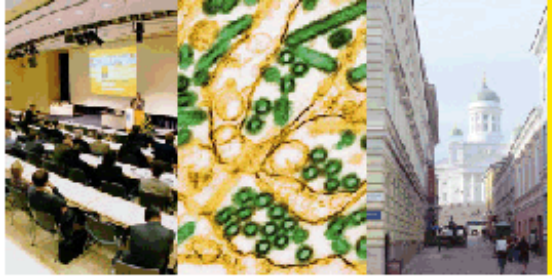

19th ECCMID

Radezolid (RX-1741), a novel oxazolidinone, is active against intracellular *S. aureus*, *L. monocytogenes* and *L. pneumophila* phagocytosed by human THP-1 macrophages

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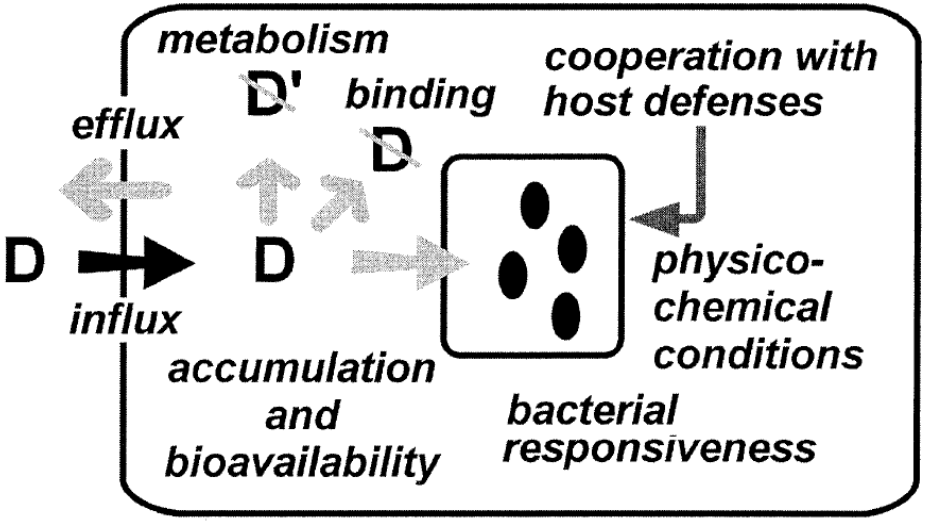
Intracellular bacteria

• major determinant in the recurrent and relapsing character of several bacterial infections

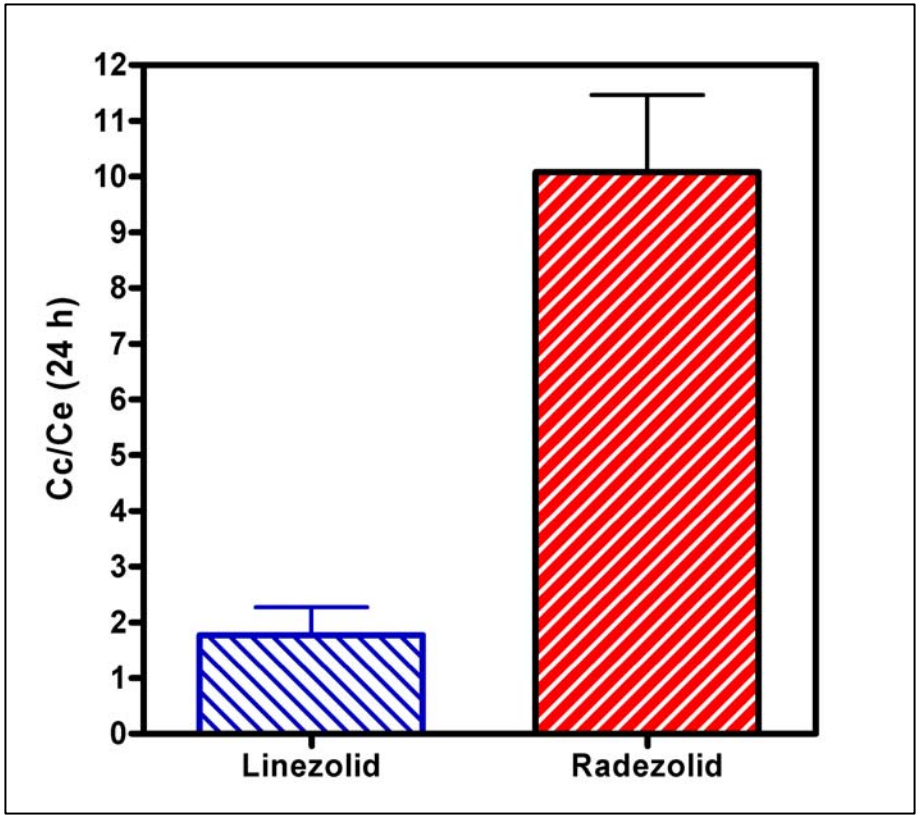
• requires that antibiotics that:

