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In vitro activity of hydroxychloroquine in combination with antibiotics against uropathogenic *Escherichia coli* intracellular bacterial colonies

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INTRODUCTION

Recurrent cystitis (RC) is common and responsible for a high consumption of antibiotics (ATBs). Some RC are due to a relapse from UPEC persistence within the superficial urothelial cell as intracellular bacterial communities (IBCs) [1].

The aim of this study was to investigate the *in vitro* activity of HCQ in combination with intracellularly acting ATBs on IBCs in a urothelial cell culture model

Hydroxychloroquine (HCQ) is a lysosomotropic agent that increases endosomal pH inhibiting lysosomal enzymes and block autophagy. Doxycycline-HCQ combination is effective against intracellular *Coxiella burnetti* [2].

METHODS

Strains

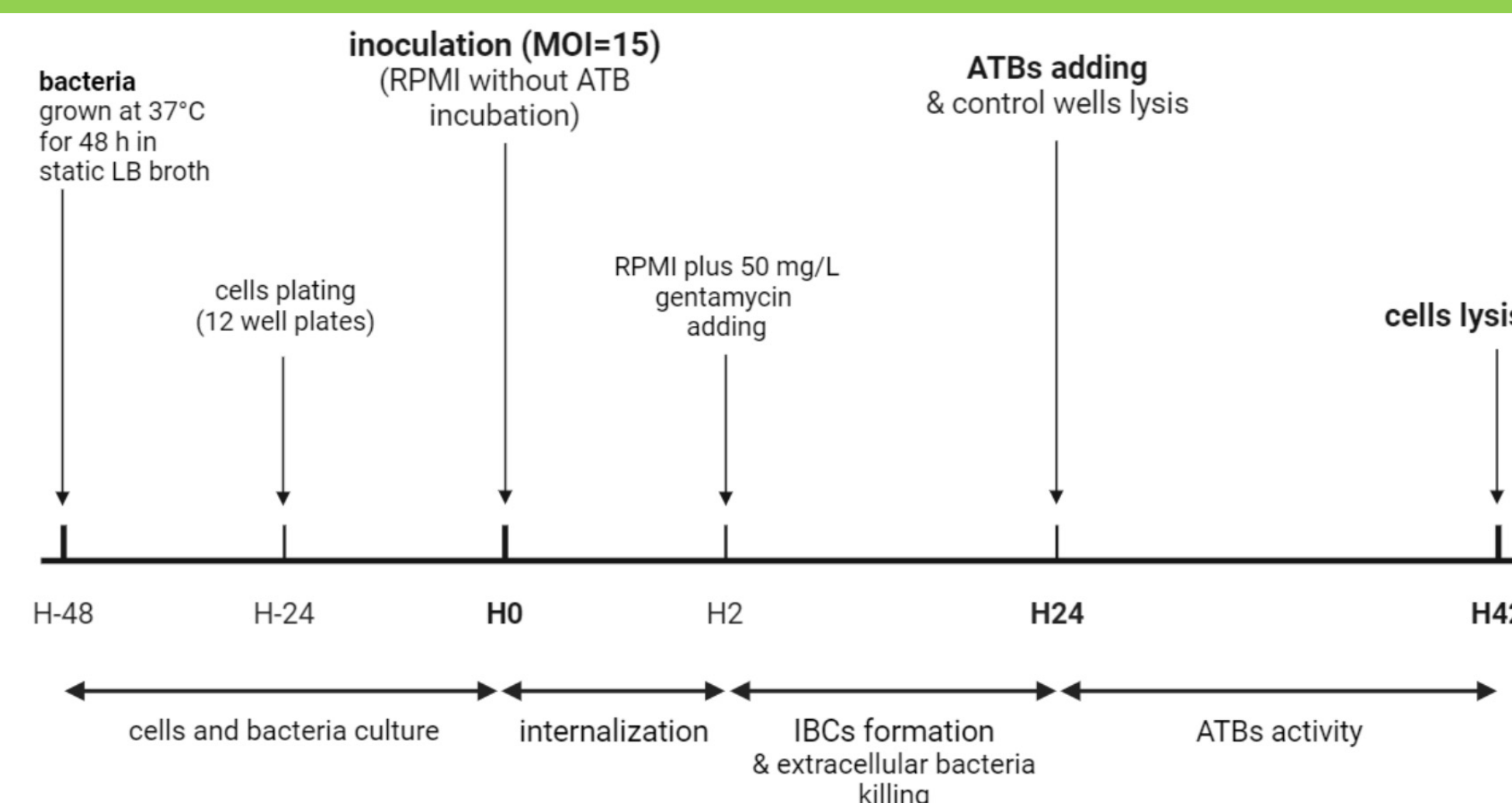
- RC clinical strains: 2206 & 2157
- Reference strain: UTI89

