SCV phenotype and reduced intracellular activity of antibiotics: a cause for persistent staphylococcal infection ?

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SCVs of *S. aureus* as a cause of persistent foreign body infection

Rev Infect Dis. 1987 Nov-Dec;9(6):1168-74.

Prosthetic valve endocarditis due to small-colony staphylococcal variants.

Baddour LM, Christensen GD.

Clin Infect Dis. 1999 Oct;29(4):932-4.

Bloodstream infections caused by small-colony variants of coagulase-negative staphylococci following pacemaker implantation.

von Eiff C, Vaudaux P, Kahl BC, Lew D, Emler S, Schmidt A, Peters G, Proctor RA.

Emerg Infect Dis. 2003 Oct;9(10):1316-8.

Small colony variants of Staphylococcus aureus and pacemaker-related infection.

Seifert H, Wisplinghoff H, Schnabel P, von Eiff C.

Int J Artif Organs. 2006 Apr;29(4):360-7.

Emerging Staphylococcus species as new pathogens in implant infections.

von Eiff C, Arciola CR, Montanaro L, Becker K, Campoccia D.

Int J Artif Organs. 2007 Sep;30(9):778-85.

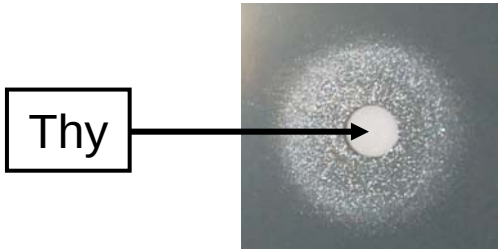
Small-colony variants (SCVs) of staphylococci: a role in foreign body-associated infections.

von Eiff C, Becker K.

SCV : case under study

- SCV isolated from a patient
  - with complicated prosthetic vascular graft infection and bacteraemia,
  - unsuccessfully treated successively with
    - cotrimoxazole (SMX/TMP),
    - minocycline (MIN),
    - a combination of vancomycin and rifampin (VAN-RIF)
    - a combination of linezolid and rifampin (LNZ-RIF)

- thymidine-auxotrophic MRSA, growing as tiny, non-pigmented and non-hemolytic colonies on Columbia blood agar.



- resistant to OXA, SXT, CLI, LIN, ERY, quinupristin and TET.

Aim of the study

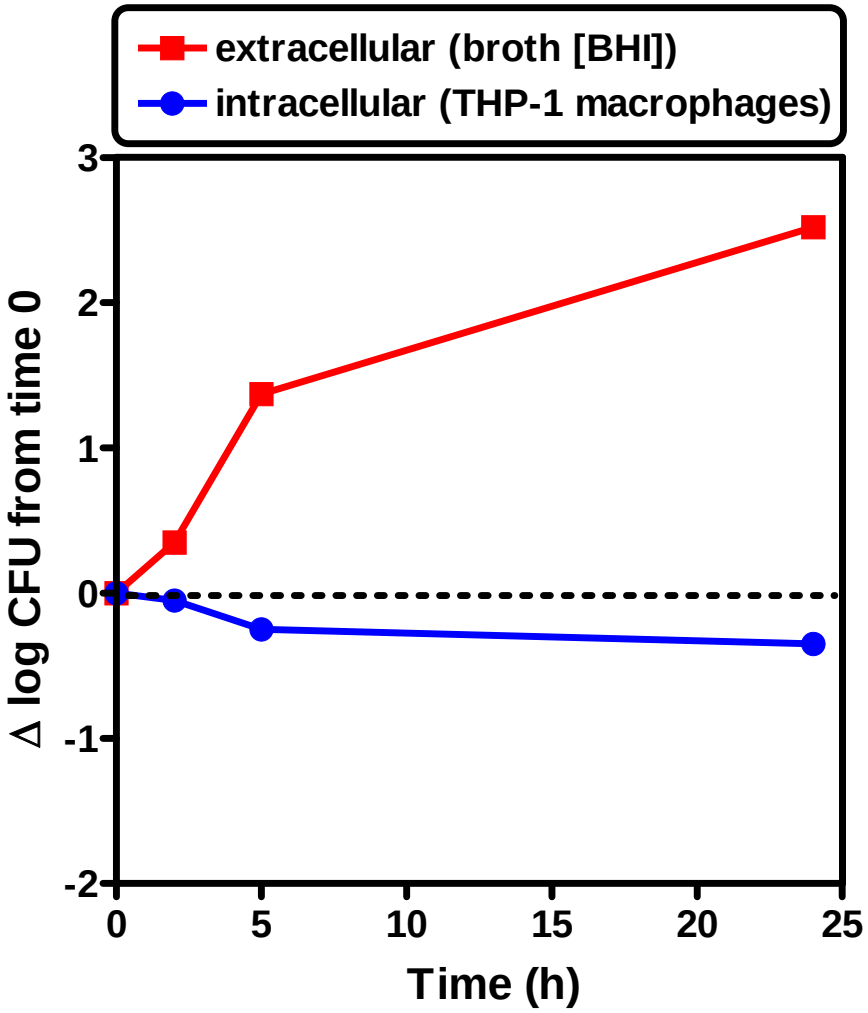
To examine the extracellular and intracellular activity against this SCV of :

- antibiotics unsuccessfully used to treat the patient
  - cotrimoxazole (SMX/TMP)
  - minocycline (MIN)
  - vancomycin + rifampin (VAN-RIF)
  - linezolid + rifampin (LNZ-RIF)

