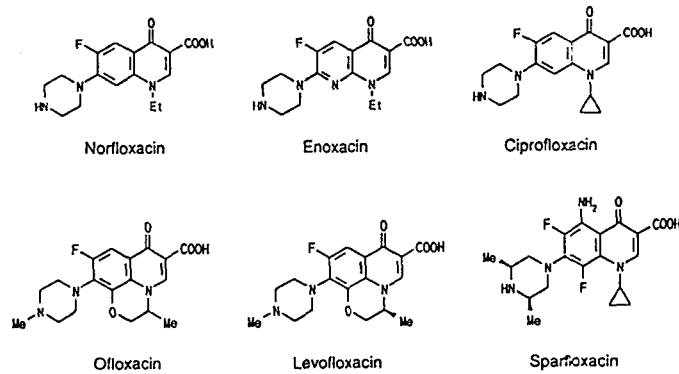


Antibacterial properties of quinolones

Hiroaki Yoshida, Dainippon Pharmaceutical Co., Ltd.

New quinolones generally have a broad antibacterial spectrum against gram-positive, gram-negative, glucose-nonfermenting and anaerobic bacteria. Some of newly developed quinolones have potent activities against *S. aureus* including MRSA, *S. pneumoniae* including PRSP, *B. fragilis*, chlamydiae, mycoplasmas and mycobacteria as well, and show good activities against various strains resistant to antibacterial agents of other classes. Quinolones display postantibiotic effects *in vitro* and are bactericidal at concentrations similar to or twice that of the minimum inhibitory concentrations (MICs) for susceptible pathogens. In experimental murine infection models including systemic infections with various pathogens such as *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *E. coli* and *P. aeruginosa*, quinolones have shown good oral efficacy as well as parenteral efficacy. Good oral absorption and good tissue penetration of quinolones account for good therapeutic effects in clinical settings. The target of quinolones are two structurally related type II topoisomerases, DNA gyrase and DNA topoisomerase IV. Quinolones are shown to stabilize the ternary quinolone-gyrase-DNA complex and inhibit the religation of the cleaved double-stranded DNA. Bacteria can acquire resistance to quinolones by mutations of these target enzymes. Mutation sites and amino acid changes in DNA gyrase and DNA topoisomerase IV are similar in the organisms examined, suggesting that the mechanism of quinolone resistance in the target enzymes is essentially the same among various organisms. Quinolones act on both the target enzymes to different degrees depending on the organisms or agents tested, and bacteria become highly resistant to quinolones in a step-wise fashion. Incomplete cross-resistance among quinolones in some strains of *E. coli* and *S. aureus* suggests the possibility of finding quinolones active against quinolone-resistant strains which are prevailing now. To find such quinolones, the potency toward two target enzymes and the membrane permeability including influx and/or efflux systems should be taken into account.

Chemical structures of various quinolones



Properties of new quinolones

1. Broad and potent antibacterial activity
2. Bactericidal activity
3. Good oral absorption
4. Applicability to systemic infection
 - Stability to metabolism
 - Good tissue distribution
5. No cross-resistance with other antibacterial agents of other classes
6. Incomplete cross-resistance with old quinolones
7. Absence of transmissible resistance