ATBs

- Ciprofloxacin (CIP), Doxycycline (DC), Azithromycin (AZT), Fosfomycin (FF)
- Hydroxychloroquine (HCQ)

Cell culture

- HTB9 cell line (ATCC 5637) : superficial urothelial cell monolayer



Strains & ATBs

MIC measured by broth microdilution
Bactericidal kinetics

Cells & ATBs

CytoTox 96[®] Cytotoxicity Assay (Promega)

RESULTS

Figure 2: Violin plots of change in IBC count (\log_{10} CFU per 10^6 cells) compared to controls at H42 post-infection according to antibiotics and HCQ combination.

IBC: intracellular bacterial communities, HCQ: hydroxychloroquine, orange: antibiotic alone, blue: HCQ-antibiotic combination, circle dot: 2157 strain, triangle dot: 2206 strain, square dot: UTI89 strain, AZT 20: azithromycin 20 mg/L, CIP 100: ciprofloxacin 100 mg/L, CIP 2: ciprofloxacin 2 mg/L, DC 10: doxycycline 10 mg/L, FF 100: fosfomycin 100 mg/L, FF 500: fosfomycin 500 mg/L, red line: IBC median change, p-value above bracket were calculated between antibiotic alone and HCQ-antibiotic combination group by Wilcoxon adjusted test.