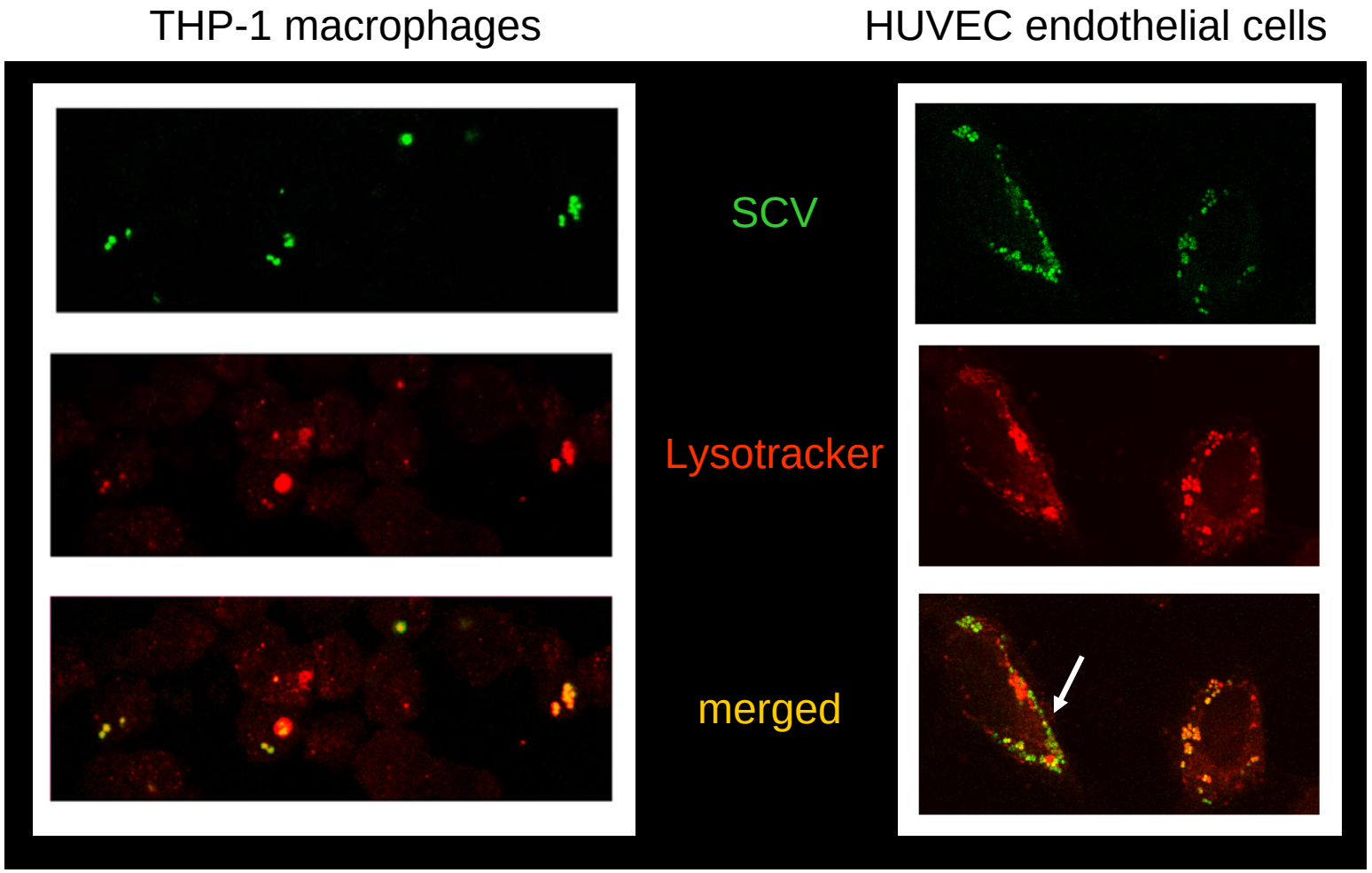
- other approved antistaphylococcal antibiotics,
  - gentamicin (GEN)
  - moxifloxacin (MXF)
  - quinupristin-dalfopristin (Q-D)
  - tigecycline (TGC)
  - daptomycin (DAP)

- antibiotics in the late stages of development: lipoglycopeptides
  - telavancin (TLV)
  - oritavancin (ORI)

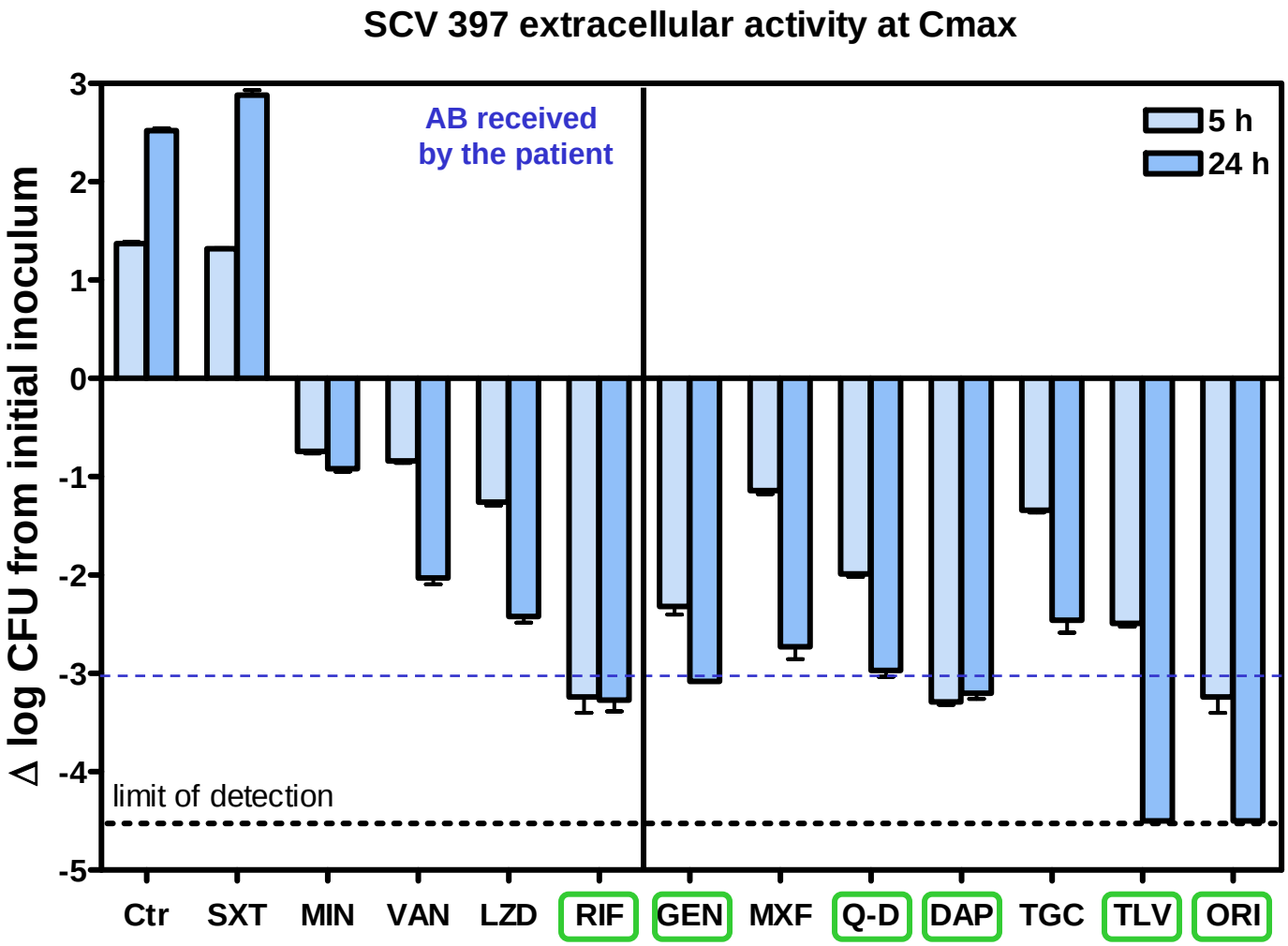
Growth of SCV in broth and within macrophages