- efficiently accumulate within the infected intracellular compartments
- express activity therein



Carryn et al, Infect.Dis.Clin.North Am., 2003

Radezolid (RX-1741)



In contrast to linezolid, radezolid accumulates extensively within THP-1 macrophages

Radezolid (RX-1741)

- **Improved intrinsic activity against several organisms, including <u>those capable of surviving within eucaryotic cells</u>**

bacteria	MICs in mg/L	
	Linezolid	Radezolid
S. pneumoniae ErmB	0.5-2	≤ 0.25
S. pyogenes	2-4	0.03-0.125
H. influenzae	2-64	0.25-2
M. catarrhalis	2-16	≤ 0.25-1
S. aureus MSSA	2-4	0.5-4
S. aureus MRSA	2-8	≤ 0.25-8
L. pneumophila	4-16	1-4
C. trachomatis	8-16	0.5-1

Lawrence et al, AAC 2008, 52:1653-62

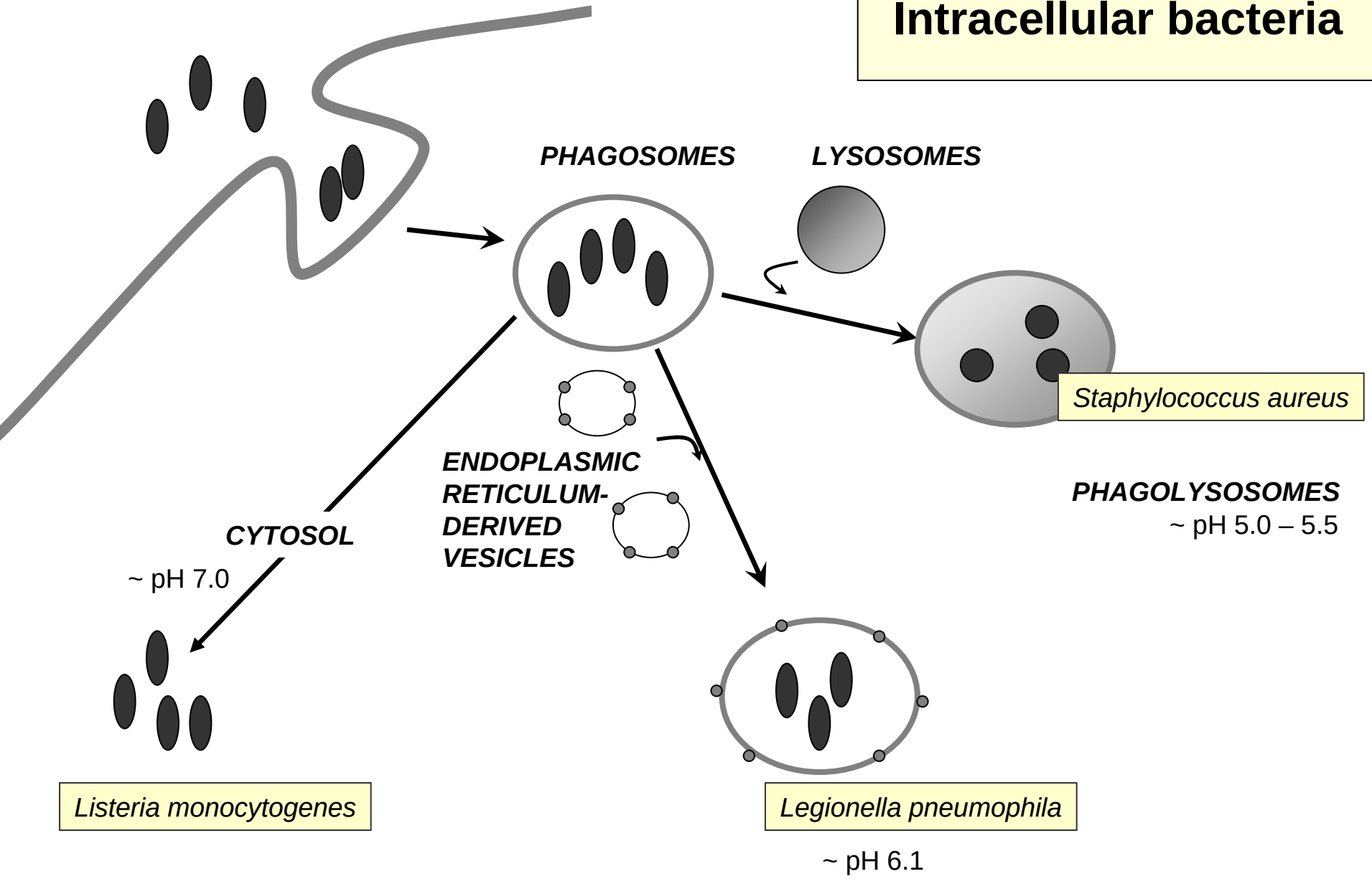
Aim of the study

To compare the intracellular activity of

radezolid and linezolid against intracellular bacteria

sojourning in different subcellular compartments

Intracellular bacteria

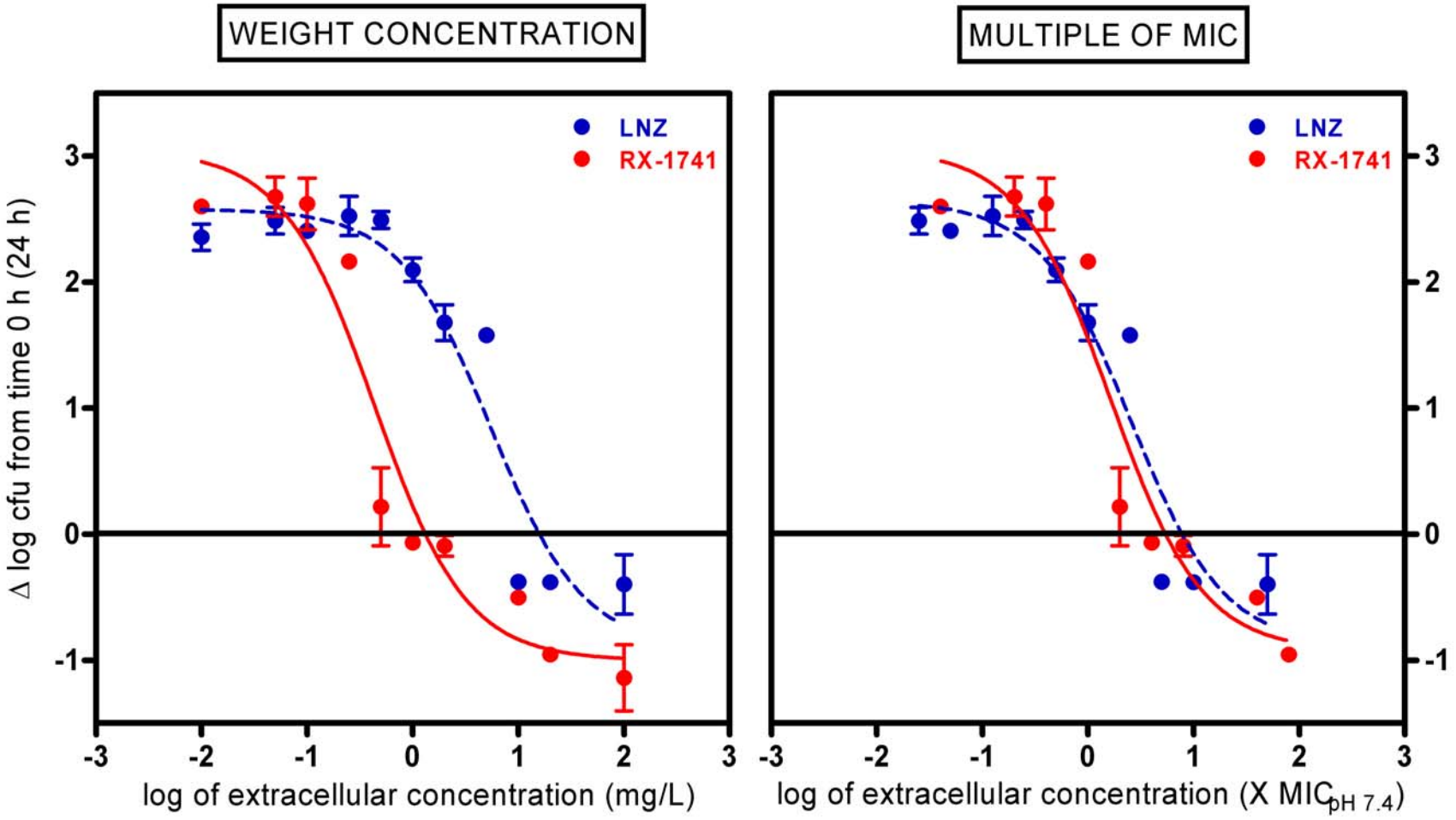


Intrinsic activities

Organisms	MICs (mg/L)	
	Linezolid	**Radezolid (RX-1741)**
Listeria monocytogenes (strain EGD)	1-2	0.03-0.06
Legionella pneumophila (strain ATCC 33153)	4-8	0.5-1
Staphylococcus aureus (strain ATCC 25923)	2	0.25-0.5

Radezolid shows lower MICs values against all tested bacteria

Conc. effects relationship in broth (*S. aureus* ATCC 25923)



Radezolid shows increased potency
(lower static concentrations) in broth

Methods

THP-1 macrophages

L. monocytogenes
L. pneumophila
Opsonized *S. aureus*

→ phagocytosis

↓

Removal of extracellular bacteria (washings)

↓

Incubation with increasing concentrations of antibiotics
(about 0.01 to 100x MIC)