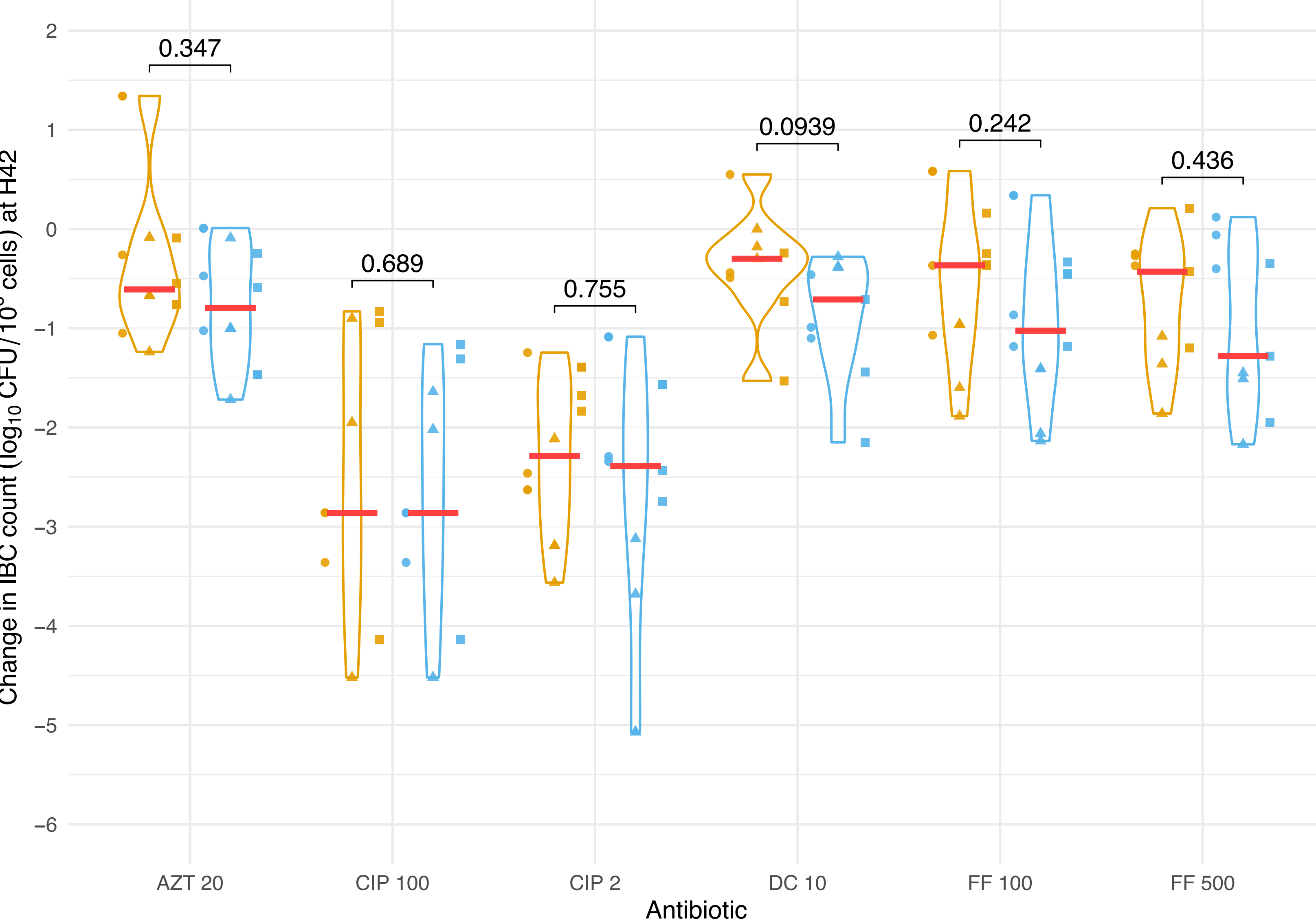
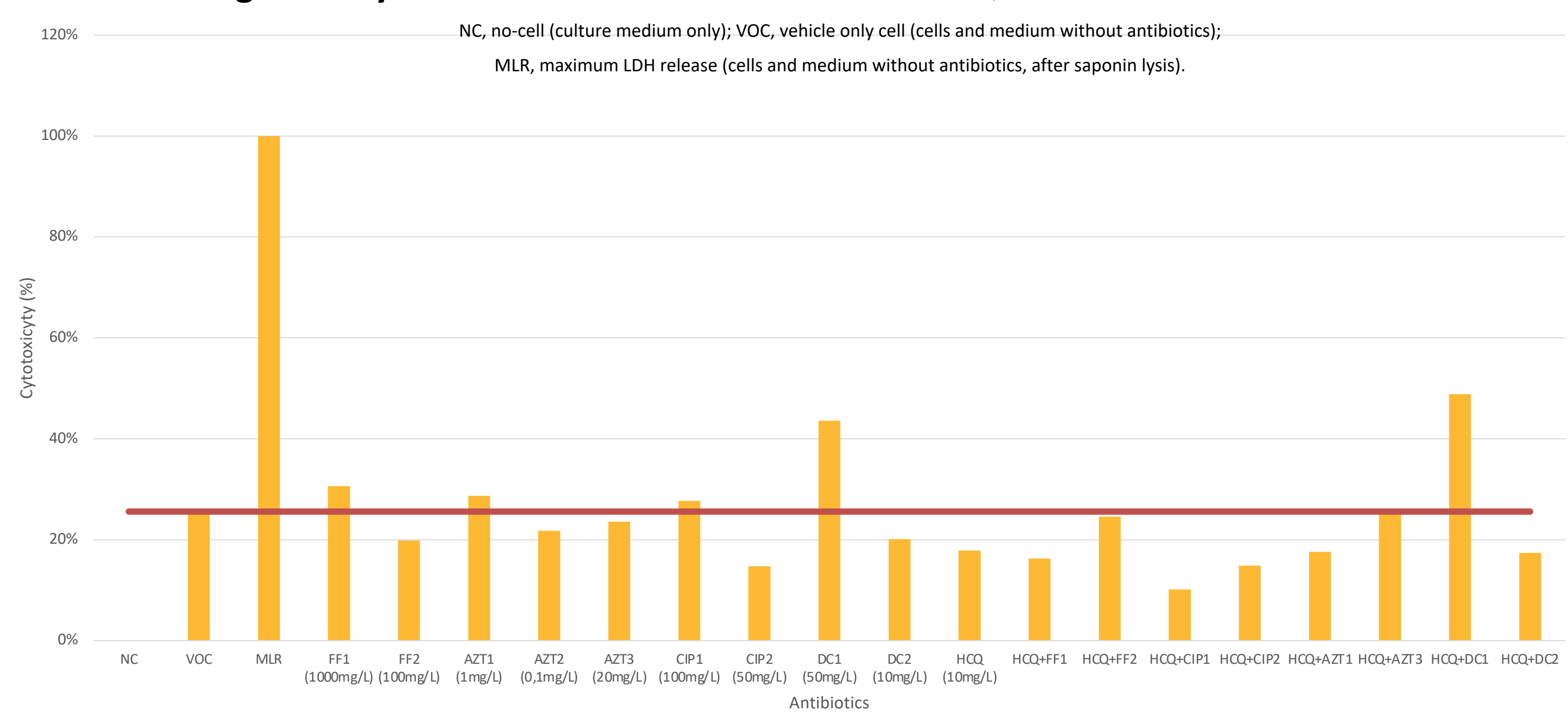