Antibacterial spectra of quinolones

- Gram-negative bacteria -

Organism	MIC (μ g/ml)				
	Sparfloxacin	Ciprofloxacin	Ofloxacin	Enoxacin	Norfloxacin
<i>E. coli</i> NIHJ JC-2	0.0125	0.0063	0.05	0.1	0.1
<i>E. coli</i> P-5101	0.0125	0.0063	0.05	0.05	0.05
<i>S. typhimurium</i> S-9	0.0125	0.0063	0.025	0.1	0.05
<i>S. typhi</i> 901	0.0063	0.0063	0.05	0.1	0.05
<i>S. pratyphi</i>	0.0125	0.0063	0.05	0.1	0.05
<i>S. schottmuelleri</i> 8006	0.0125	0.0031	0.025	0.05	0.05
<i>S. enteritidis</i> 1891	0.0063	0.0031	0.025	0.05	0.05
<i>S. flexneri</i> 2a EW10	0.0125	0.0125	0.05	0.1	0.1
<i>S. sonnei</i> EW33	0.0063	0.0031	0.025	0.05	0.05
<i>Y. enterocolitica</i> MY-79	0.025	0.0125	0.1	0.1	0.1
<i>V. parahaemolyticus</i> S-1	0.1	0.05	0.2	0.2	0.2
<i>M. morgani</i> IFO 3848	0.0125	0.0063	0.025	0.05	0.05
<i>P. vulgaris</i> OX-19	0.05	0.0125	0.05	0.1	0.1
<i>P. mirabilis</i> IFO 3849-4	0.78	0.1	0.39	0.78	0.1
<i>P. rettgeri</i> IFO 3850	0.05	0.025	0.2	0.2	0.1
<i>P. inconstans</i> P-5415	0.025	0.0063	0.025	0.1	0.1
<i>K. pneumoniae</i> PCI602	0.0031	0.0016	0.0125	0.1	0.1
<i>K. pneumoniae</i> P-5709	0.025	0.025	0.1	0.2	0.1
<i>K. oxytoca</i> P-5708	0.025	0.0125	0.1	0.1	0.1
<i>E. aerogenes</i> ATCC 13048	0.05	0.0125	0.1	0.1	0.2
<i>E. cloacae</i> 963	0.05	0.0125	0.1	0.2	0.2
<i>C. freundii</i> P-6802	0.025	0.0125	0.1	0.1	0.1
<i>C. freundii</i> P-6801	0.025	0.0125	0.1	0.1	0.1
<i>S. marcescens</i> IFO 3736	0.39	0.05	0.2	0.2	0.2
<i>S. marcescens</i> S-9	0.2	0.05	0.2	0.2	0.2
<i>P. aeruginosa</i> IFO 3445	0.39	0.2	1.56	1.56	0.78
<i>P. aeruginosa</i> 12	0.39	0.1	0.78	0.78	0.78
Geometric mean	0.032	0.0135	0.0812	0.132	0.108

Antibacterial spectra of quinolones

- Gram-positive bacteria -

Organism	MIC (μ g/ml)				
	Sparfloxacin	Ciprofloxacin	Ofloxacin	Enoxacin	Norfloxacin
<i>S. aureus</i> 209P JC-1	0.05	0.1	0.2	0.39	0.39
<i>S. aureus</i> Terajima	0.025	0.2	0.2	0.39	0.78
<i>S. aureus</i> Smith	0.05	0.2	0.2	0.78	0.78
<i>S. aureus</i> 50774	0.05	0.2	0.2	0.39	0.78
<i>S. aureus</i> 80	0.025	0.39	0.2	1.56	1.56
<i>S. epidermidis</i> 8	0.05	0.1	0.2	0.39	0.78
<i>S. pyogenes</i> A65	0.39	0.2	0.39	3.13	1.56
<i>S. pyogenes</i> Cook	0.39	0.39	0.78	3.13	1.56
<i>S. pneumoniae</i> I	0.39	0.78	1.56	6.25	3.13
<i>E. faecalis</i> 2473	0.78	1.56	1.56	6.25	3.13
<i>A. pyogenes</i> C-21	0.1	0.1	0.39	0.78	0.39
<i>B. subtilis</i> PCI219	0.025	0.05	0.1	0.2	0.2
<i>L. monocytogenes</i> LI-2402	0.78	0.78	1.56	6.25	3.13
Geometric mean	0.109	0.245	0.375	1.2	1.02

Antibacterial spectra of quinolones

- Glucose-nonfermenters -

Organism	MIC (μ g/ml)				
	Sparfloxacin	Ciprofloxacin	Ofloxacin	Enoxacin	Norfloxacin
<i>P. putida</i> P-5522	1.56	0.39	6.25	3.13	3.13
<i>P. maltophilia</i> P-5523	0.2	0.78	1.56	6.25	12.5
<i>A. calcoaceticus</i> P-6901	0.02	0.2	0.39	0.78	3.13
<i>A. faecalis</i> P-7001	0.39	0.78	0.78	1.56	6.25
<i>M. bovis</i> P-7101	0.39	3.13	1.56	3.13	3.13
<i>M. lacunata</i> P-7102	0.78	6.25	6.25	12.5	25
<i>Flavobacterium</i> sp P-7201	0.05	0.39	0.39	1.56	3.13
<i>B. abortus</i> Kusayanagi	0.78	3.13	3.13	6.25	12.5
Geometric mean	0.276	1.02	1.56	3.12	6.25