↓

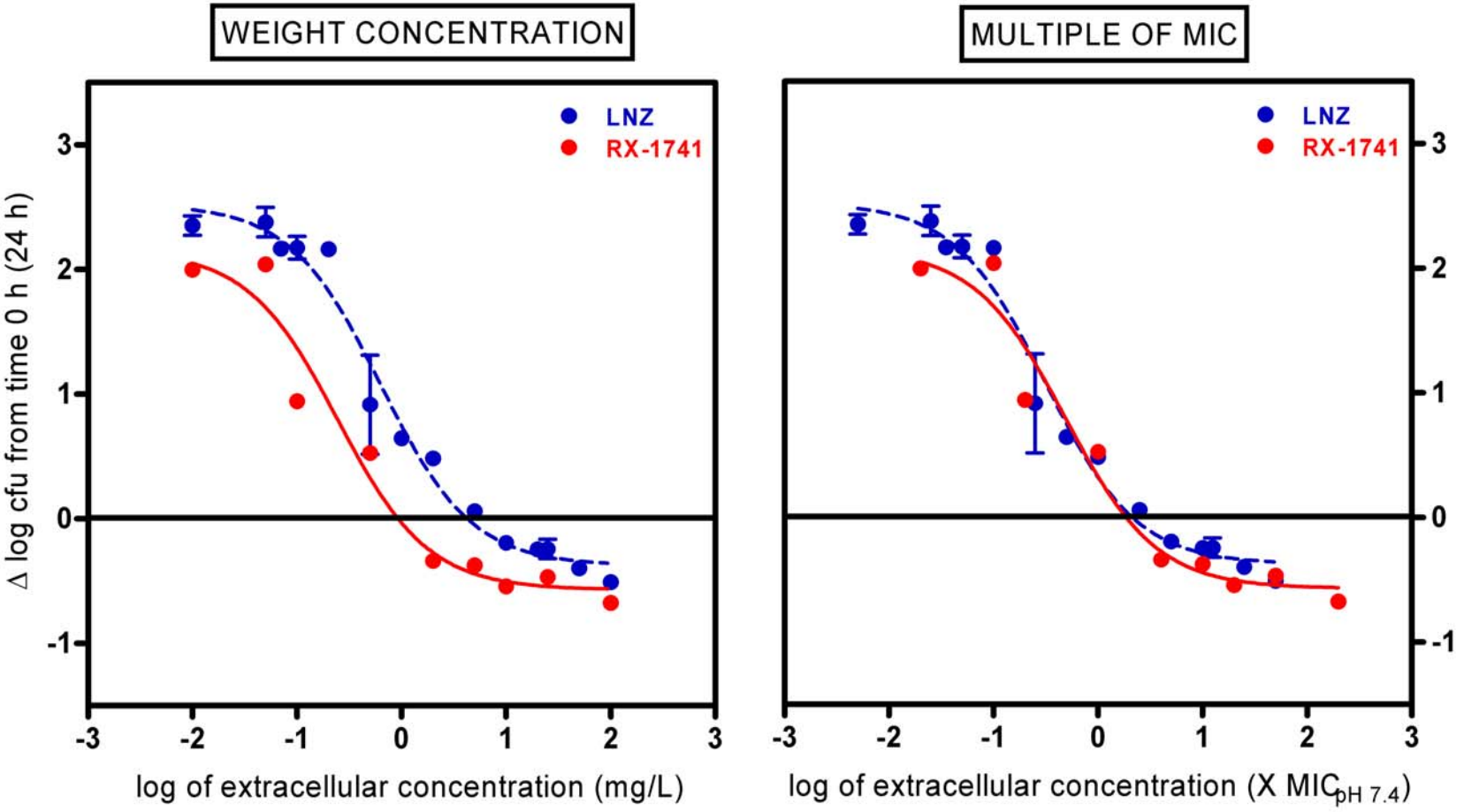
At 24h (SA/LM) and 48 h (LP): removal of extracellular bacteria/antibiotics and cell lysis

