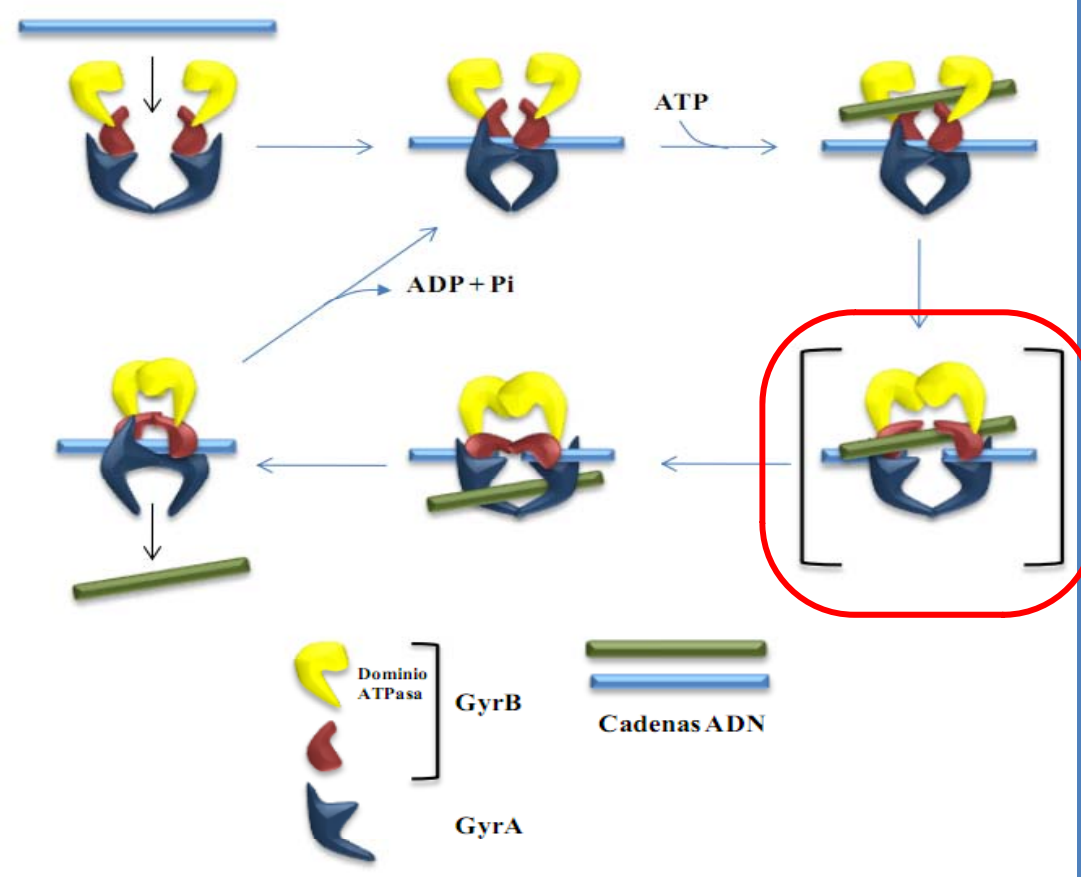
81,9(56,'$'# (#5(9,//$
)°˝°º–° ¸#¸ˇ#Ð ˇ ¸Ł˝Ł1°
' ˇø°ß–°æ ˇ1–Ł#¸ˇ#Ð Ł˝ßŁ ¸Ł‡°ŁÆÇ°

Resistencia a quinolonas transferible

José Manuel Rodríguez Martínez

Bilbao, 2012

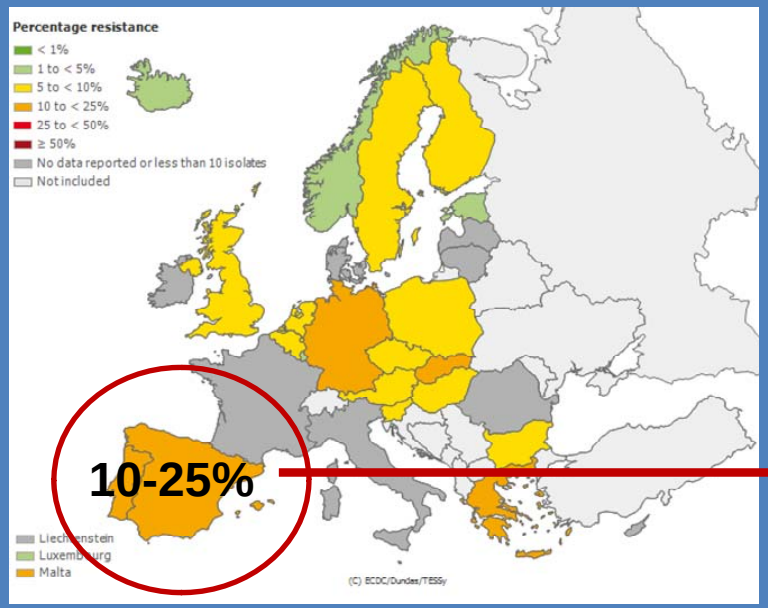
Quinolonas: mecanismo de acción



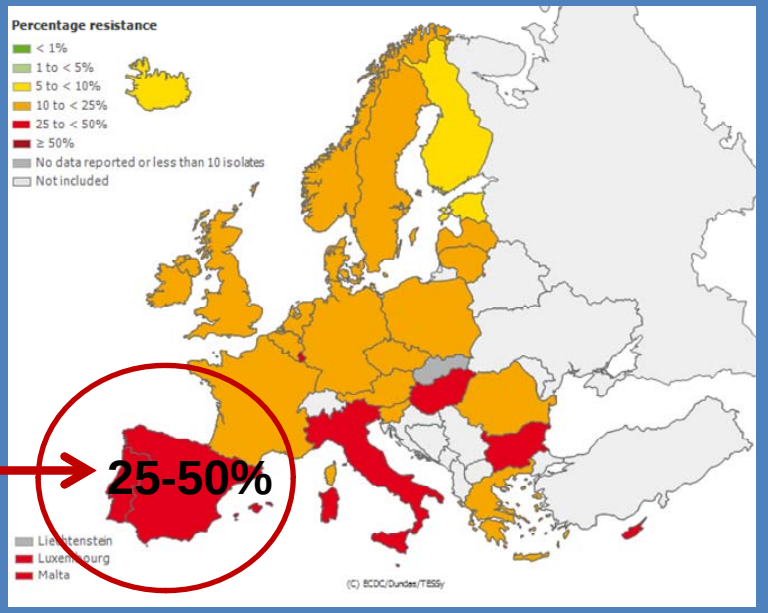
Consecuencias:

- Inhibición de la síntesis de ADN
- Activación de la respuesta SOS
- Filamentación
- Fragmentación cromosómica
- Muerte celular

Resistencia a quinolonas



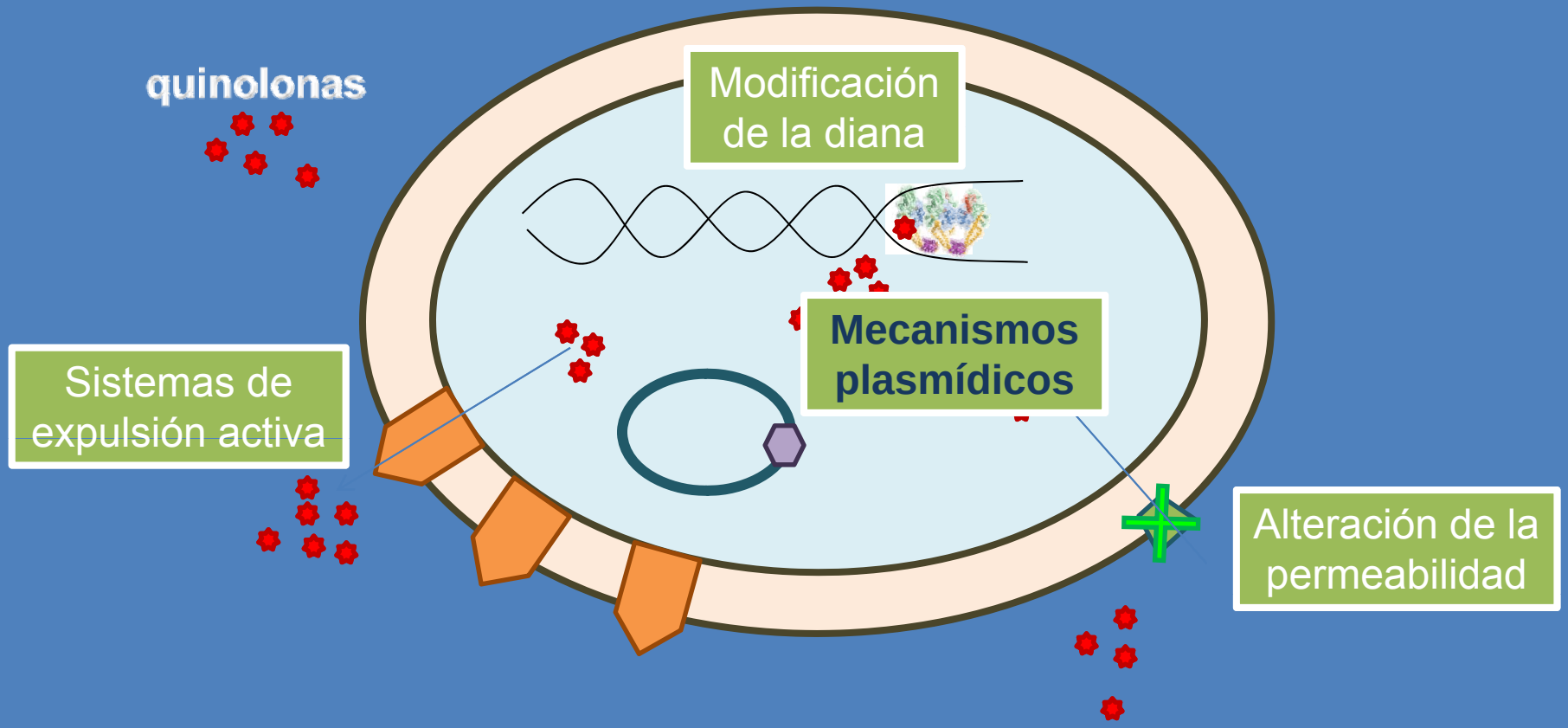
E. coli R+I FQs
2001



E. coli R+I FQs
2009

Fuente : datos 2001-2009 *European Antimicrobial Resistance Surveillance System* (http://www.earss.rivm.nl/)