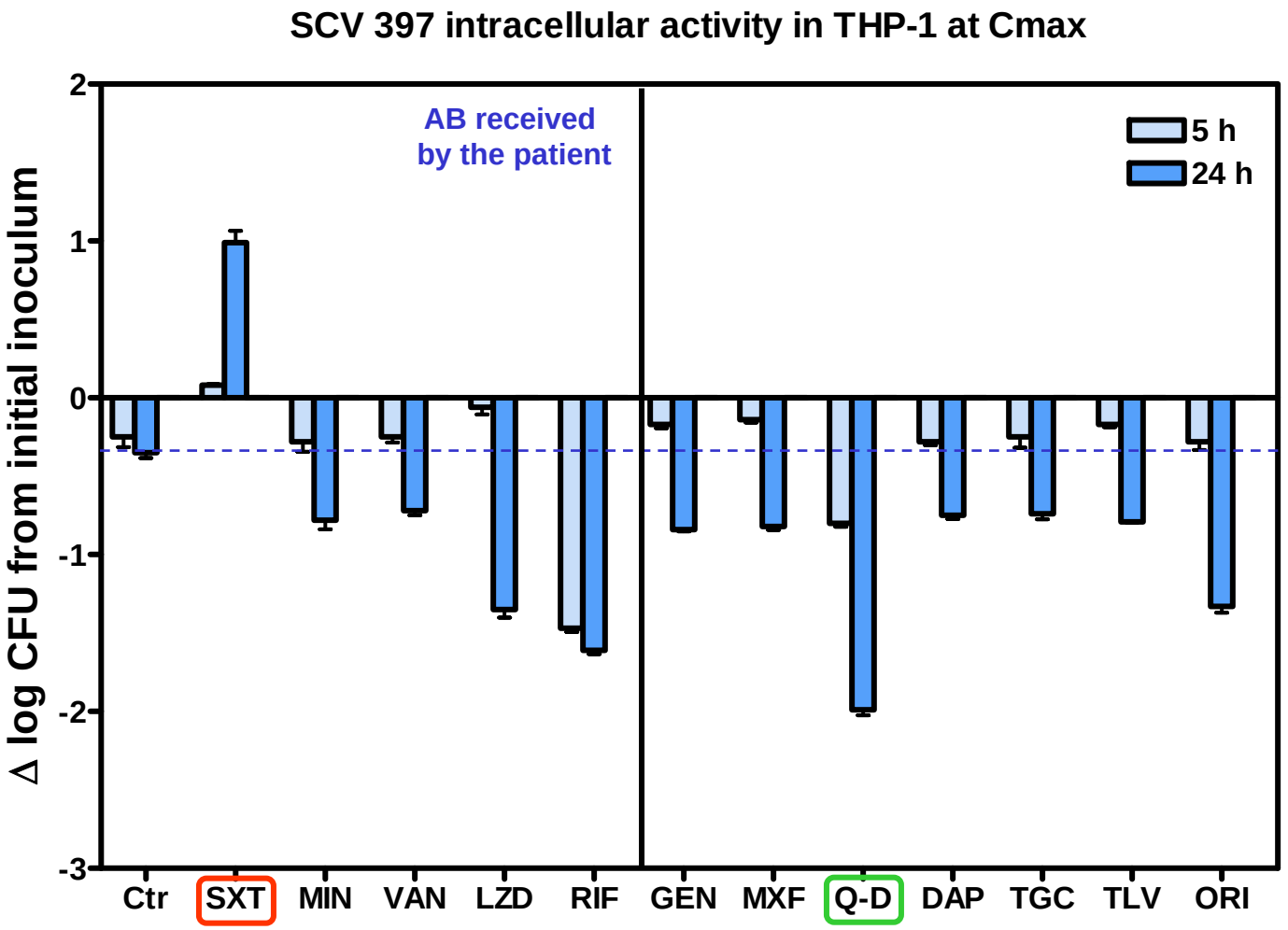
Subcellular localization of SCV



Extracellular activity



Intracellular activity in THP-1 macrophages