Antibacterial spectra of quinolones

- Anaerobes -

Organism	MIC (μ g/ml)				
	Sparfloxacin	Ciprofloxacin	Ofloxacin	Enoxacin	Norfloxacin
<i>S. intermedius</i> 17408	1.56	3.13	6.25	25	25
<i>P. asaccharolyticus</i> GAI 0290	0.2	3.13	12.5	6.25	12.5
<i>P. saccharolyticus</i> ATCC 13953	0.39	0.39	0.78	1.56	1.56
<i>P. parvulus</i> VPI 0546	0.39	0.78	1.56	12.5	3.13
<i>C. perfringens</i> ATCC 13123	0.2	0.39	0.78	3.13	1.56
<i>E. limosum</i> ATCC 8486	0.78	1.56	3.13	12.5	6.25
<i>E. aerofaciens</i> ATCC 25966	0.39	1.56	1.56	12.5	6.25
<i>P. acnes</i> ATCC 11827	0.39	1.56	1.56	12.5	6.25
<i>P. granulosum</i> ATCC 25564	0.2	0.78	0.39	6.25	3.13
<i>B. fragilis</i> ATCC 25285	0.78	6.25	1.56	12.5	25
<i>B. vulgatus</i> ATCC 29327	0.78	25	3.13	25	100
<i>B. thetaiotaomicron</i> WAL 3304	1.56	12.5	6.25	25	>100
<i>B. distasonis</i> GM 7007	3.13	25	12.5	25	>100
<i>F. varium</i> ATCC 8501	6.25	12.5	12.5	50	100
<i>F. varium</i> B 1083	12.5	12.5	12.5	50	50
<i>F. mortiferum</i> GAI 0341	12.5	12.5	12.5	50	50
<i>F. mortiferum</i> ATCC 9817	12.5	12.5	12.5	50	50
<i>F. nucleatum</i> GAI 0476	1.56	3.13	3.13	12.5	50
Geometric mean	1.15	3.64	3.51	15.2	19.1

Antibacterial spectra of quinolones

- Mycoplasma -

Organism	MIC (μ g/ml)					
	Sparfloxacin	Ciprofloxacin	Ofloxacin	Enoxacin	Norfloxacin	Erythromycin
<i>M. pneumoniae</i> Mac	0.1	0.39	0.78	3.13	3.13	0.0063
<i>M. pneumoniae</i> FH-Liu NIH	0.1	0.39	0.78	3.13	6.25	0.0063
<i>M. pneumoniae</i> ASPM 195	0.1	0.39	0.78	3.13	6.25	0.0063
<i>M. pneumoniae</i> ASPM 287	0.1	0.39	0.78	3.13	6.25	0.0063
<i>M. pneumoniae</i> ASPM 310	0.1	0.39	0.78	6.25	6.25	0.0063
<i>M. pneumoniae</i> ASPM 557	0.1	0.39	0.78	3.13	3.13	0.0063
<i>M. pneumoniae</i> EM 151	0.1	0.78	0.78	6.25	6.25	0.0063
<i>M. pneumoniae</i> EM 352	0.1	0.78	0.78	6.25	6.25	0.0063
<i>M. pneumoniae</i> EM 375	0.1	0.78	0.78	6.25	6.25	0.0063
<i>M. pneumoniae</i> EM 459	0.1	0.39	0.78	6.25	6.25	0.0063
<i>M. pneumoniae</i> EM 526	0.1	0.39	0.78	6.25	6.25	0.0063
<i>M. buccale</i> CH-20247	0.0125	0.39	0.39	1.56	1.56	>100
<i>M. fermentans</i> PG-18	0.0125	0.1	0.1	0.78	0.39	25
<i>M. hominis</i> PG-21	0.05	1.56	0.78	12.5	12.5	>100
<i>M. orale</i> CH-19299	0.2	1.56	1.56	6.25	12.5	>100
<i>M. salivarium</i> PG-20	0.1	3.13	6.25	25	25	>100
Geometric mean	0.0771	0.553	0.781	4.62	5.26	0.147

Antibacterial spectra of quinolones and reference antibacterial agents
- Legionella spp. -