Resistencia a quinolonas



Early report

Quinolone resistance from a transferable plasmid

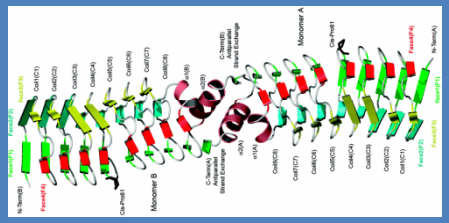
Luis Martínez-Martínez, Alvaro Pascual, George A Jacoby

Strain	*K pneumoniae*						*E coli*		*P aeruginosa*	
	C1	C1 pMG252	C2	C2 pMG252	C3	C3 pMG252	J53	J53 pMG252	PU21	PU21 pMG252
Ciprofloxacin	4	32	0·5	4	0·004	0·125	0·008	0·25	0·125	0·5
Clinafloxacin	0·5	8	0·06	0·5	0·002	0·03	0·004	0·125	0·125	0·25
Levofloxacin	8	64	0·5	4	0·03	0·06	0·03	0·5	0·5	2
Nalidixic acid	>256	>256	>256	>256	1	4	4	32	64	256
Norfloxacin	16	64	4	16	0·03	0·5	0·125	1	0·5	2
Pefloxacin mesilate	64	256	2	16	0·03	0·25	0·06	2	2	8
Sparfloxacin	4	64	0·25	4	0·015	0·5	0·015	1	0·5	8
Trovafloxacin	64	>256	1	4	0·015	0·25	0·015	1	0·5	4

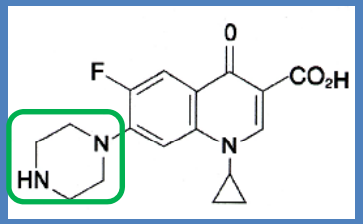
Table 1: **Quinolone resistance (MIC µg/mL) in *K pneumoniae*, *E coli*, and *P aeruginosa***

Resistencia plasmídica a quinolonas

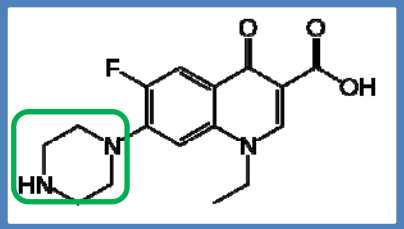
- Protección de la diana: *qnr*



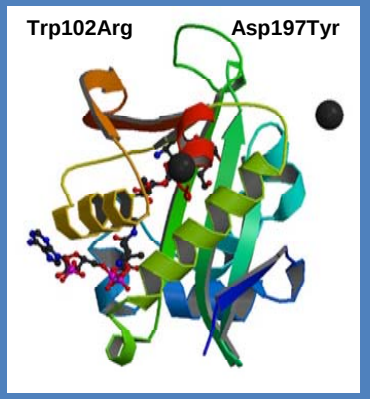
- Modificación del antimicrobiano: *aac(6')Ib-cr*



Ciprofloxacino

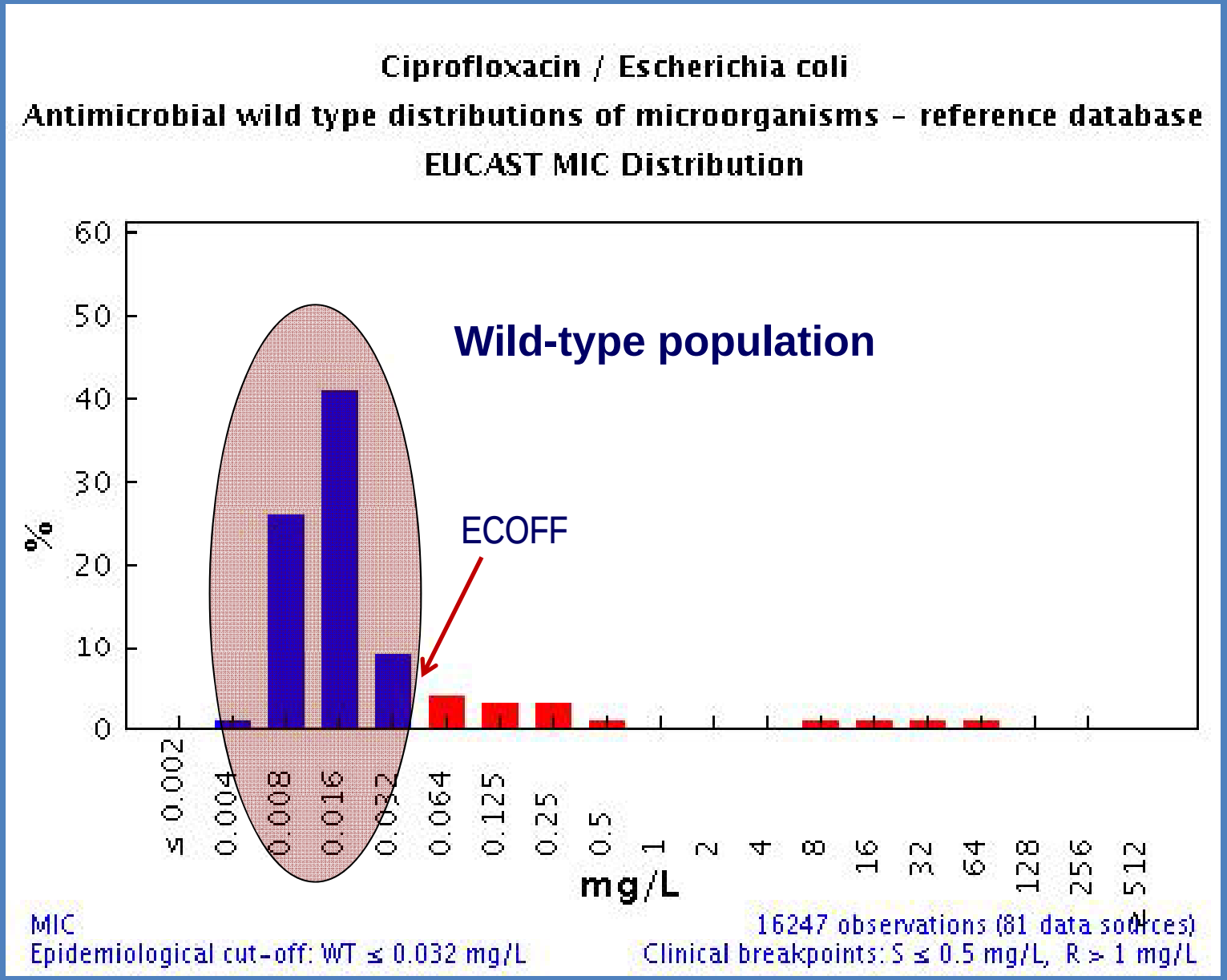


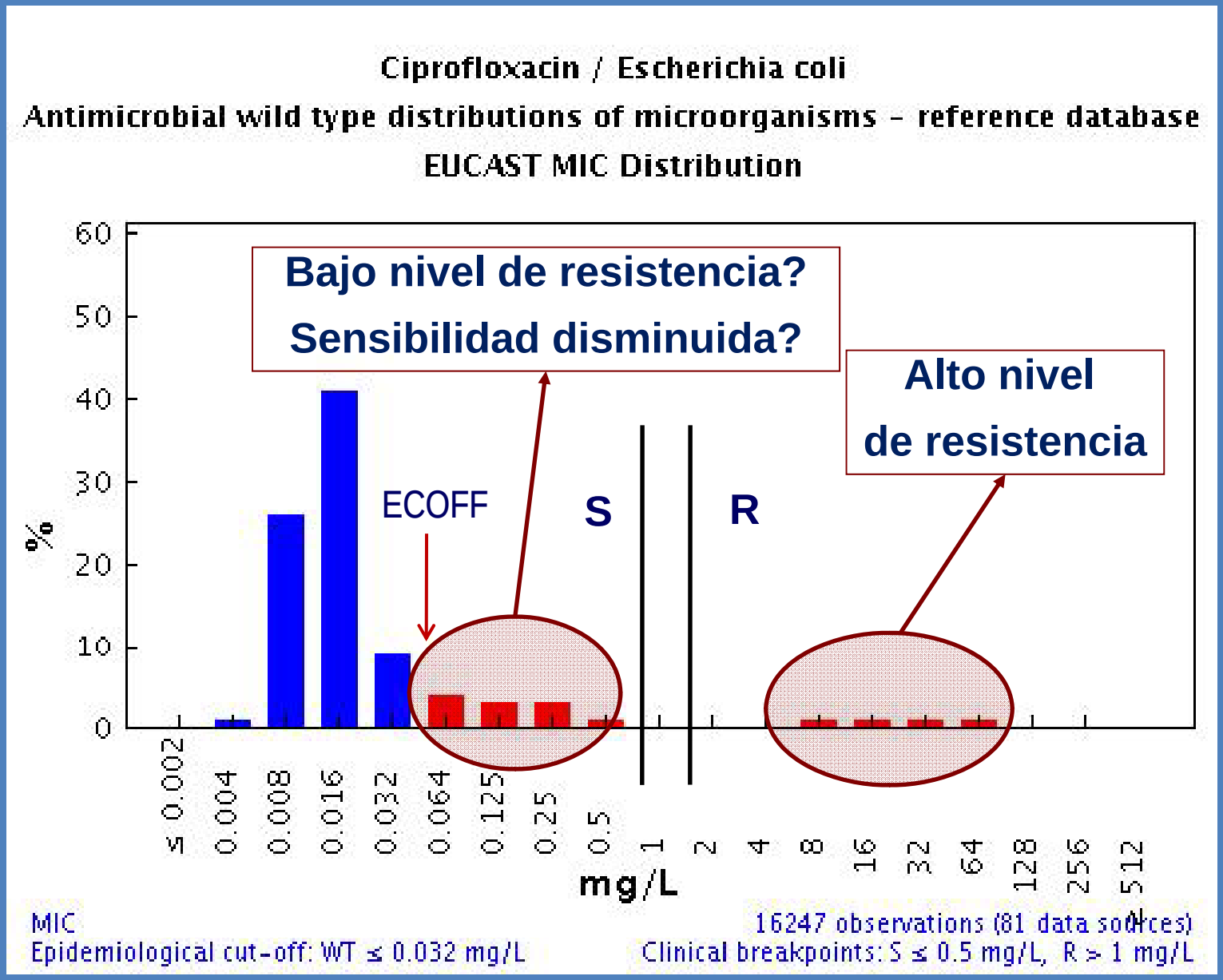
Norfloxacino



- Sistemas de expulsión:
  - QepA → MFS
  - OqxAB → RND

Mecanismos que confieren bajo nivel de resistencia a quinolonas


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST MIC Distribution
Wild-type population
ECOFF
%
mg/L
≤ 0.002
0.004
0.008
0.016
0.032
0.064
0.125
0.25
0.5
1
2
4
8
16
32
64
128
256
512
MIC
Epidemiological cut-off: WT ≤ 0.032 mg/L
16247 observations (81 data sources)
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L



www.eucast.org

Genes *qnr*

- 1998: primer gen *qnr* descrito: *qnrA1*
- A partir de 2005 se han descrito nuevas proteínas Qnr :