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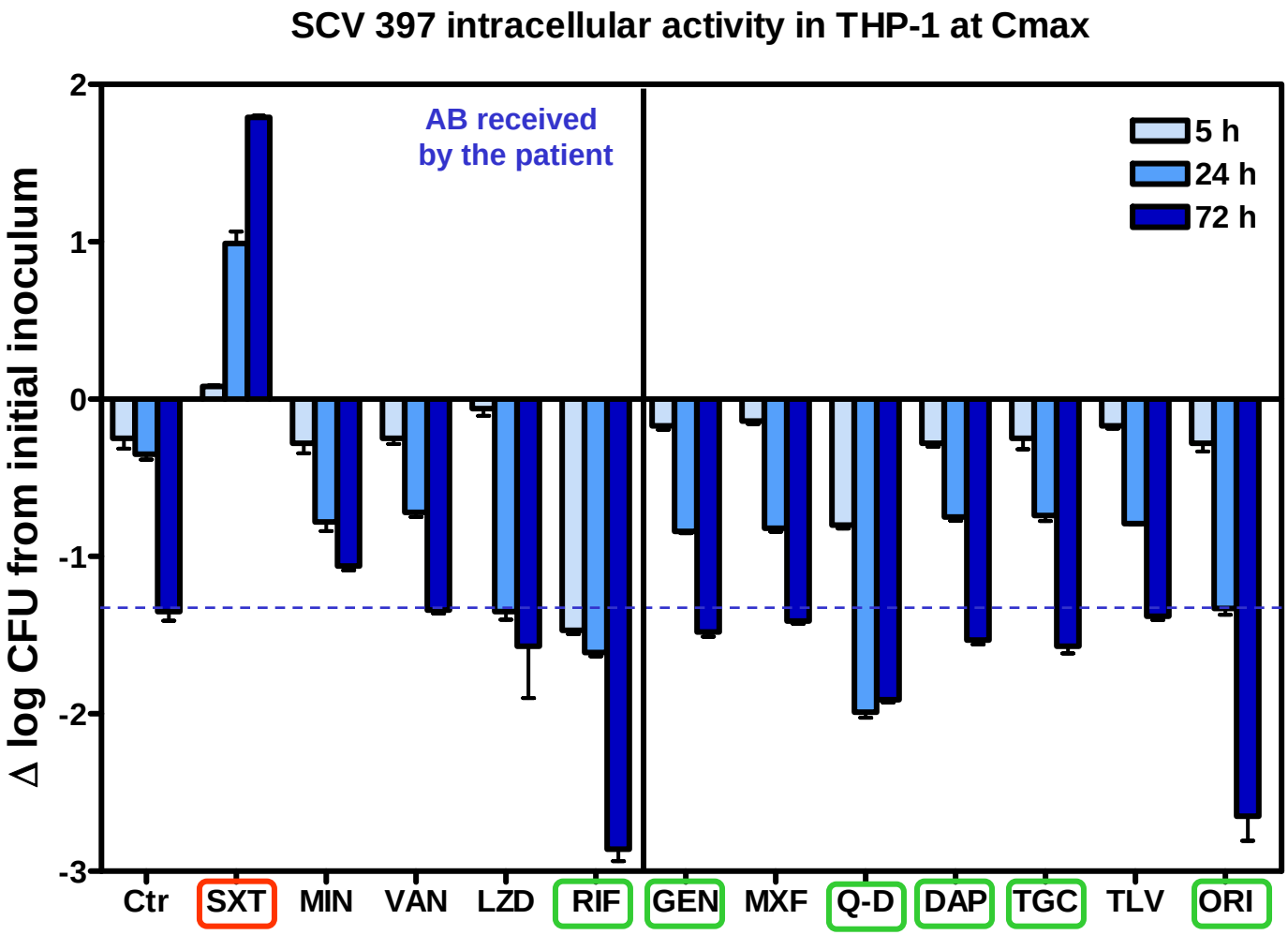
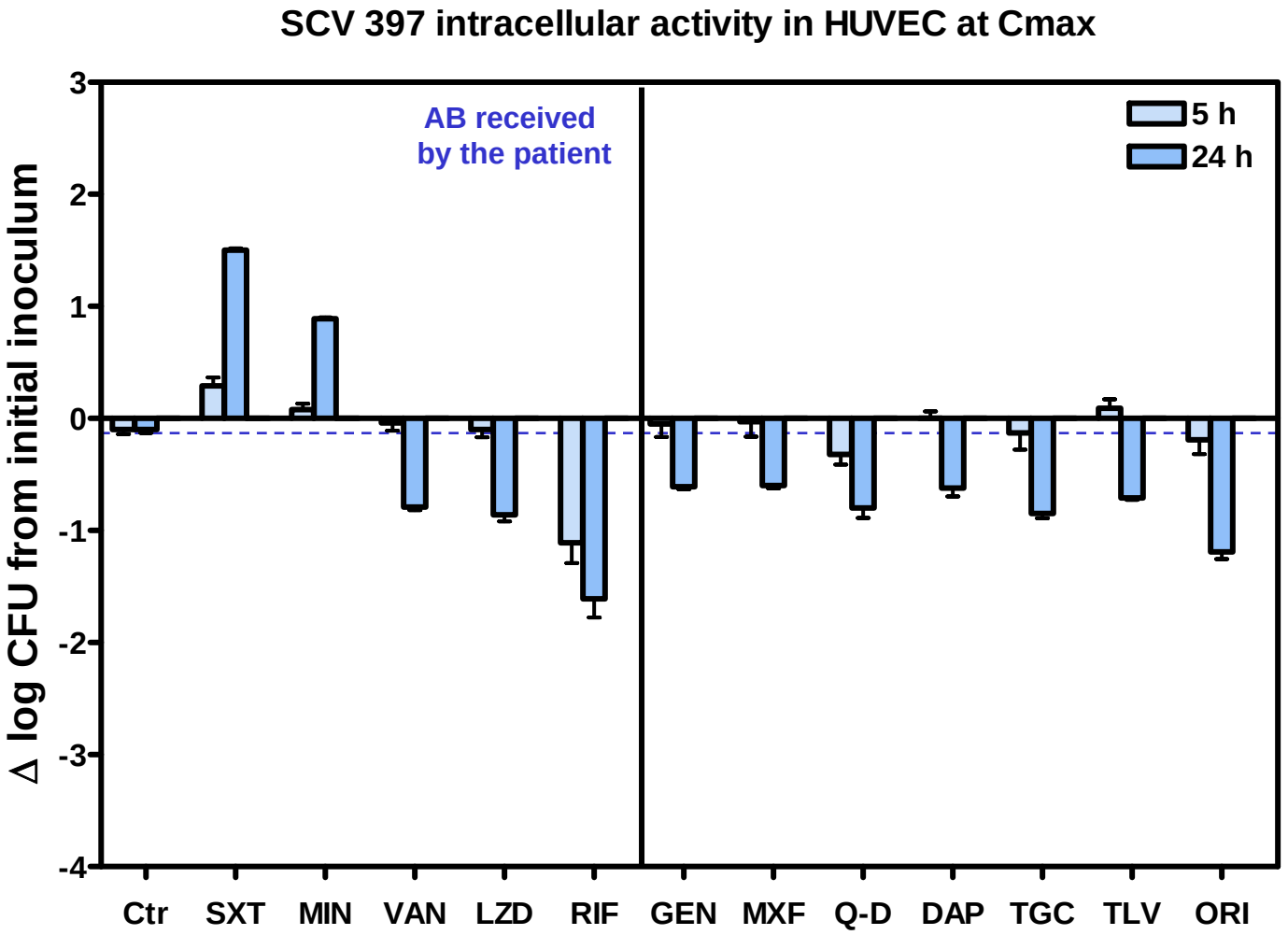
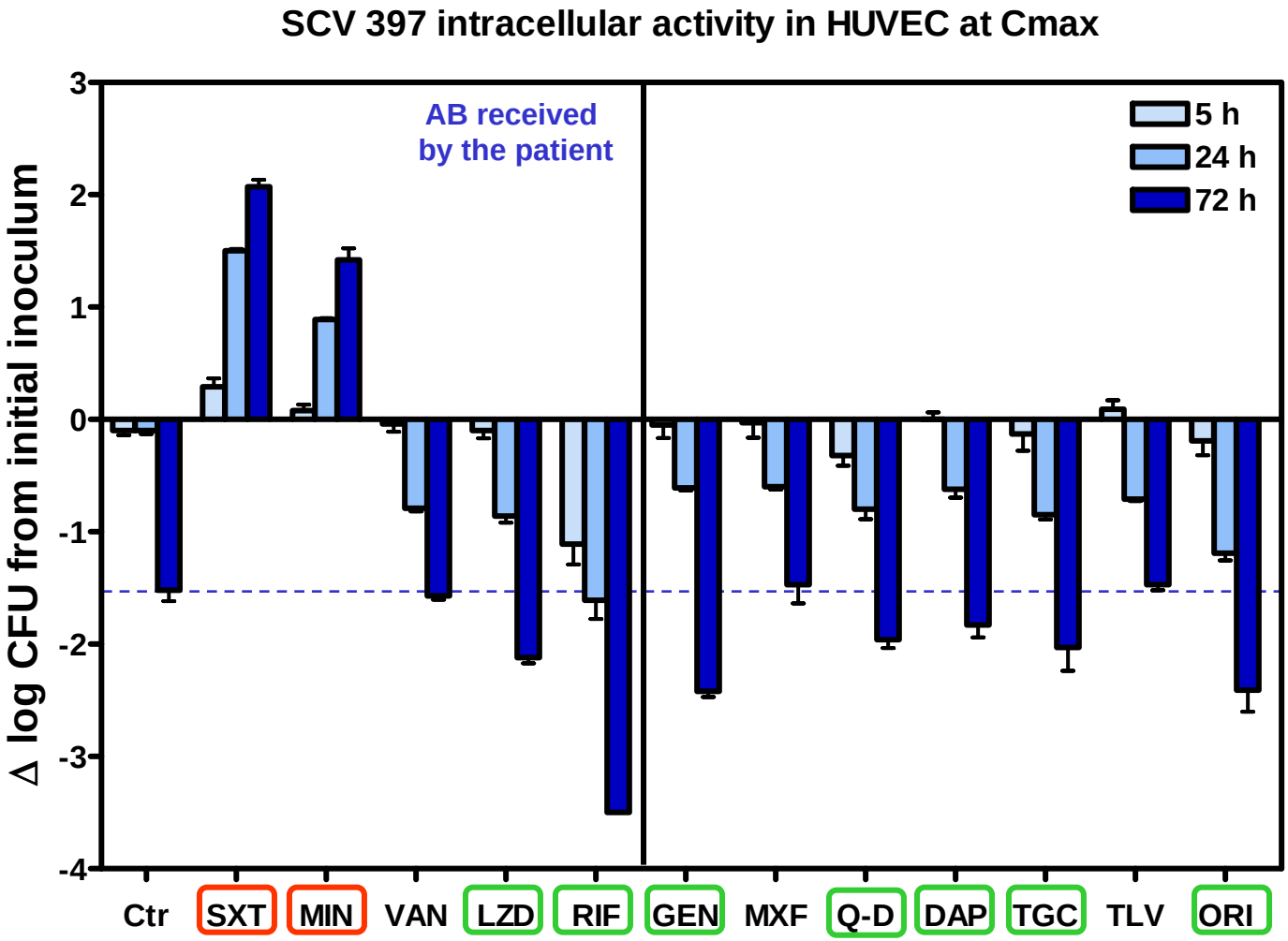