↓

CFU counting and assay of protein content

Lemaire et al, JAC, 2005; Barcia-Macay et al, AAC, 2006

Intracellular *S. aureus*

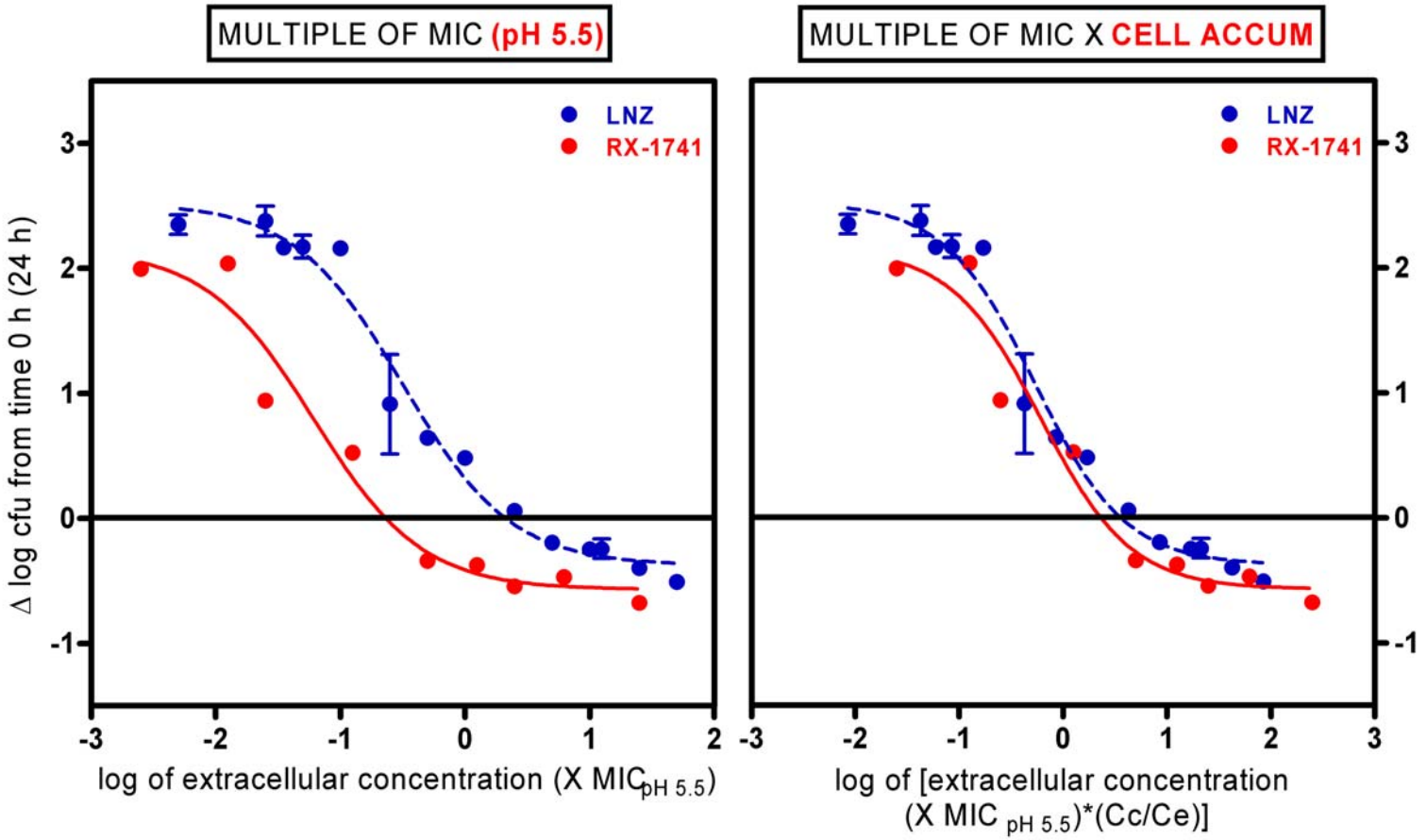


Against phagolysosomal *S. aureus*, the intracellular potency (in mg/L) of radezolid (RX-1741) is superior to linezolid