  QnrB (53 variantes), QnrS (6 variantes), QnrC, QnrD

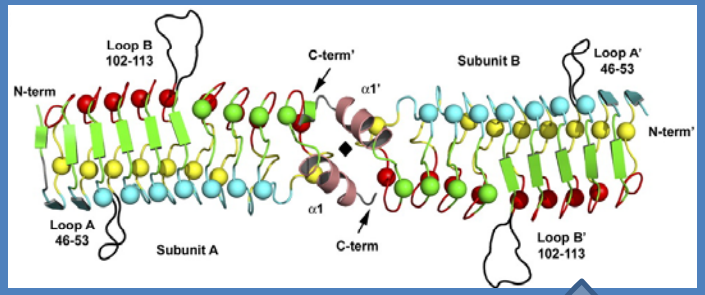
  http://www.lahey.org/qnrStudies/
- Originan una reducción de la sensibilidad a quinolonas en las cepas que los expresan
- Localizados en estructuras móviles complejas
- Asociados a otros determinantes de resistencia: principalmente betalactamasas

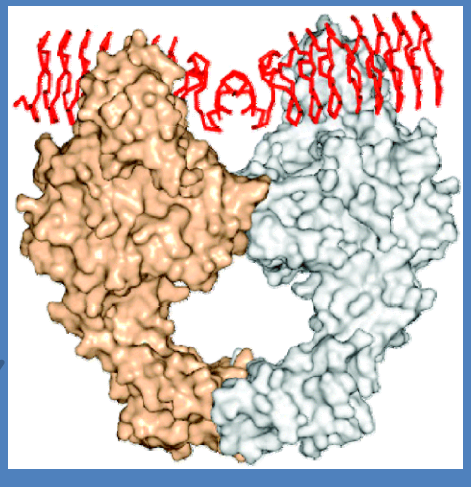
Genes *qnr*

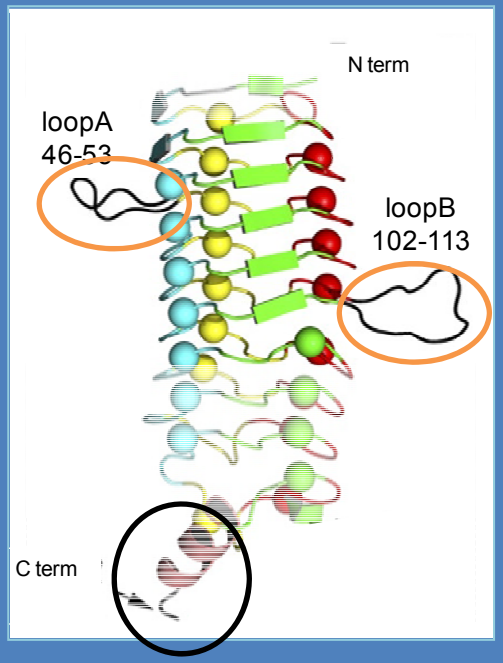
- Familia de las proteínas con repeticiones pentapeptídicas

[S,T,A,V] [D,N] [L,F] [S,T,R] [G]

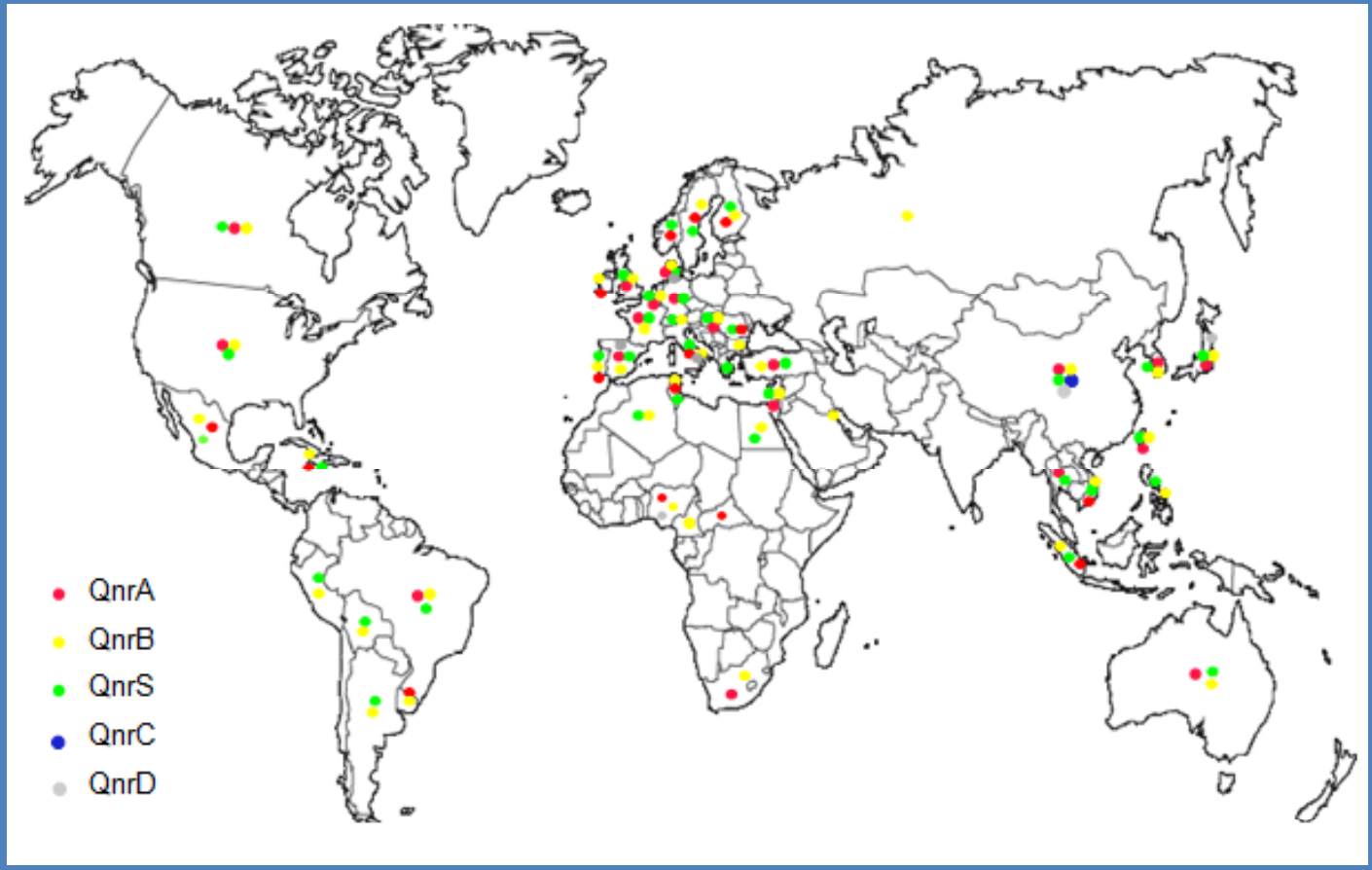
- Estructura en beta-hélice cuadrangular.
- Dímeros con características similares a la forma B del ADN.







Epidemiología



Actualizado en Septiembre de 2011

Ampliamente distribuidos

Descritos mayoritariamente en enterobacterias

Epidemiología de Qnr

- Principalmente descritos en *Enterobacteriaceae*:

Bacterial species	Prevalence of *qnr*-like genes[a]:		
	qnrA	***qnrB***	***qnrS***
E. coli	+++	++	++
K. pneumoniae	++++	++++	+++
K. oxytoca	+	+	-
E. cloacae	++++	++++	+++
E. aerogenes	+	+	-
E. sakazakii	+	-	-
C. freundii	+	++	-
C. koseri	-	+	-
C. werkmanii	-	+	-
S. marcescens	+	+	+
P. mirabilis	+	+	-
M .morganii	-	-	-
S. enterica	++	++	++++
Shigella spp.	-	-	+
Aeromomnas spp.	-	-	+
Pseudomonas spp.	-	+	-
Campylobacter spp.	-	-	-

[a] No. of published *qnr*-like positive isolates: -, 0; +, 1-10; ++, 10-50; +++, 50-100; ++++, >100.