Intracellular activity in HUVEC endothelial cells

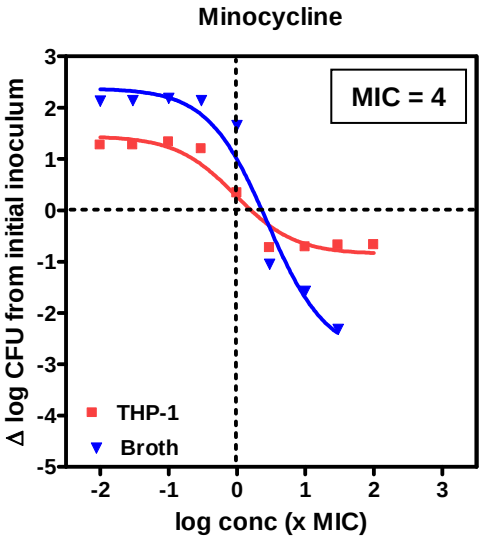


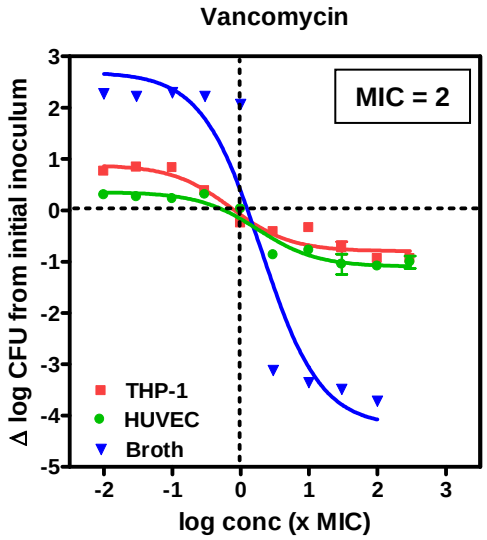
Intracellular activity in HUVEC endothelial cells