Organism	MIC (μ g/ml)						
	Sparfloxacin	Ciprofloxacin	Olofloxacin	Enoxacin	Norfloxacin	Erythromycin	Rifampicin
<i>L. pneumophila</i> ATCC 33152	0.0125	0.05	0.05	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> ATCC 33153	0.0125	0.025	0.025	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> ATCC 33154	0.0125	0.025	0.025	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> ATCC 33155	0.0125	0.025	0.025	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> ATCC 33156	0.05	0.05	0.05	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> ATCC 33215	0.0125	0.05	0.05	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> ATCC 33216	0.05	0.05	0.05	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> Mr. Livero	0.0125	0.025	0.05	0.2	0.1	1.56	≤ 0.003
<i>L. pneumophila</i> B1-163	0.0063	0.025	0.025	0.2	0.1	0.78	≤ 0.003
<i>L. pneumophila</i> B1-166	0.0125	0.025	0.025	0.2	0.1	1.56	≤ 0.003
<i>L. pneumophila</i> B2-258	0.0063	0.025	0.025	0.2	0.05	0.78	≤ 0.003
<i>L. pneumophila</i> B4-281	0.0125	0.025	0.05	0.2	0.1	0.39	≤ 0.003
<i>L. pneumophila</i> B5-1	0.0125	0.025	0.025	0.2	0.1	0.39	≤ 0.003
<i>L. pneumophila</i> B6-8	0.0125	0.025	0.025	0.2	0.05	0.2	≤ 0.003
<i>L. bozemanii</i> ATCC 33217	0.025	0.0125	0.0125	0.2	0.05	0.78	≤ 0.003
<i>L. micdadei</i> ATCC 33218	0.0125	0.0125	0.05	0.2	0.05	3.13	≤ 0.003
<i>L. micdadei</i> B6-11	0.0125	0.0125	0.05	0.2	0.05	3.13	≤ 0.003
<i>L. dumoffii</i> ATCC 33279	0.05	0.025	0.05	0.2	0.1	0.78	≤ 0.003
Geometric mean	0.015	0.026	0.034	0.2	0.086	0.88	≤ 0.003

Antibacterial spectra of quinolones and reference antibacterial agents
- Chlamydia spp. -

Organism	MIC (μ g/ml)						
	Sparfloxacin	Ciprofloxacin	Olofloxacin	Enoxacin	Erythromycin	Minocycline	
<i>C. trachomatis</i> G/ur 931	0.063	1	1	8	0.13	0.016	
<i>C. trachomatis</i> G/ur 1242	0.063	1	1	4	0.13	0.031	
<i>C. trachomatis</i> G/ur 1317	0.063	2	1	8	0.13	0.031	
<i>C. trachomatis</i> G/ur 1448	0.063	1	1	4	0.13	0.031	
<i>C. trachomatis</i> G/ur 1467	0.063	1	1	8	0.063	0.016	
<i>C. trachomatis</i> G/ur 1481	0.063	1	0.5	4	0.063	0.016	
<i>C. trachomatis</i> G/ur 1483	0.063	1	1	8	0.13	0.016	
<i>C. trachomatis</i> G/ur 1488	0.063	1	1	8	0.13	0.016	
<i>C. psittaci</i> MP	0.031	1	0.5	8	0.13	0.031	
<i>C. psittaci</i> Izawa	0.031	1	1	8	0.13	0.031	
<i>C. psittaci</i> Nose	0.031	1	0.5	8	0.13	0.031	
Geometric mean	0.052	1.1	0.83	6.6	0.11	0.023	

Antibacterial spectra of quinolones
- Mycobacterium tuberculosis -

Organism	MIC (μ g/ml)		
	M. tuberculosis	M. tuberculosis	M. tuberculosis
	H37Rv	Kurono	H37Rv 3-R
Sparfloxacin	0.1	0.1	0.1
Ciprofloxacin	0.3	0.3	0.3
Olofloxacin	1	1	1
Enoxacin	3	3	3
Norfloxacin	3	3	3
Isoniazid	0.03	0.03	>30
p-aminosalicylic acid	0.1	0.1	100
Ethambutol	3	3	3
Streptomycin	3	3	>100
Kanamycin	1	0.3	1
Rifampicin	0.1	0.1	0.1

Antibacterial spectra of quinolones and reference antibacterial agents
- Nontuberculous Mycobacterium spp. -

Compound	MIC (μ g/ml)				
	Mycobacterium intracellulare			Mycobacterium fortuitum	
	ATCC 15985	P-23-7	Tasaka	Yano	Toneyama
Sparfloxacin	0.1	0.3	0.3	0.3	0.3
Ciprofloxacin	0.1	0.3	0.3	0.3	1
Olofloxacin	0.3	1	3	0.3	0.3
Enoxacin	1	3	3	1	3
Norfloxacin	1	1	3	1	10
Isoniazid	10	100	10	30	100
Ethambutol	1	10	10	30	>100
Streptomycin	0.3	10	3	30	30
Kanamycin	3	10	10	100	100
Rifampicin	≤ 0.01	0.1	0.1	30	100