Prevalencia:
qnrA ~ 1.5%
qnrB ~ 4.5%
qnrS ~ 2.5%

Cattoir & Nordmann, *CMC* 2009

- ✓ ***qnrC1*** **identificado en** ***Proteus mirabilis*** **en China** (Wang *et al.*, AAC 2009)
- ✓ ***qnrD1*** **identificado en** ***Salmonella*** **en China** (Cavaco *et al.*, AAC 2009)

Asociación con β-lactamasas

- ESBLs:

  - *qnrA* : SHV-2/7/12/92, CTX-M-1/9/14/15/24, VEB-1, PER-1
  - *qnrB* : TEM-52, SHV-12/30, CTX-M-3/12/14/15/24, VEB-1
  - *qnrS* : TEM-52, SHV-2/5/12, CTX-M-1/9/14/15/24

- Plasmid-mediated cephalosporinases (AmpC):

  - *qnrA* : FOX-5 (pMG252), CMY-2
  - *qnrB* : CMY-1, DHA-1 (*qnrB4*)

- Carbapenemasas (class A and B):

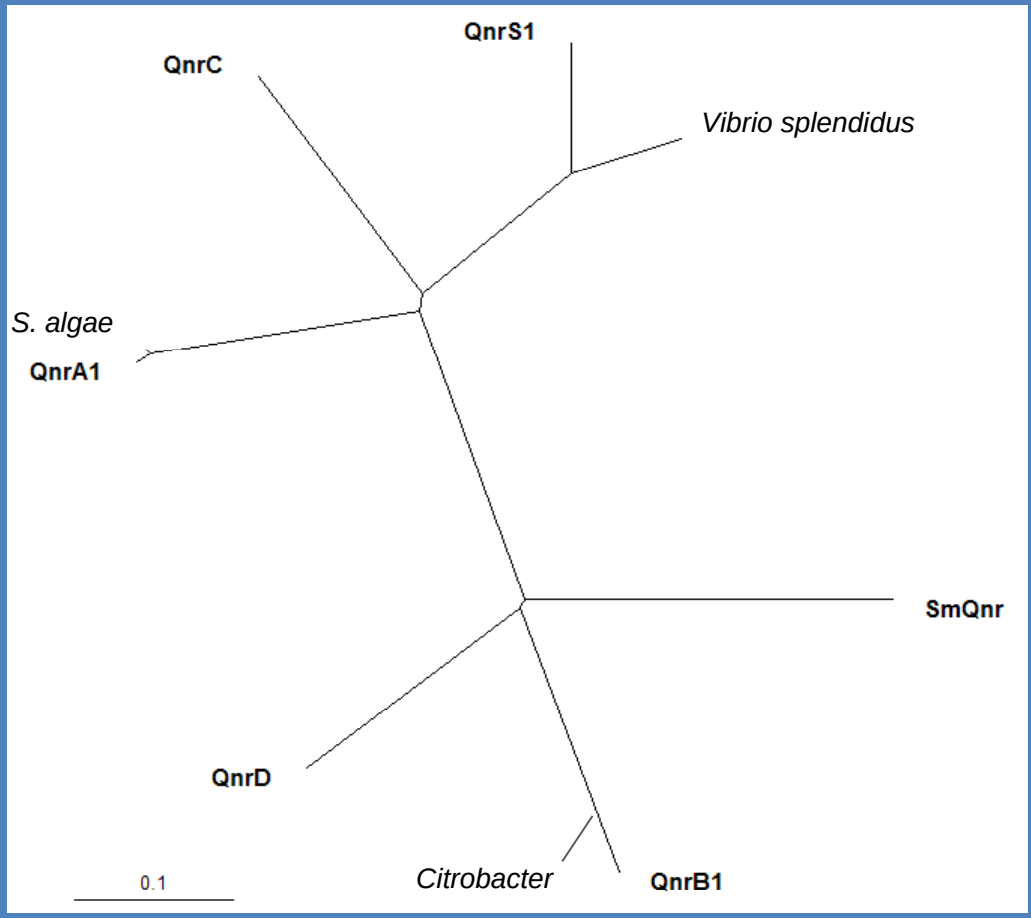
  - *qnrA* : IMP-4, KPC-3
  - *qnrB* : IMP-8, KPC-2, KPC-3
  - *qnrS* : IMP-8, VIM-1

Origen de los genes *qnr*

QnrA → *Shewanella algae*

QnrS → *Vibrio splendidus*

QnrB → *Citrobacter spp.*



Journal of Antimicrobial Chemotherapy (2008) **61**, 1240–1243
doi:10.1093/jac/dkn115
Advance Access publication 13 March 2008

JAC

Qnr-like pentapeptide repeat proteins in Gram-positive bacteria

J. M. Rodríguez-Martínez[1*], C. Velasco[1], A. Briales[2], I. García[1], M. C. Conejo[1] and A. Pascual[1,2]

Table 2. Percentage of amino acid identity between chromosome-encoded Qnr-like proteins of Gram-negative (Vibrionaceae)[9] and Gram-positive species and plasmid-mediated QnrA1, QnrB1 and QnrS1 proteins

Qnr homologue	QnrB1	QnrS1	VvQnr	VpQnr	VfQnr	PpQnr	EfsQnr	EfmQnr	LmQnr	CpQnr	CdQnr	BcQnr	BsQnr
QnrA1	40	59	58	57	65	64	**19**	**17**	**22**	**19**	**18**	**21**	**19**
QnrB1		38	39	42	41	41	18	16	21	18	19	19	16
QnrS1			52	54	62	61	17	18	18	16	16	18	21
VvQnr				67	61	59	20	14	21	16	16	18	18
VpQnr					58	58	22	15	20	16	16	21	14
VfQnr						74	19	16	23	16	16	21	20
PpQnr							20	18	20	19	16	21	20
EfsQnr								**25**	**29**	**26**	**25**	**32**	**27**
EfmQnr									27	26	21	31	24
LmQnr										27	29	27	33
CpQnr											43	33	28
CdQnr												31	29
BcQnr													31

Amino acid identities for QnrA1 and EfsQnr (compared with Gram-positive species) are indicated in bold.
VvQnr is from *Vibrio vulnificus*, VpQnr is from *Vibrio parahaemolyticus*, VfQnr is from *Vibrio fischeri* and PpQnr is from *Photobacterium profundum*.

Gram +: potencial reservorio de proteinas tipo Qnr

Journal of Antimicrobial Chemotherapy (2009) **63**, 1128–1134
doi:10.1093/jac/dkp111
Advance Access publication 8 April 2009

JAC

Mutational analysis of quinolone resistance in the plasmid-encoded pentapeptide repeat proteins QnrA, QnrB and QnrS

J. M. Rodríguez-Martínez[1]*†, A. Briales[2]†, C. Velasco[1], M. C. Conejo[1], Luis Martínez-Martínez[3,4] and A. Pascual[1,2]

[1]*Department of Microbiology, University of Seville, Seville, Spain;* [2]*Service of Microbiology, University Hospital Virgen Macarena, Seville, Spain;* [3]*Service of Microbiology, University Hospital Marqués de Valdecilla, Santander, Spain;* [4]*Department of Molecular Biology, University of Cantabria, Santander, Spain*

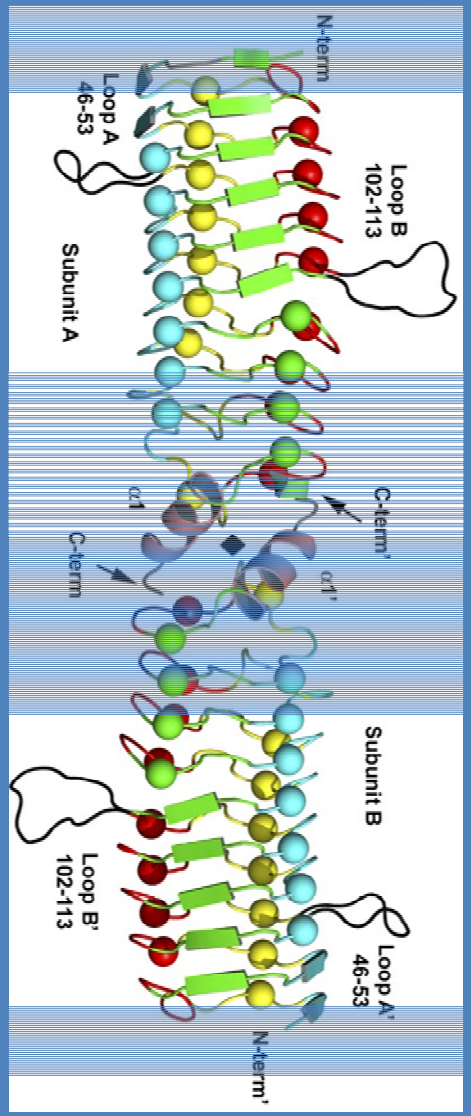
Guo *et al. BMC Structural Biology* 2010, **10**:33
http://www.biomedcentral.com/1472-6807/10/33

BMC Structural Biology

RESEARCH ARTICLE **Open Access**

A mutational analysis and molecular dynamics simulation of quinolone resistance proteins QnrA1 and QnrC from *Proteus mirabilis*

Qinglan Guo[1†], Jingwei Weng[2†], Xiaogang Xu[1], Minghua Wang[1], Xiaoying Wang[1], Xinyu Ye[1], Wenning Wang[2,3*], Minggui Wang[1,3*]



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2011, p. 1266–1269 Vol. 55, No. 3
0066-4804/11/$12.00 doi:10.1128/AAC.00927-10

In Vitro Effect of *qnrA1*, *qnrB1*, and *qnrS1* Genes on Fluoroquinolone Activity against Isogenic *Escherichia coli* Isolates with Mutations in *gyrA* and *parC*[▽]

A. Briales,[1] J. M. Rodríguez-Martínez,[1]* C. Velasco,[1] P. Díaz de Alba,[1] J. Domínguez-Herrera,[2] J. Pachón,[2] and A. Pascual[1,3]

Department of Microbiology, University of Seville,[1] Infectious Diseases Service, Biomedicine Institute of Seville (IBiS), University Hospitals Virgen del Rocío/CSIC/University of Seville,[2] and University Hospital Virgen Macarena,[3] Seville, Spain

Efecto de los genes *qnr* y/o mecanismos cromosómicos en la actividad frente a quinolonas

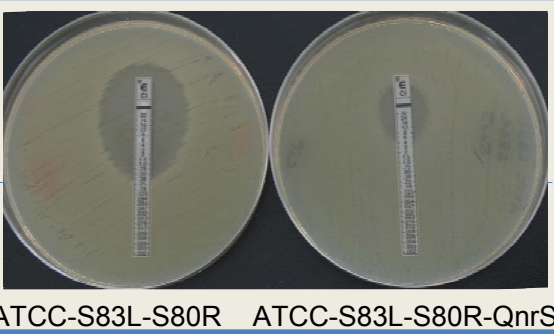
Cepa isogénica	**Mutaciones *gyrA/parC***	**Construcciones plasmídicas**
E. coli ATCC 25922	Silvestre	
E. coli ATCC/*qnrA*	Silvestre	pBK-QnrA1
E. coli ATCC/*qnrB*	Silvestre	pBK-QnrB1
E. coli ATCC/*qnrS*	Silvestre	pBK-QnrS1
E. coli ATCC 25922-S83L	GyrA Ser83Leu	
E. coli ATCC-S83L/*qnrA*	GyrA Ser83Leu	pBK-QnrA1
E. coli ATCC-S83L/q*nrB*	GyrA Ser83Leu	pBK-QnrB1
E. coli ATCC-S83L/*qnrS*	GyrA Ser83Leu	pBK-QnrS1
E. coli ATCC 25922-S80R	ParC Ser80Arg	
E. coli ATCC-S80R/*qnrA*	ParC Ser80Arg	pBK-QnrA1
E. coli ATCC-S80R/*qnrB*	ParC Ser80Arg	pBK-QnrB1
E. coli ATCC-S80R/*qnrS*	ParC Ser80Arg	pBK-QnrS1
E. coli ATCC 25922-S83L-S80R	GyrA Ser83Leu, ParC Ser80Arg	
E. coli ATCC-S83L-S80R/*qnrA*	GyrA Ser83Leu, ParC Ser80Arg	pBK-QnrA1
E. coli ATCC-S83L-S80R/*qnrB*	GyrA Ser83Leu, ParC Ser80Arg	pBK-QnrB1
E. coli ATCC-S83L-S80R/*qnrS*	GyrA Ser83Leu, ParC Ser80Arg	pBK-QnrS1