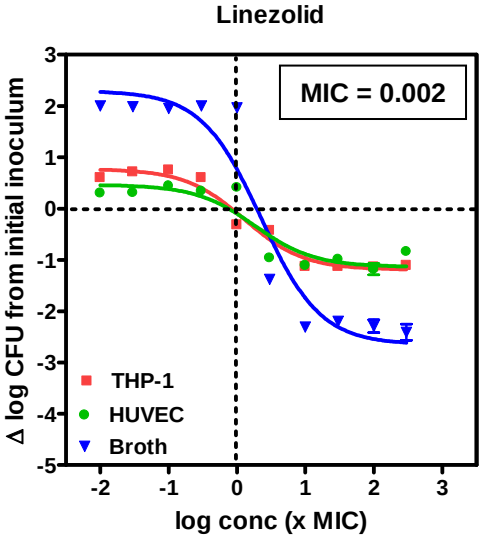


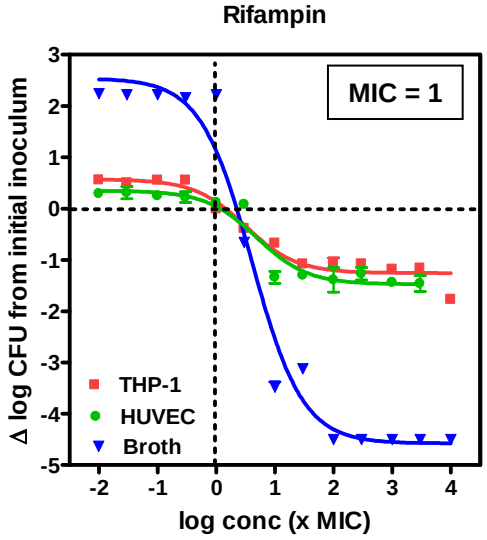
Dose-effect at 24 h

antibiotics received by the patient

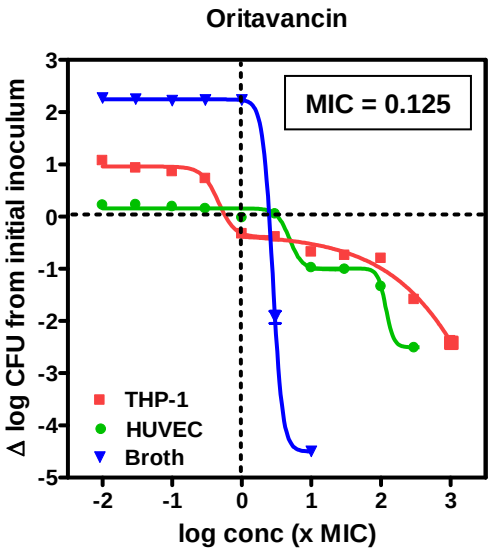






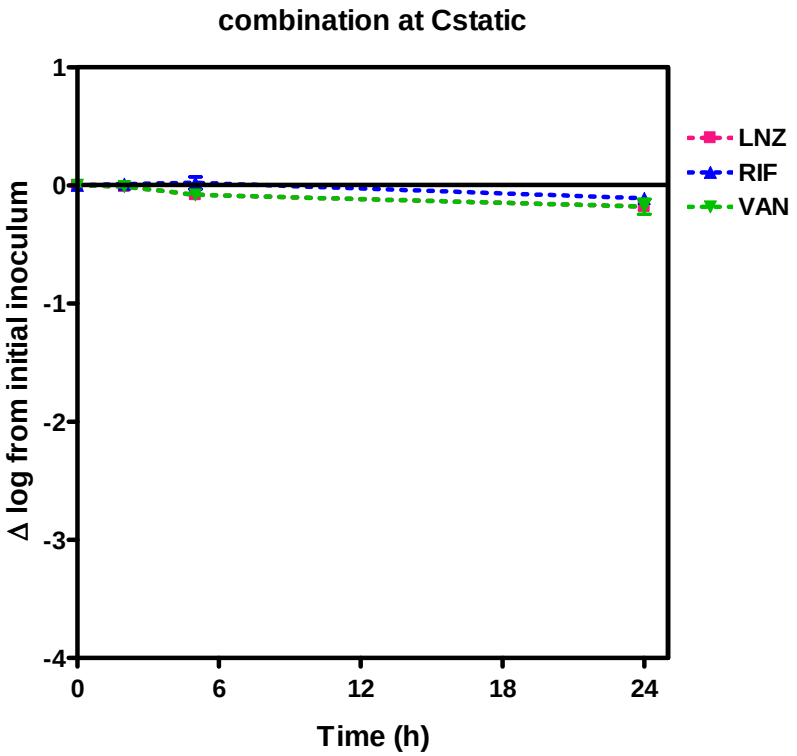


most active drug



Combinations at 24 h

combinations received by the patient



Combinations at 24 h

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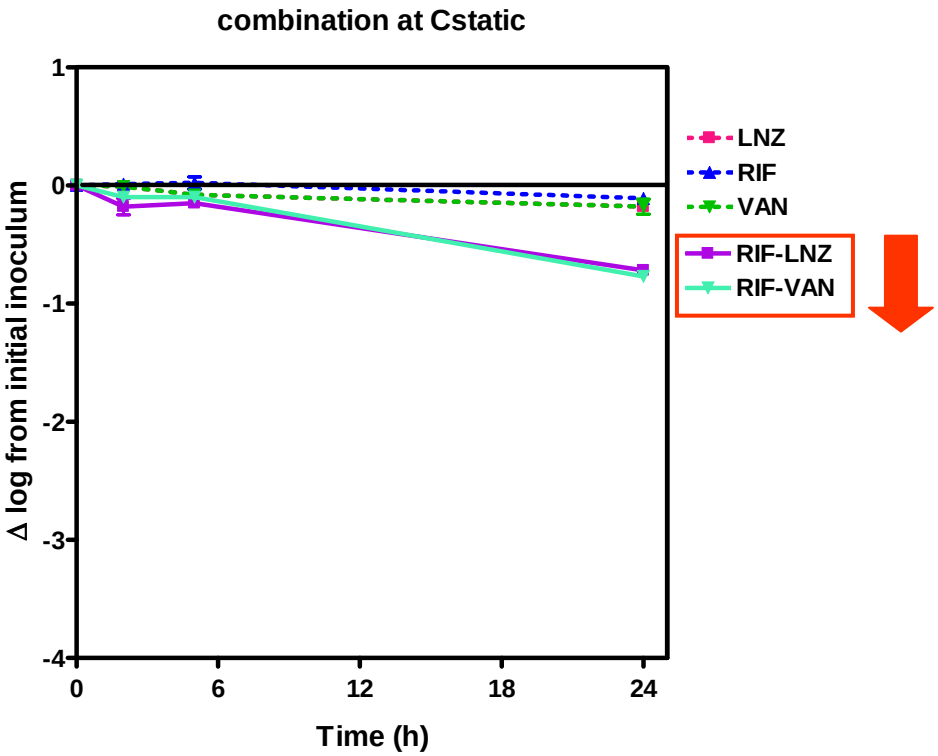