**Antibacterial activity of some newer quinolones
to have been improved**

1. Activity against streptococci
2. Activity against *Mycoplasma pneumoniae*
3. Activity against *Chlamydia* species
4. Activity against *Mycobacterium* species

Prophylactic effect of quinolones on systemic infections in mice

Infecting organism	Drug	MIC (μ g/ml)	ED ₅₀ (mg/kg)	
			iv	po
S. aureus 50774	Sparfloxacin	0.05	0.705	1.27
	Ciprofloxacin	0.2	2.14	8.24
	Ofloxacin	0.2	2.16	5.18
	Enoxacin	0.39	5.92	9.89
	Norfloxacin	0.78	6.84	27.0
S. pyogenes A65	Sparfloxacin	0.39	3.04	3.36
	Ciprofloxacin	0.2	4.24	23.9
	Ofloxacin	0.39	6.76	10.8
	Enoxacin	1.56	23.1	86.4
	Norfloxacin	1.56	76.4	188
S. pneumoniae I Neufeld	Sparfloxacin	0.39	8.02	8.32
	Ciprofloxacin	0.78	16.7	31.3
	Ofloxacin	1.56	38.1	41.7
	Enoxacin	6.25	279	247
	Norfloxacin	3.13	184	340
E. coli P-5101	Sparfloxacin	0.0125	0.0881	0.478
	Ciprofloxacin	0.0063	0.0699	0.468
	Ofloxacin	0.05	0.249	0.749
	Enoxacin	0.05	0.426	2.15
	Norfloxacin	0.05	0.371	4.84
P. aeruginosa 12	Sparfloxacin	0.39	0.865	2.02
	Ciprofloxacin	0.1	0.366	2.78
	Ofloxacin	0.78	2.82	6.62
	Enoxacin	0.78	2.75	8.41
	Norfloxacin	0.78	2.21	17.1

Fluoroquinolone resistance prevalences for common pathogens in Japan and Korea 1992-1993

Organism	Japan (%)		Korea (%)	
	1992	1993	1992	1993
Acinetobacter spp.	9.4	8.4	34.0	41.0
Citrobacter freundii	14.9	8.0	6.0	14.0
E. coli, urinary		2.0	12.0	25.0
Enterobacter spp.	7.2	5.0	13.0	11.0
Klebsiella spp.	3.2	2.0	4.0	5.0
Providencia spp.			8.0	1.0
Pseudomonas aeruginosa	35.2	40.0	14.0	21.0
Serratia spp.	27.3	18.0		
Staphylococcus aureus	54.9	59.0		
Staphylococcus, coagulase negative	14.7	39.0		

J. Turnidge, Drugs 49(Suppl. 2)1995

Quinolone resistance mutations in bacteria

1. Mutations of target enzymes

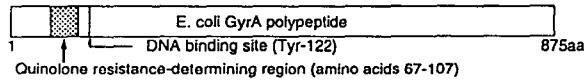
	E. coli	S. aureus
DNA gyrase	gyrA, gyrB	gyrA, gyrB
DNA topo IV	parC, parE	grlA, grlB

2. Mutations on drug accumulation

	E. coli	S. aureus
Active efflux pump	marA	nfoA
Changes of outer membrane	norB, norC	-

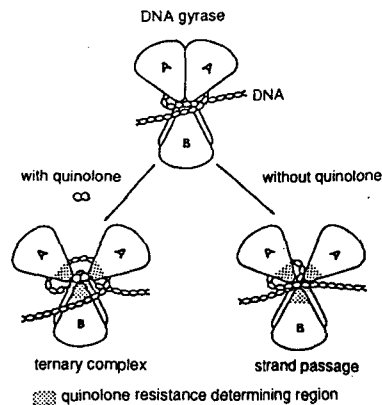
Quinolone resistance mutations in the gyrA gene of E. coli KL16

No. of strains	MIC (μ g/ml)				Mutation
	Nalidixic acid	Norfloxacin	Ciprofloxacin	Sparfloxacin	
1 (KL16)	3.13	0.05	0.0125	0.0125	wild-type
4	400	0.78	0.39	0.39	Ser-83 \rightarrow Leu
1	400	0.78	0.39	0.39	Ser-83 \rightarrow Trp
1	200	0.39	0.2	0.2	Asp-87 \rightarrow Asn
1	50	0.39	0.1	0.1	Gly-81 \rightarrow Cys
1	25	0.39	0.1	0.1	Ala-84 \rightarrow Pro
1	25	0.2	0.05	0.05	Ala-67 \rightarrow Ser
1	12.5	0.1	0.05	0.05	Gln-106 \rightarrow His