Efecto de los genes *qnr* y/o mecanismos cromosómicos en la actividad frente a quinolonas

Efecto sobre la CMI en distintas cepas isogénicas de *E. coli*

La presencia de genes *qnr* aumenta los valores de CMI en todos los fondos genéticos

Cepa *E. coli*	CMI (µg/ml)			
	CIP	LVX	MXF	NFX
ATCC 25922	0.002	0.008	0.008	0.015
ATCC-QnrA	0.125	0.5	0.25	0.5
ATCC-QnrB	0.125	0.125	0.25	0.25
ATCC-QnrS	0.125	0.5	0.25	0.5
ATCC-S83L	0.125	0.125	0.06	0.125
ATCC-S83L-QnrA	0.5	0.5	0.5	2
ATCC-S83L-QnrB	0.5	0.25	0.5	1
ATCC-S83L-QnrS	1	1	1	2
ATCC-S80R	0.004	0.008	0.008	0.03
ATCC-S80R-QnrA	0.25	0.25	0.5	0.5
ATCC-S80R -QnrB	0.125	0.25	0.5	0.5
ATCC-S80R -QnrS	0.125	0.25	0.25	0.5
ATCC-S83L-S80R	0.25	0.25	0.25	2
ATCC-S83L-S80R -QnrA	2	2	2	8
ATCC-S83L-S80R -QnrB	1	1	1	4
ATCC-S83L-S80R -QnrS	2	4	2	8



Efecto de los genes *qnr* y/o mecanismos cromosómicos en la actividad frente a quinolonas

J Antimicrob Chemother 2011; **66:** 1405–1413
doi:10.1093/jac/dkr117
Advance Access publication 21 March 2011

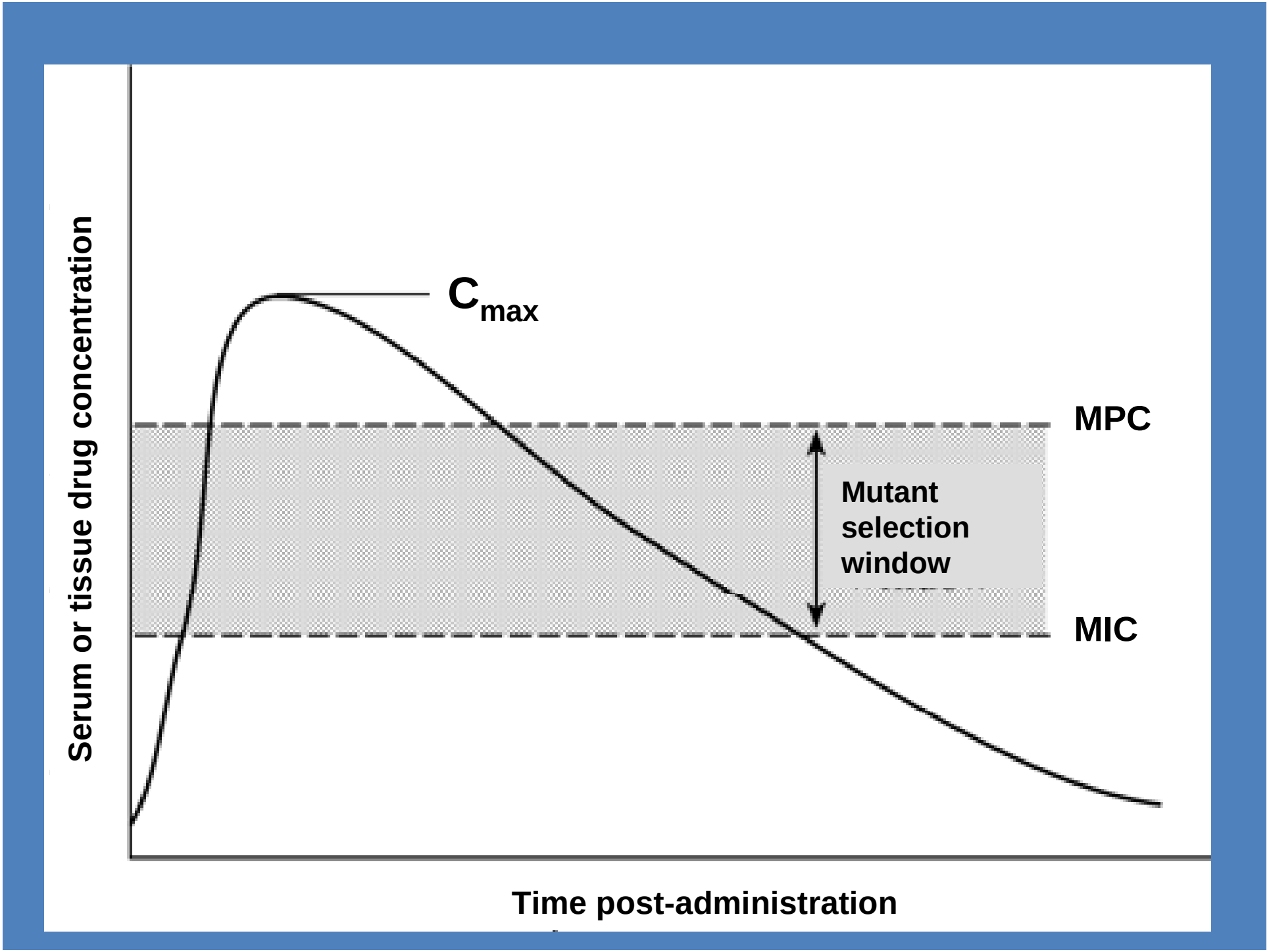
Discrepancies in fluoroquinolone clinical categories between the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and CLSI for *Escherichia coli* harbouring *qnr* genes and mutations in *gyrA* and *parC*

Jose M. Rodríguez-Martínez[1]*, Alejandra Briales[1], Carmen Velasco[1], Paula Díaz de Alba[1], Luis Martínez-Martínez[2,3] and Alvaro Pascual[1,4]

	CLSI			EUCAST	
	S	I	R	S	R
CIP	≤1	2	≥4	≤0.5	≥1
LVX	≤2	4	≥8	≤1	≥2
MXF	ND	ND	ND	≤0.5	≥1
NFX	≤4	8	≥16	≤0.5	≥1

Table 1. Comparison of fluoroquinolone MIC values (in mg/L) and clinical categories of bacterial strains according to CLSI and EUCAST guidelines

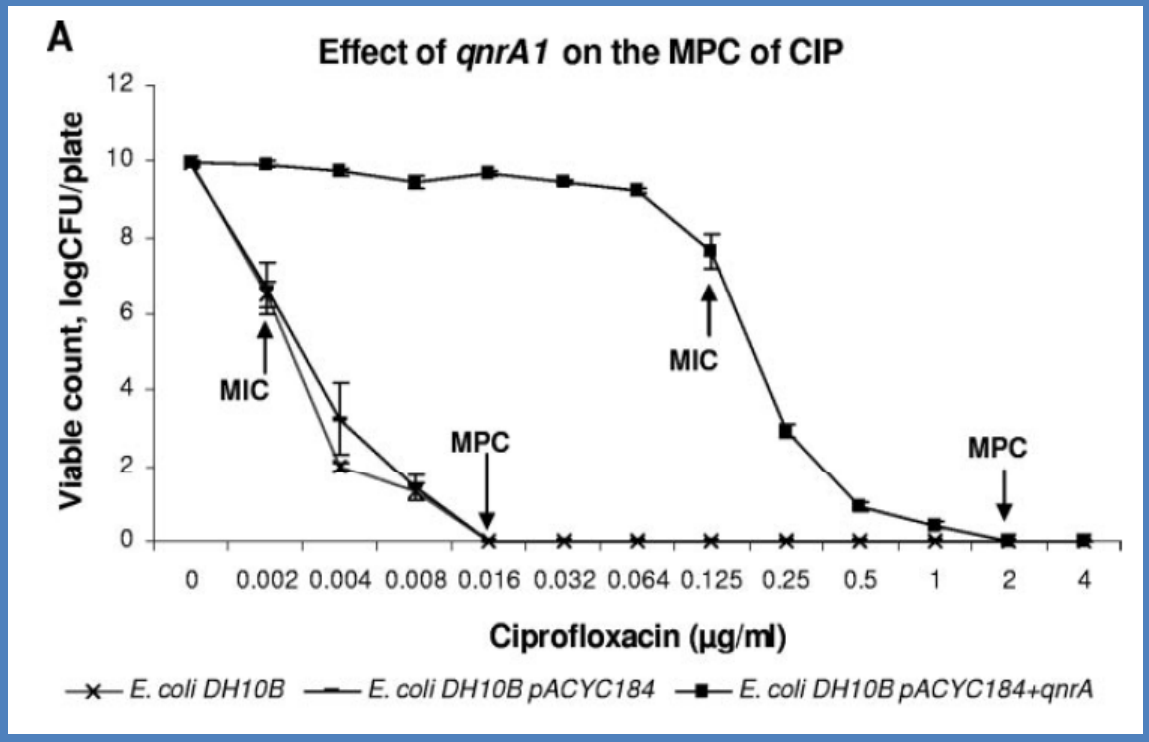
			MIC/CLSI/EUCAST[a,b,c]			
Strain	Relevant features	PMQR genes	CIP	LVX	MXF	NOR
E. coli ATCC 25922	wild-type	none	0.002/S/S	0.008/S/S	0.008/S/S	0.015/S/S
E. coli ATCC/*qnrA*	wild-type	pBK-QnrA1	0.125/S/S	0.5/S/S	0.25/S/S	0.5/S/S
E. coli ATCC/*qnrB*	wild-type	pBK-QnrB1	0.125/S/S	0.125/S/S	0.25/S/S	0.25/S/S
E. coli ATCC/*qnrS*	wild-type	pBK-QnrS1	0.125/S/S	0.5/S/S	0.25/S/S	0.5/S/S
E. coli ATCC 25922-S83L	GyrA Ser83Leu	none	0.125/S/S	0.125/S/S	0.06/S/S	0.125/S/S
E. coli ATCC-S83L/*qnrA*	GyrA Ser83Leu	pBK-QnrA1	0.5/S/S	0.5/S/S	0.5/S/S	**2/S/R**
E. coli ATCC-S83L/*qnrB*	GyrA Ser83Leu	pBK-QnrB1	0.5/S/S	0.25/S/S	0.5/S/S	**1/S/R**
E. coli ATCC-S83L/*qnrS*	GyrA Ser83Leu	pBK-QnrS1	**1/S/R**	1/S/S	**1/S/R**	**2/S/R**
E. coli ATCC 25922-S83L-S80R	GyrA Ser83Leu, ParC Ser80Arg	none	0.25/S/S	0.25/S/S	0.25/S/S	**2/S/R**
E. coli ATCC-S83L-S80R/*qnrA*	GyrA Ser83Leu, ParC Ser80Arg	pBK-QnrA1	**2/I/R**	**2/S/R**	**2/I/R**	**8/I/R**
E. coli ATCC-S83L-S80R/*qnrB*	GyrA Ser83Leu, ParC Ser80Arg	pBK-QnrB1	**1/S/R**	1/S/S	**1/S/R**	**4/S/R**
E. coli ATCC-S83L-S80R/*qnrS*	GyrA Ser83Leu, ParC Ser80Arg	pBK-QnrS1	**2/I/R**	**4/I/R**	**2/I/R**	**8/I/R**