Combinations at 24 h

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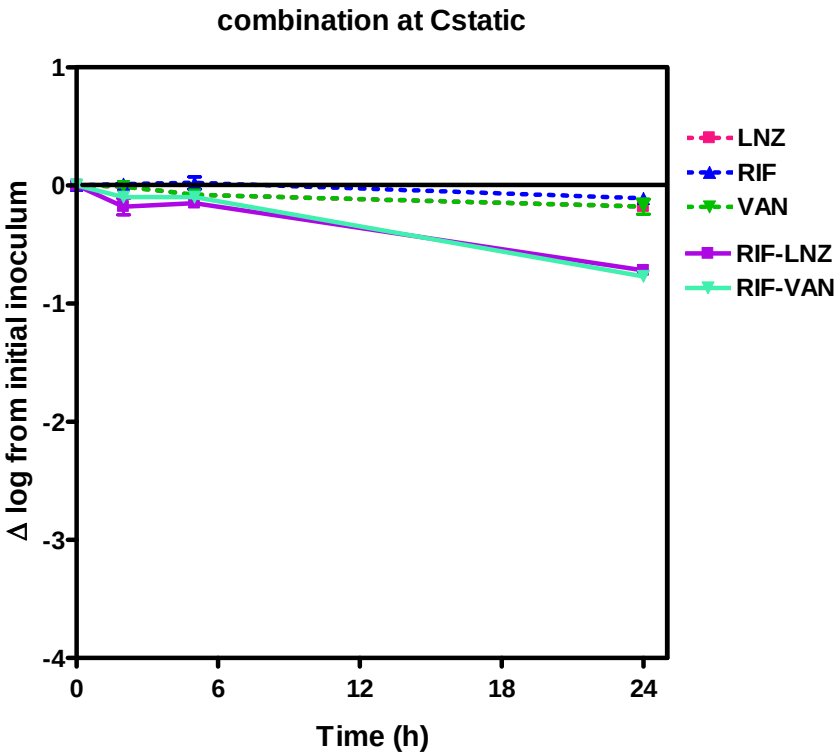
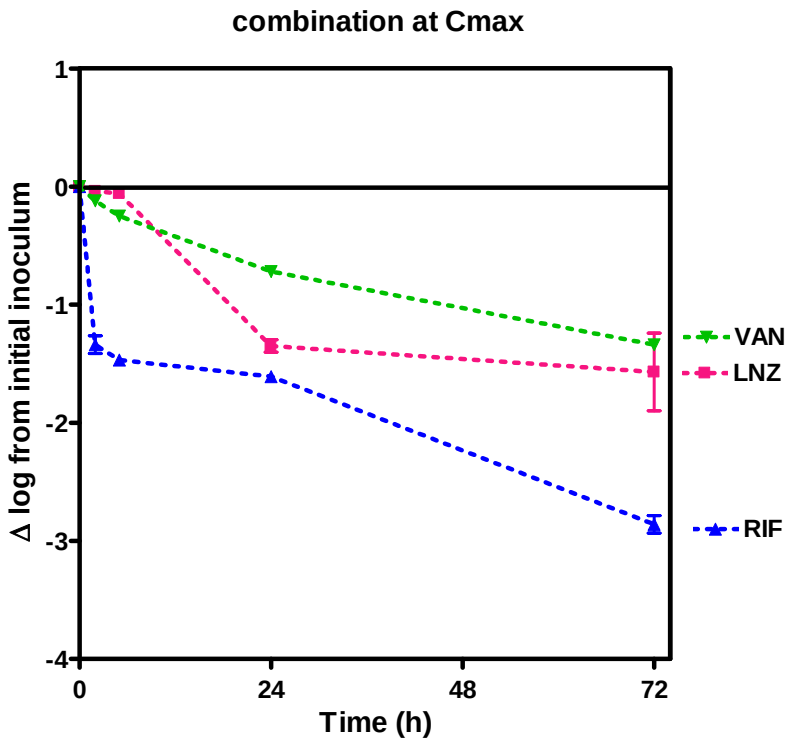
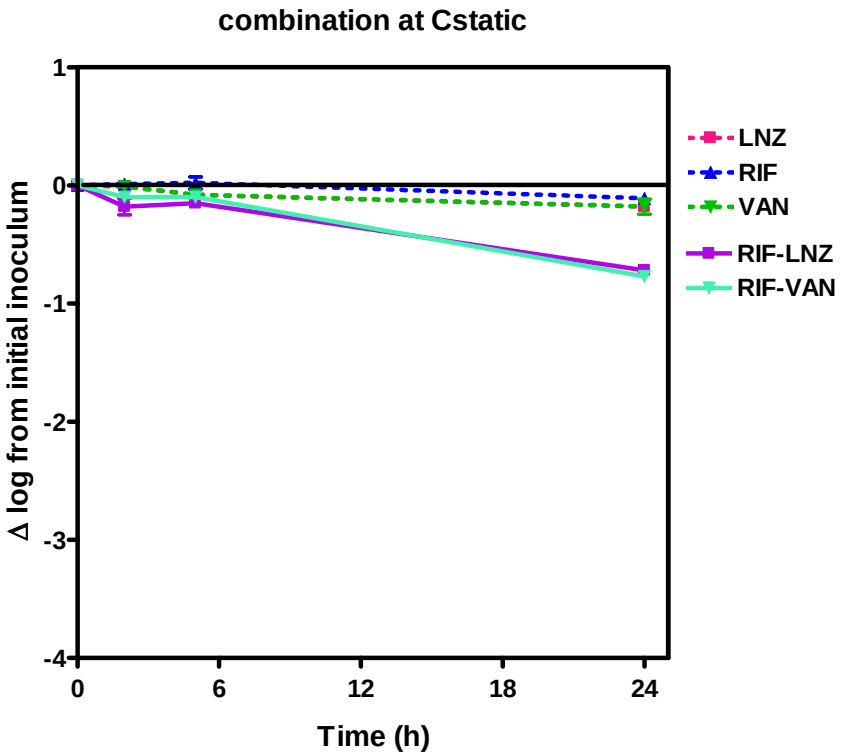
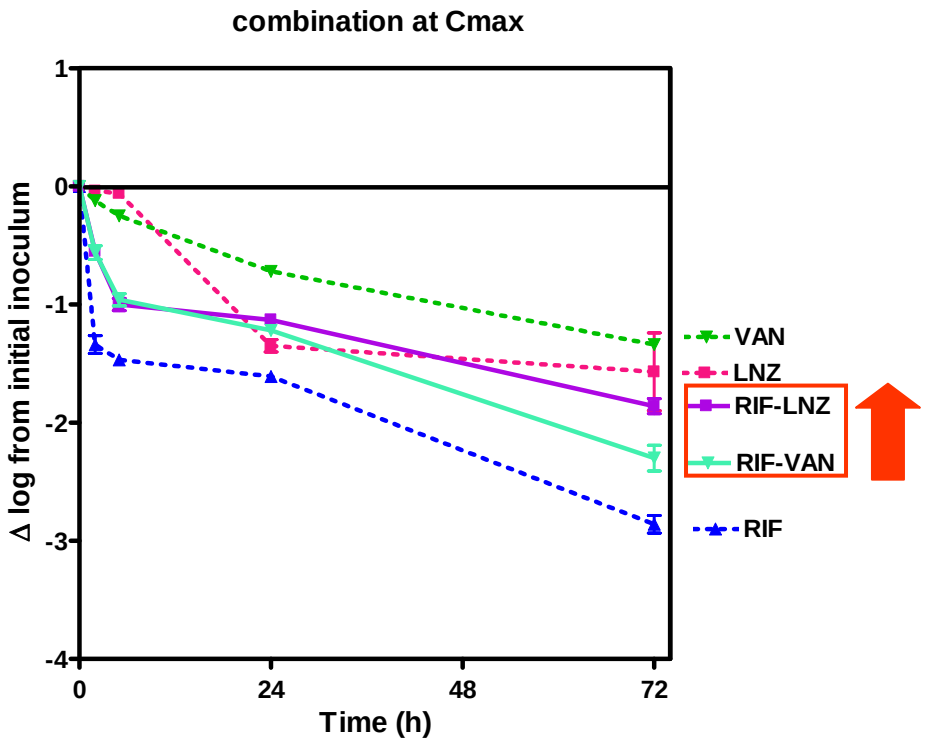