Table 1: MICs, MBCs and Time-killing curves parameters for each strain and tested molecules.

Strains	Origin	Phylo group	MIC (mg/L)					MBC (mg/L)				Bactericidal kinetics															
			CIP	FF	AZT	DC	HCQ	(n x MIC)				(4 x CMI of each tested antibiotics)															
			Bacterial count minimum (\log_{10} UFC/mL) ; time (H) ; bactericidal at H24 (yes/no)																								
			CIP				FF				AZT				DC												
2157	VITALE study Recurrent cystitis	A	0,008	1	8	0,5	> 10	0,016	2	> 128	> 8	4,6	2,8	0,7	0,7	(2)	(2)	(> 16)	(> 16)	H6	H1	H24	H6	no	no	no	no
			0,008	1	4	0,5	> 10	0,008	2	> 64	> 8	6,2	2,5	1,3	1,7	(1)	(2)	(> 16)	(> 16)	H24	H6	H6	H24	yes	no	no	no
2206	VITALE study Recurrent cystitis	B2	0,008	1	4	0,5	> 10	0,016	2	> 128	> 8	4,6	2,8	0,7	0,7	(2)	(2)	(> 16)	(> 16)	H24	H1	H24	H3	yes	no	no	no
UTI 89	IAME UMR 1137 Acute cystitis	B2	0,008	2	8	1	> 10	0,016	4	> 128	> 8	7,2	3,2	1,3	1,3	(2)	(2)	(> 16)	(> 8)	H24	H1	H24	H3	yes	no	no	no

Figure 1: cytotoxic effects of antibiotics and HCQ combinations on HTB-9 cells.



CONCLUSION

HCQ exposure didn't enhance antibiotics activity against IBC.

Further works are needed to assess potential efficacy of HCQ-antibiotics combination with new models as mature stratified urothelium or organoid model.

1. Klein RD, Hultgren SJ. Urinary tract infections: microbial pathogenesis, host-pathogen interactions and new treatment strategies. Nature Reviews Microbiology 2020;18:211–26.
2. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. Clin Microbiol Rev 2001;14:177–207.