Serum or tissue drug concentration
C_{max}
MPC
Mutant selection window
MIC
Time post-administration

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2007, p. 2236–2239 Vo
0066-4804/07/$08.00+0 doi:10.1128/AAC.01444-06

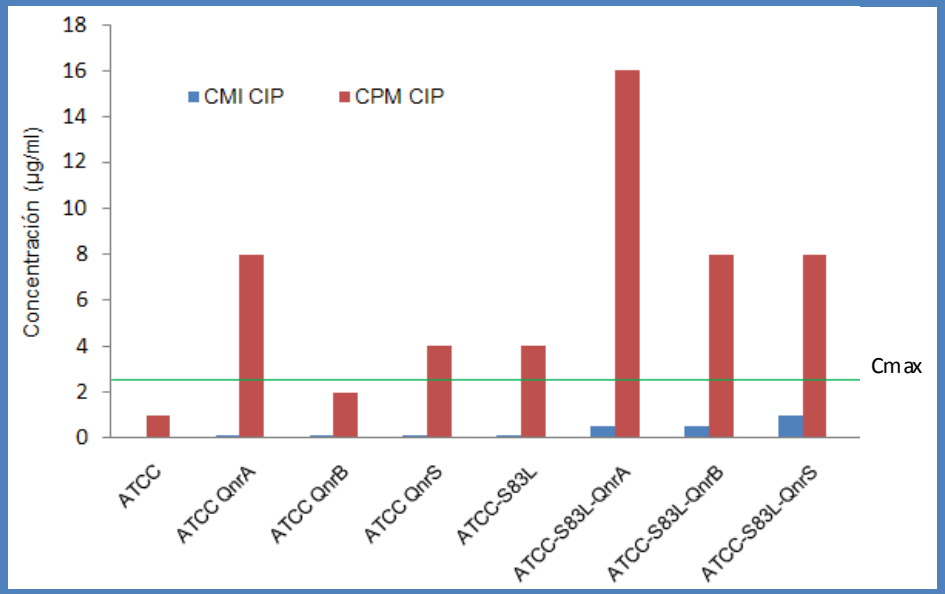
Mutant Prevention Concentrations of Fluoroquinolones for *Enterobacteriaceae* Expressing the Plasmid-Carried Quinolone Resistance Determinant *qnrA1*▽

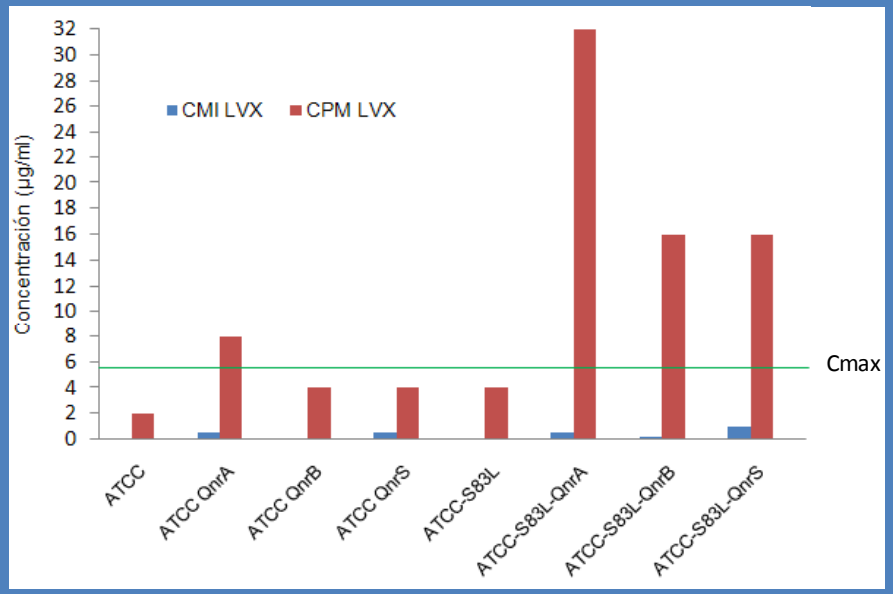
J. M. Rodríguez-Martínez,[1]* C. Velasco,[1] I. García,[1] M. E. Cano,[3] L. Martínez-Martínez,[3] and A. Pascual[1,2]



Efecto de los genes *qnr* y/o mecanismos cromosómicos en la actividad frente a quinolonas

Predictor de eficacia ⟶ Cmax/CMI





Pequeñas variaciones en la CMI a fluoroquinolonas pueden ocasionar modificaciones en la categoría clínica

In Vivo Selection of Fluoroquinolone-Resistant *Escherichia coli* Isolates Expressing Plasmid-Mediated Quinolone Resistance and Expanded-Spectrum β-Lactamase

Laurent Poirel,[1] Johann D. D. Pitout,[2,3,4] Lucy Calvo,[1] Jose-Manuel Rodriguez-Martinez,[1,6] Deirdre Church,[2,3,5] and Patrice Nordmann[1]*

The presence of *qnrA1* in *E. coli* from a patient with a UTI (treated with norfloxacin) preceeds the emergence of changes in Ser83Leu and Asp87Asn, (GyrA gyrase subunit) and Ser80Ile (ParC topoisomerase IV subunit)

MICs of ciprofloxacin increased from 0.5 to >32 mg/l

ORIGINAL ARTICLE *Clin Microbiol Infect* 2008; **14:** 691–697

Activity of ciprofloxacin and levofloxacin in experimental pneumonia caused by *Klebsiella pneumoniae* deficient in porins, expressing active efflux and producing QnrA1

J. M. Rodríguez-Martínez[1], C. Pichardo[2], I. García[1], M. E. Pachón-Ibañez[2], F. Docobo-Pérez[2], A. Pascual[1,3], J. Pachón[2,4] and L. Martínez-Martínez[1,3]

Antimicrobial agent	C_{max} (mg/L)	$t_{1/2}$ (h)	AUC (mg·h/L)	C_{max}/MIC		AUC_{0-24}/MIC	
				K. pneumoniae C2	*K. pneumoniae* C2pMG252	*K. pneumoniae* C2	*K. pneumoniae* C2pMG252
Ciprofloxacin (20 mg/kg)	11.57 ± 2.3	0.38	6.56	23.14	2.89	52.48	6.56
Levofloxacin (25 mg/kg)	7.89 ± 0.8	0.39	3.98	15.78	1.97	31.84	3.98

Treatment	Dosage (mg/kg/day)	*K. pneumoniae* C2			*K. pneumoniae* C2pMG252		
		N	Survival (%)	Log CFU/g of lung, $X \pm SD$	*N*	Survival (%)	Log CFU/g of lung, $X \pm SD$
Control		15	4 (26.7)	9.16 ± 2.16	15	2 (13.3)	9.65 ± 2.49
Ciprofloxacin	80	15	15 (100)[a,b]	3.53 ± 1.04[a,c]	15	8 (53.3)[d]	7.74 ± 2.67
Levofloxacin	100	15	15 (100)[a,b]	3.38 ± 0.46[a,c]	15	8 (53.3)[d]	7.57 ± 3.84

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2009, p. 4292–4297 Vol. 53, No. 10
0066-4804/09/$08.00+0 doi:10.1128/AAC.01664-08

Impact of Low-Level Resistance to Fluoroquinolones Due to *qnrA1* and *qnrS1* Genes or a *gyrA* Mutation on Ciprofloxacin Bactericidal Activity in a Murine Model of *Escherichia coli* Urinary Tract Infection▽

Nicolas Allou,[1] Emmanuelle Cambau,[1,2] Laurent Massias,[3] Françoise Chau,[1] and Bruno Fantin[1,4]*

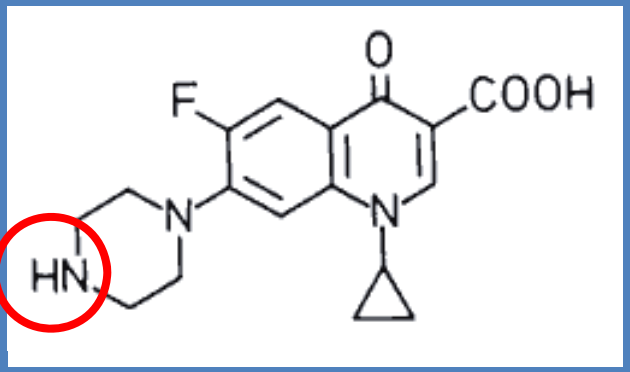
TABLE 2. Pharmacokinetic-pharmacodynamic parameters of the ciprofloxacin dosing regimen used in experimental UTI against the four *E. coli* strains used in the study