Quinolone resistance mutations in the gyrB gene of E. coli KL16

No. of strains	MIC (μ g/ml)				Mutation
	Nalidixic acid	Norfloxacin	Ciprofloxacin	Sparfloxacin	
1 (KL16)	3.13	0.05	0.0125	0.0125	wild-type
9 (type 1)	50	0.39	0.1	0.05	Asp-426 \rightarrow Asn
4 (type 2)	50	0.0125	0.0031	0.0031	Lys-447 \rightarrow Glu



Quinolone pocket model for the quinolone, DNA gyrase and DNA ternary complex formation

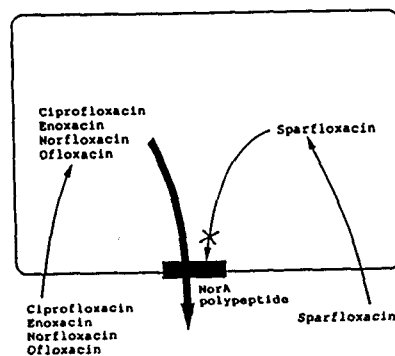
J Infect Chemother. 1995;1:16-29

Quinolone susceptibilities of *S. aureus* RN4220 transformed with the DNA topoisomerase IV

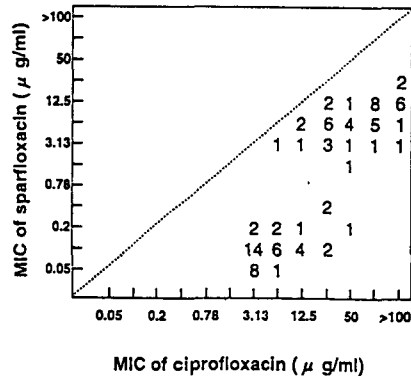
Strain	Genes on a plasmid	MIC (μ g/ml)			
		Sparfloxacin	Norfloracin	Ciprofloxacin	Oxolinic acid
<i>S. aureus</i> RN4220	-	0.1	0.78	0.39	1.56
<i>S. aureus</i> RN4220	wild-type <i>grlA</i>	0.1	0.78	0.39	1.56
<i>S. aureus</i> RN4220	mutant <i>grlA</i> (Ser80→Phe)	0.2	6.25	1.56	3.13

Quinolone susceptibilities of strains transformed with the *norA* gene

Strain	Gene on a plasmid	MIC (μ g/ml)				
		Sparfloxacin	Norfloracin	Ciprofloxacin	Ofloxacin	Oxolinic acid
<i>S. aureus</i> RN4220	-	0.1	0.78	0.39	0.39	1.56
	<i>norA</i>	0.2	50	12.5	6.25	3.13
<i>E. coli</i> HB101	-	0.0016	0.025	0.0063	0.0125	0.39
	<i>norA</i>	0.0016	1.56	0.1	0.1	0.39



Susceptibilities to sparfloxacin of ciprofloxacin-resistant MRSA strains



Sequential acquisition of high levels of quinolone resistance in *S. aureus* RN4220

Strain	Selective compound	MIC (µg/ml)				Mutations			
		SPFX	CPFX	NFLX	OA	Unknown	NorA pump	Topo IV	Gyrase
RN4220	-	0.1	0.2	0.78	1.56	-	-	-	-
1st-step mutant	CPFX	0.2	1.56	6.25	3.13	Yes	-	-	-
2nd-step mutant	CPFX	0.39	6.25	25	3.13	Yes	Yes	Yes	-
3rd-step mutants	OA	0.78-25	12.5-50	50-200	50-100	Yes	Yes	Yes	Yes

SPFX, sparfloxacin; CPFX, ciprofloxacin; NFLX, norfloxacin; OA, oxolinic acid.

An expected profile of quinolones

1. Quinolones with potent activities against both DNA gyrase and DNA topoisomerase IV equally.
2. Quinolones which are hardly excreted from the bacterial cells so as to maintain the effective concentration of the drugs.
 - Quinolones with this antibacterial profile will be useful in the future clinical settings.