Combinations at 24 h

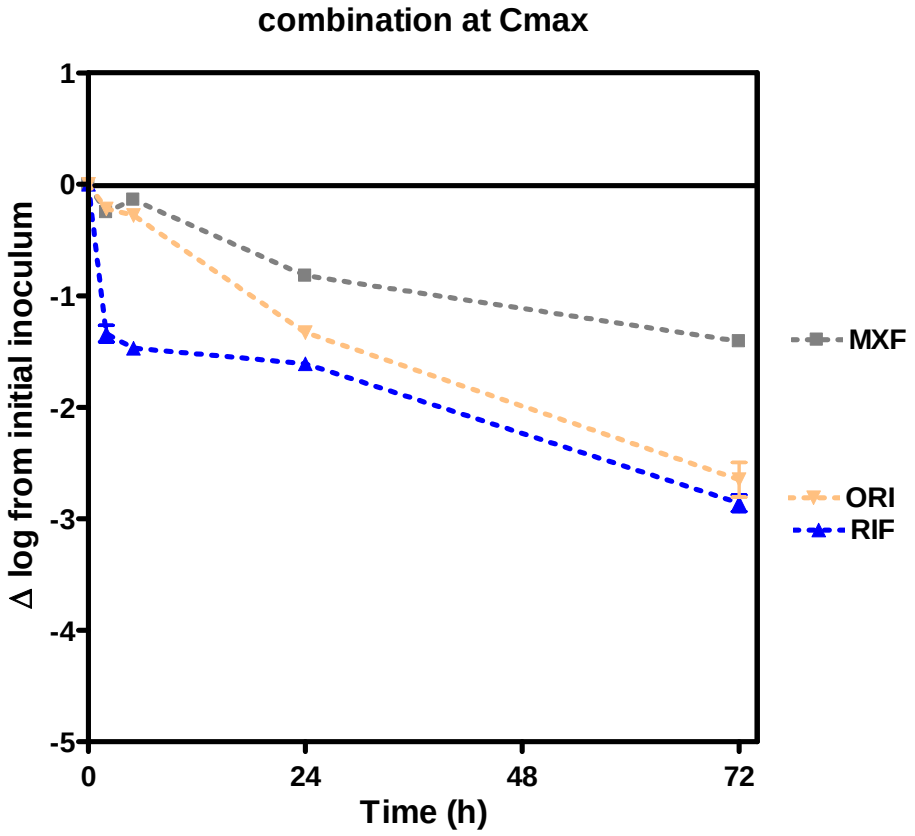
combinations received by the patient





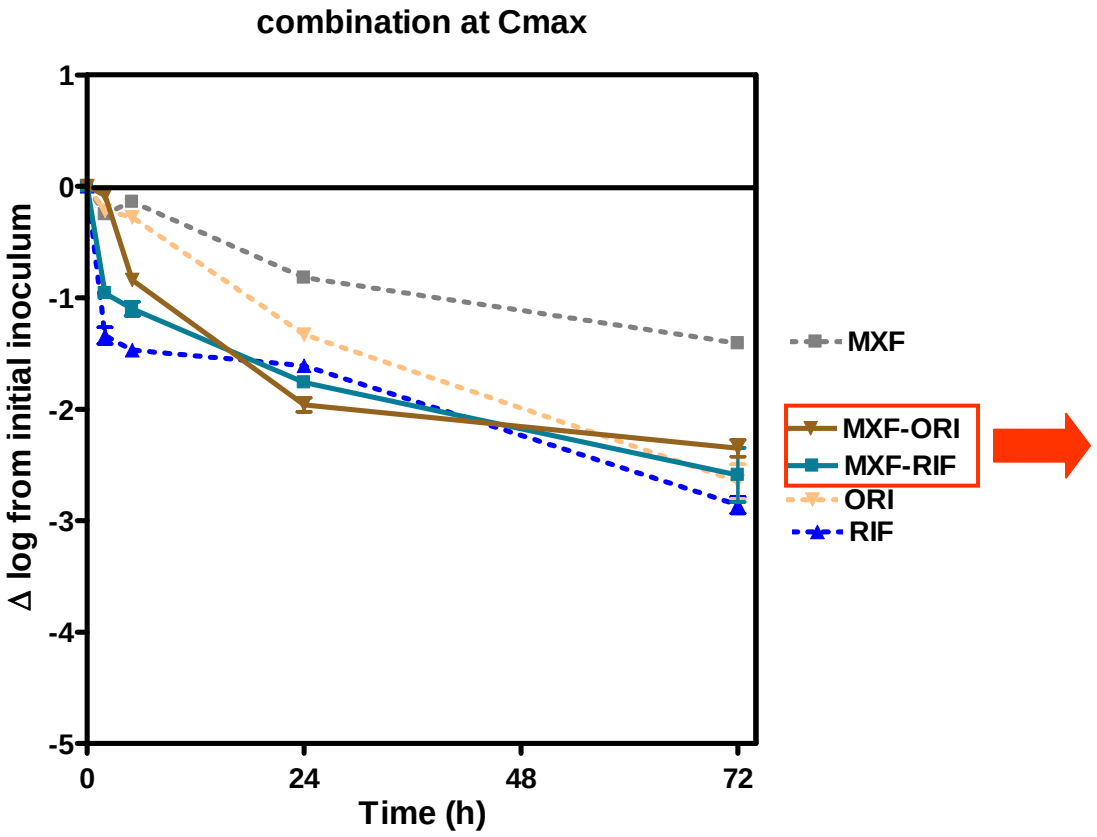
Combinations at 24 h

combinations between more active drugs



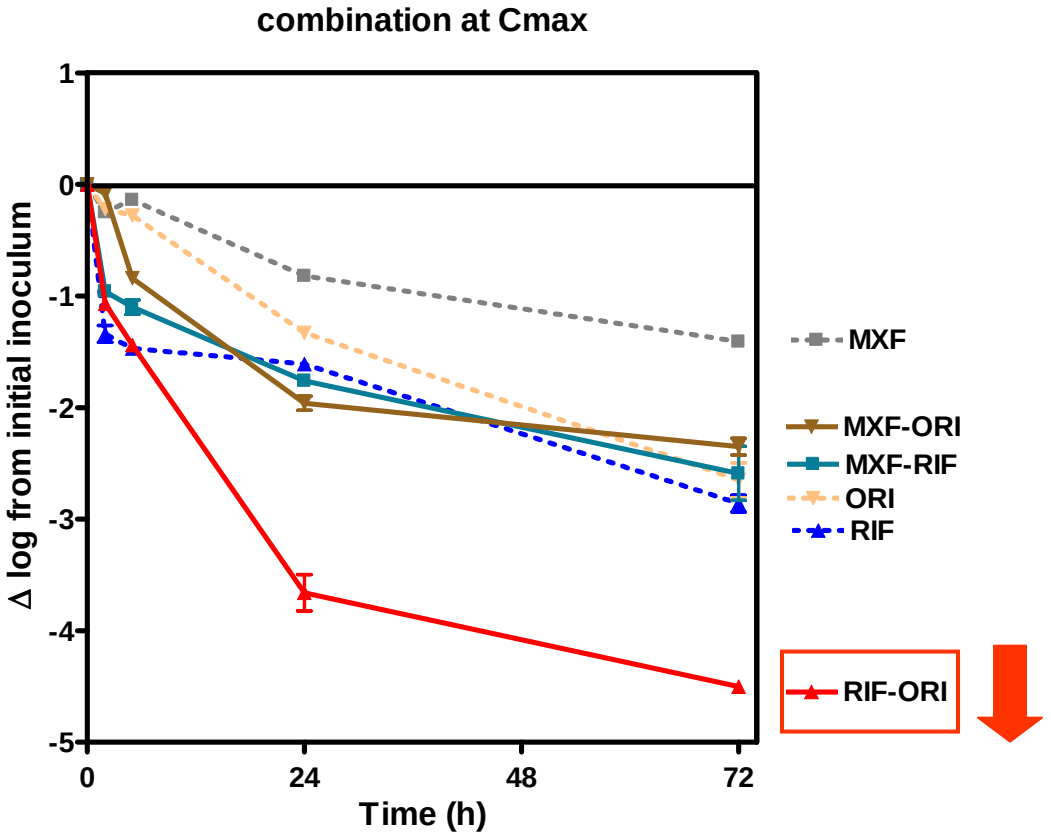
Combinations at 24 h

combinations between more active drugs



Combinations at 24 h

combinations between more active drugs



Conclusions

- SCV can persist intracellularly for prolonged periods of time;
  they remain totally (THP-1) or mainly (HUVEC) confined in acidic vacuoles.
- All antibiotics were considerably less active intracellularly than extracellularly against SCVs.
- As anticipated for thymidine-dependent SCVs, SMX-TMP was ineffective against both extracellular and intracellular forms.
  The use of this drug may have contributed to select SCV phenotype upon treatment.
- None of the antibiotics administered to the patient reached a bactericidal effect against intracellular SCVs. Activity of RIF was decreased in combination with LZD or VAN.
  This may explain the observed failure of antibiotic treatment in this patient and the difficulty of eradicating these organisms in general.
- In infected cells, ORI was the most active drug, and this activity wass further improved when combined with RIF.
- Our cellular model may serve to evaluate antibiotic susceptibility in infections for which intracellular reservoirs and SCVs could play an important role.