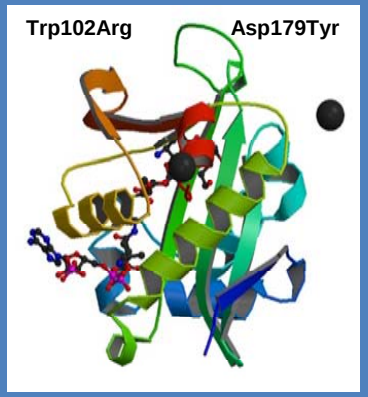
E. coli strain (plasmid)	Pharmacokinetic-pharmacodynamic ratios[b]	
	C_{max}/MIC[a]	AUC_{0-24}/MIC[c]
CFT703-RR	147	827
CFT703-RR Tc (pQnrA1)	2.2	12.4
CFT703-RR Tc (pQnrS1)	4.4	24.8
CT073-RR-*gyr*A	4.4	24.8

Inactivación Enzimática: *aac(6')-Ib-cr*

N-acetilation del grupo piperacynil

No compromete la actividad frente a aminoglicosidos





Afecta a ciprofloxacino, norfloxacino,… (pero no otras quinolonas)

Moderado aumento de la CMI que también favorece la emergencia de mutantes

Robicsek A et al, Nature Med 2006

Prevalencia de *aac-(6´)-Ib-cr* y resistencia a quinolonas

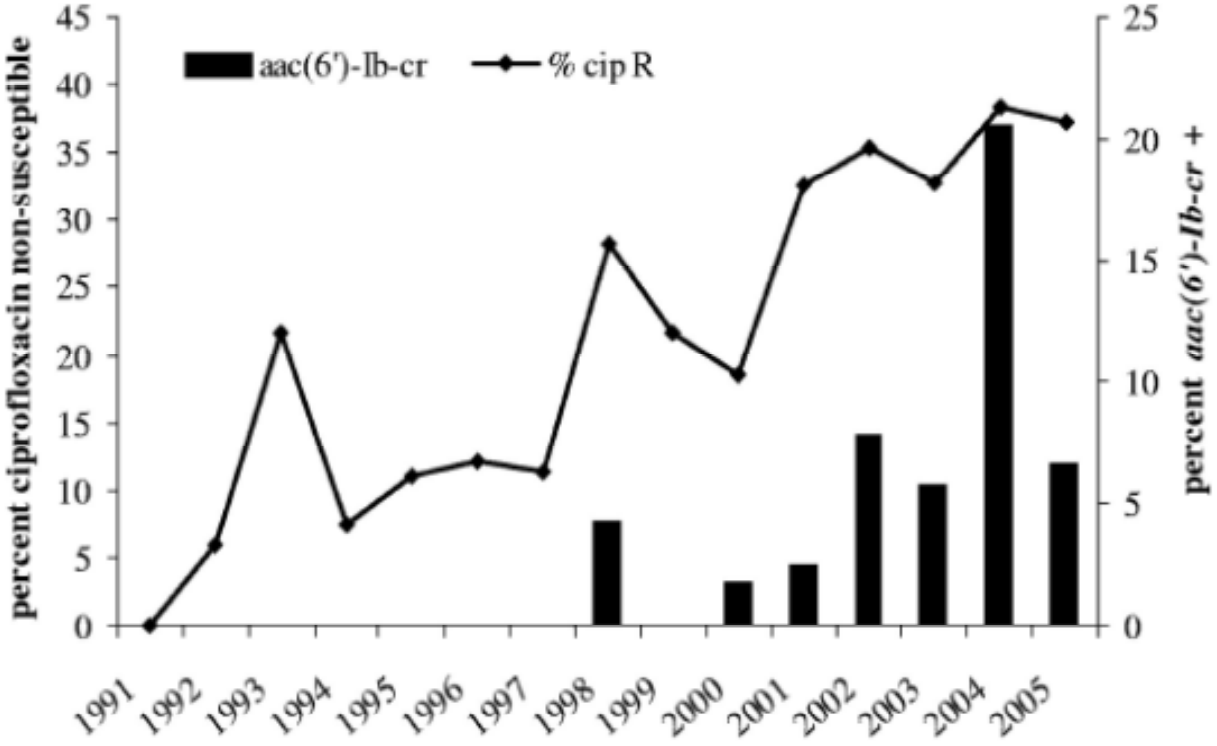


FIG. 2. Percentage of clinical *E. coli* isolates (n = 718) harboring resistance to ciprofloxacin (MIC ≥ 2 μg/ml) and harboring *aac(6')-Ib-cr*. No *aac(6')-Ib-cr* genes were found before 1998.

Warburg et al. AAC 2009

Available online at www.sciencedirect.com
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Diagnostic Microbiology and Infectious Disease 70 (2011) 253–259
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

Rapid detection of *qnr* and *qepA* plasmid-mediated quinolone resistance genes using real-time PCR☆,☆☆

Thomas Guillard[a,b,d], Hélène Moret[c], Lucien Brasme[a], Antoine Carlier[a], Véronique Vernet-Garnier[a,b], Emmanuelle Cambau[d,e], Christophe de Champs[a,b,*]

JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 2010, p. 286–289 Vol. 48, No. 1
0095-1137/10/$12.00 doi:10.1128/JCM.01498-09

Rapid Detection of *aac(6′)-Ib-cr* Quinolone Resistance Gene by Pyrosequencing▽

Thomas Guillard,[1]* Véronique Duval,[1] Hélène Moret,[2] Lucien Brasme,[1] Véronique Vernet-Garnier,[1] and Christophe de Champs[1]

Allele-specific polymerase chain reaction (PCR) for rapid detection of the *aac(6′)-Ib-cr* quinolone resistance gene

Letters to the Editor / International Journal of Antimicrobial Agents 36 (2010) 467–482

Disponible en ligne sur ScienceDirect www.sciencedirect.com
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PATHOLOGIE BIOLOGIE
Pathologie Biologie 58 (2010) 430–433

Article original

Mise au point d'une technique de PCR en temps réel pour la détection rapide des gènes *qnr* chez des entérobactéries productrices de bêta-lactamases à spectre étendu

Real-time PCR for fast detection of plasmid-mediated qnr genes in extended spectrum beta-lactamase producing Enterobacteriaceae

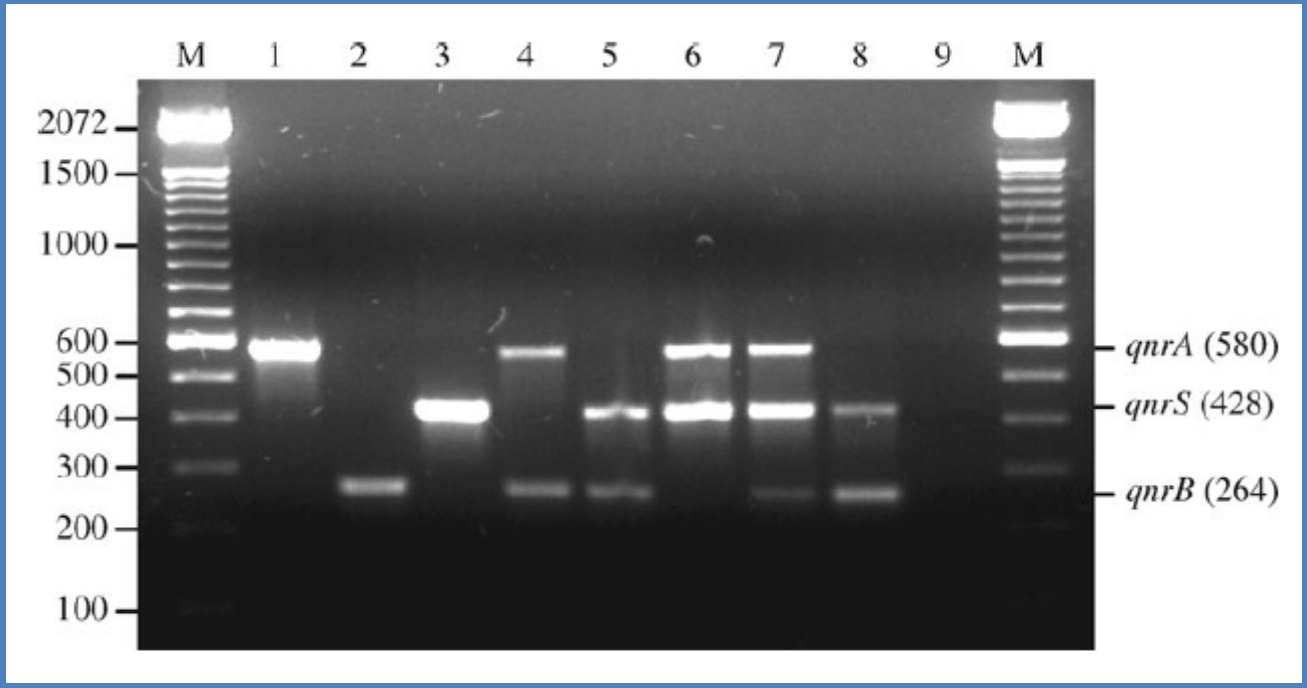
T. Guillard[a,*], J.-D. Cavallo[b,c], E. Cambau[d], V. Duval[a], O. Bajolet[a], L. Brasme[a], C. de Champs[a], V. Vernet-Garnier[a]

Journal of Antimicrobial Chemotherapy (2007) **60**, 394–397
doi:10.1093/jac/dkm204
Advance Access publication 8 June 2007

JAC

Multiplex PCR for detection of plasmid-mediated quinolone resistance *qnr* genes in ESBL-producing enterobacterial isolates

Vincent Cattoir[1,2], Laurent Poirel[1], Vincent Rotimi[3], Claude-James Soussy[2] and Patrice Nordmann[1]*



JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2009, p. 2751–2758 Vol. 47, No. 9
0095-1137/09/$08.00+0 doi:10.1128/JCM.00456-09

Evaluation of Quinolones for Use in Detection of Determinants of Acquired Quinolone Resistance, Including the New Transmissible Resistance Mechanisms *qnrA*, *qnrB*, *qnrS*, and *aac*(6′)*Ib-cr*, in *Escherichia coli* and *Salmonella enterica* and Determinations of Wild-Type Distributions▽

L. M. Cavaco* and F. M. Aarestrup

TABLE 1. *Escherichia coli* and *Salmonella enterica* strains included in this study[a]

Strain	No. of strains	Serotype (no. of isolates)	Origin	Resistance status	Resistance gene or mutation
E. coli, susceptible	31	NA	Swine	S	None
E. coli 1 mut	29	NA	Swine	1 mut	One mutation in *gyrA* gene
E. coli, resistant	5	NA	Swine	2 mut	Two or more mutations in *gyrA* and *parC* or *parE* gene
E. coli H88	1	NA	Human	*qnr*	*qnrS1*
E. coli H93	1	NA	Human	*qnr*	*qnrA1*
E. coli KAM 3	1	NA	Sewage	*qnr*	*qnrS2*
E. coli E12	1	NA	Human-blood	*aac*(6′)*Ib-cr*	*aac*(6′)*Ib-cr*
Salmonella, susceptible	29	Typhimurium (3)	Human, cattle, poultry, swine	S	None
Salmonella, susceptible		Enteritidis (5)			
Salmonella, susceptible		Schwarzengrund (5)			
Salmonella, susceptible		Bovismorbificans (2)			
Salmonella, susceptible		Anatum (1)			
Salmonella, susceptible		Corvallis (5)			
Salmonella, susceptible		Dublin (3)			
Salmonella, susceptible		Mbandaka (2)			
Salmonella, 1 mut	18	Typhimurium (8)	Cattle, poultry swine	1 mut	One mutation in *gyrA*
Salmonella, 1 mut		Enteritidis (5)			
Salmonella, 1 mut		Dublin (5)			
Salmonella, resistant	5	Schwarzengrund (5)	Human, poultry	2 mut	Mutation in *gyrA* or *parC* gene
Salmonella qnrS1	5	Corvallis (4)	Human, poultry, beef	*qnr*	*qnrS1*
		Bovismorbificans (1)			
Salmonella qnrB5	2	Berta (2)	Human	*qnr*	*qnrB5*
Salmonella qnrB2	1	Mbandaka (1)	Human	*qnr*	*qnrB2*
Salmonella qnrS2	1	Anatum (1)	Human	*qnr*	*qnrS2*
Salmonella aac(6′)*Ib-cr*	1	Typhimurium (1)	Human	*aac*(6′)*Ib-cr*	*aac*(6′)*Ib-cr*

Acido nalidixico resulta útil para detección de mutantes cromosómicos pero, pero no es eficiente para la detección de *qnr* y *aac(6')Ib-cr.*

CMI o disco difusión con ciprofloxacino o norfloxacino resulta de utilidad para la detección de PMQR.

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Diagnostic Microbiology and Infectious Disease 64 (2009) 455–457
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
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Vitek2® system: a reliable tool to detect *qnr* determinants in Enterobacteriaceae without quinolone resistance-determining region modifications

Stéphane Corvec[a,b,*], Lise Crémet[a], Alain Reynaud[a,b], Didier Lepelletier[a,b], Nathalie Caroff[a,b]

Quinolone interpretative susceptibility patterns obtained with Vitek2® automatic system and correlation with *qnr* genes detected in 12 clinical isolates of Enterobacteriaceae

Isolate no.	Specimen	Date	Species	NAL				NOR			
				Vitek2®		AES expert*		Vitek2®		AES expert*	
				MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation
1	Blood	Jan 2008	*Klebsiella pneumoniae*	4	S	≥32	R	2	R	2	R
2	Blood	Jan 2008	*E. coli*	8	S	≥128	R	2	R	2	R
3	Lung	Jan 2008	*Serratia marcescens*	4	S	≥16	R	1	I	1	I
4	Urine	Feb 2008	*E. coli*	8	S	≥128	R	2	R	2	R
5	Urine	Feb 2008	*E. coli*	16	I	16	R	≤0.5	S	≤0.5	S
6	Bile	Feb 2008	*Enterobacter aerogenes*	16	I	16	R	2	R	2	R
7	Urine	May 2008	*Citrobacter freundii*	16	I	16	R	≤0.5	S	≥1	I
8	Blood	Jun 2008	*K. pneumoniae*	8	S	≥32	R	2	R	2	R
9	Blood	Jun 2008	*Enterobacter cloacae*	16	I	16	R	2	R	2	R
10	Urine	Aug 2008	*K. pneumoniae*	8	S	≥32	R	2	R	2	R
11	Urine	Sep 2008	*K. pneumoniae*	16	I	16	R	1	I	1	I
12	Urine	Oct 2008	*E. cloacae*	16	I	16	R	2	R	2	R

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Vitek2® system: a reliable tool to detect *qnr* determinants in Enterobacteriaceae without quinolone resistance-determining region modifications

Stéphane Corvec[a,b,*], Lise Crémet[a], Alain Reynaud[a,b], Didier Lepelletier[a,b], Nathalie Caroff[a,b]

OFX				CIP				*qnr* gene detected
Vitek2®		AES expert*		Vitek2®		AES expert*		
MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation	MIC (mg/L)	Interpretation	
2	R	2	R	≤0.25	S	≤0.25	S	*qnrS*
1	I	1	I	0.5	S	0.5	S	*qnrS*
1	I	1	I	≤0.25	S	≤0.25	S	*qnrB*
2	R	2	R	0.5	S	0.5	S	*qnrS*
1	I	≤0.25	I	≤0.25	S	≤0.25	S	*qnrB*
1	I	1	I	≤0.25	S	≤0.25	S	none
1	I	1	I	≤0.25	S	≤0.25	S	*qnrB*
2	R	2	R	1	S	1	S	*qnrB*
2	R	2	R	2	I	2	I	*qnrA*
2	R	2	R	0.5	S	0.5	S	*qnrS*
0.5	S	0.5	S	≤0.25	S	≤0.25	S	*qnrS*
2	R	2	R	1	S	1	S	*qnrB*

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2011, p. 3343–3345 Vol. 49, No. 9
0095-1137/11/$12.00 doi:10.1128/JCM.00563-11

Evaluation of Three Automated Systems for Susceptibility Testing of Enterobacteria Containing *qnrB*, *qnrS*, and/or *aac(6′)-Ib-cr*[▽]

Jorge Calvo,[1]* María Eliecer Cano,[1] Cristina Pitart,[2] Francesc Marco,[2] José Manuel Rodríguez-Martínez,[3,4] Álvaro Pascual,[3,4] and Luis Martínez-Martínez[1,5]

TABLE 2. Summary of the results obtained with automated methods compared to the results with reference microdilution

Antimicrobial agent	System (concns in mg/liter)	% agreement in clinical categories	% essential agreement	No. of errors of indicated type		
				Very major	Major	Minor
Nalidixic acid	MicroScan (4, 16)	99	88	1	0	0
	Vitek-2 (2, 4, 8, 16, 32)	97	93	0	2	0
Ciprofloxacin	MicroScan (0.12, 1, 2)	91	75	0	0	6
	BD Phoenix (0.12, 0.25, 0.5, 1, 2)	90	91	0	1	6
	Vitek-2 (0.25, 0.5, 1, 2, 4)	96	96	0	0	3
Norfloxacin	MicroScan (1, 4, 8)	96	90	0	0	3
	BD Phoenix (2, 4, 8)	96	100	0	0	3
Levofloxacin	MicroScan (0.25, 2, 4)	99	99	0	0	1
Gentamicin	MicroScan (4, 8)	93	97	0	1	4
	BD Phoenix (2, 4, 8)	91	97	0	1	5
	Vitek-2 (1, 2,	97	97	0	0	2

JOURNAL OF CLINICAL MICROBIOLOGY, June 2011, p. 2378–2379 Vol. 49, No. 6
0095-1137/11/$12.00 doi:10.1128/JCM.00278-11

Letters to the Editor

Practical Disk-Based Method for Detection of *Escherichia coli* Clinical Isolates Producing the Fluoroquinolone-Modifying Enzyme AAC(6′)-Ib-cr[▽]

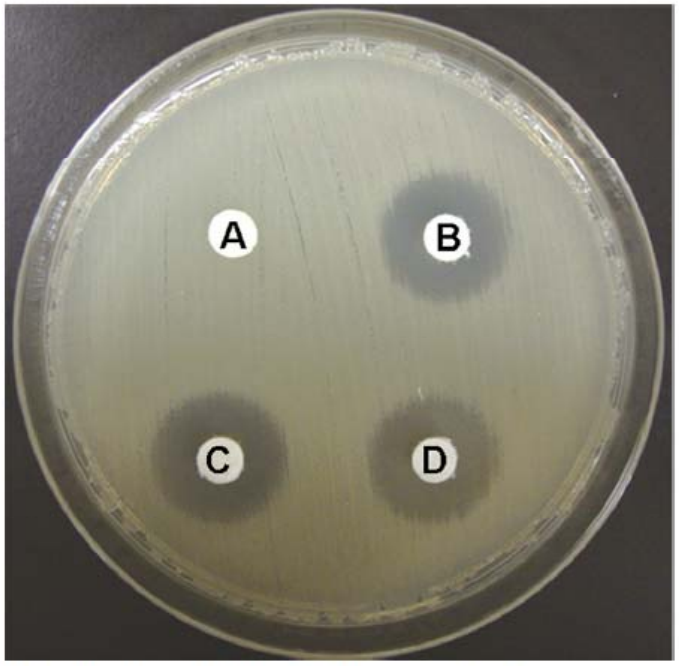

FIG. 1. Result of disk-based detection. (A) *E. coli* strain CR1 [*aac(6′)-Ib-cr* (+)]; (B) *E. coli* strain N64 [*aac(6′)-Ib* (+)]; (C) *E. coli* strain BN41 (negative for both genes); (D) control medium.

¿Cuáles son las consecuencias clínicas de PMQR?

- MPC > Picos de Concentración Sérica
- Selección de Mutantes → Fracaso terapéutico?
- Aumento del fracaso terapéutico en modelos experimentales.

Resistencia a quinolonas transferible

Gracias

José Manuel Rodríguez Martínez
Bilbao, 2012