S. A. (MHB)	LNZ	RX-1741
MICs (mg/L)	2	**0.25-0.5**

Intracellular *S. aureus*

S. aureus is found in phagolysosomes, where pH is acidic (pH 5.5)

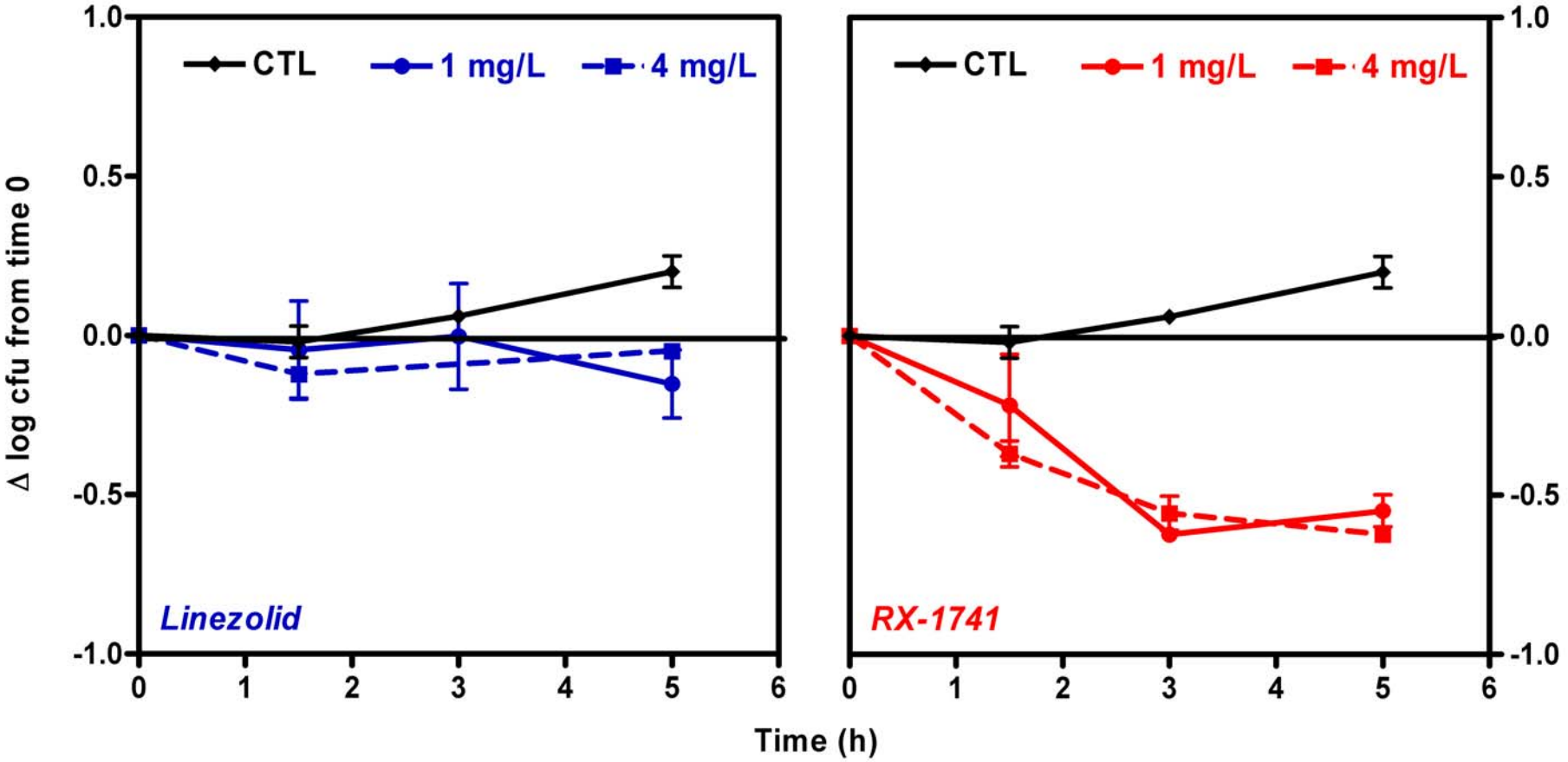


Higher levels of cellular accumulation give radezolid an advantage over linezolid, despite the similar potency of the two molecules at low pH

S. A. (MHB)	LNZ	RX-1741
MICs (mg/L)	2	4

Intracellular *S. aureus* (ATCC 25923)

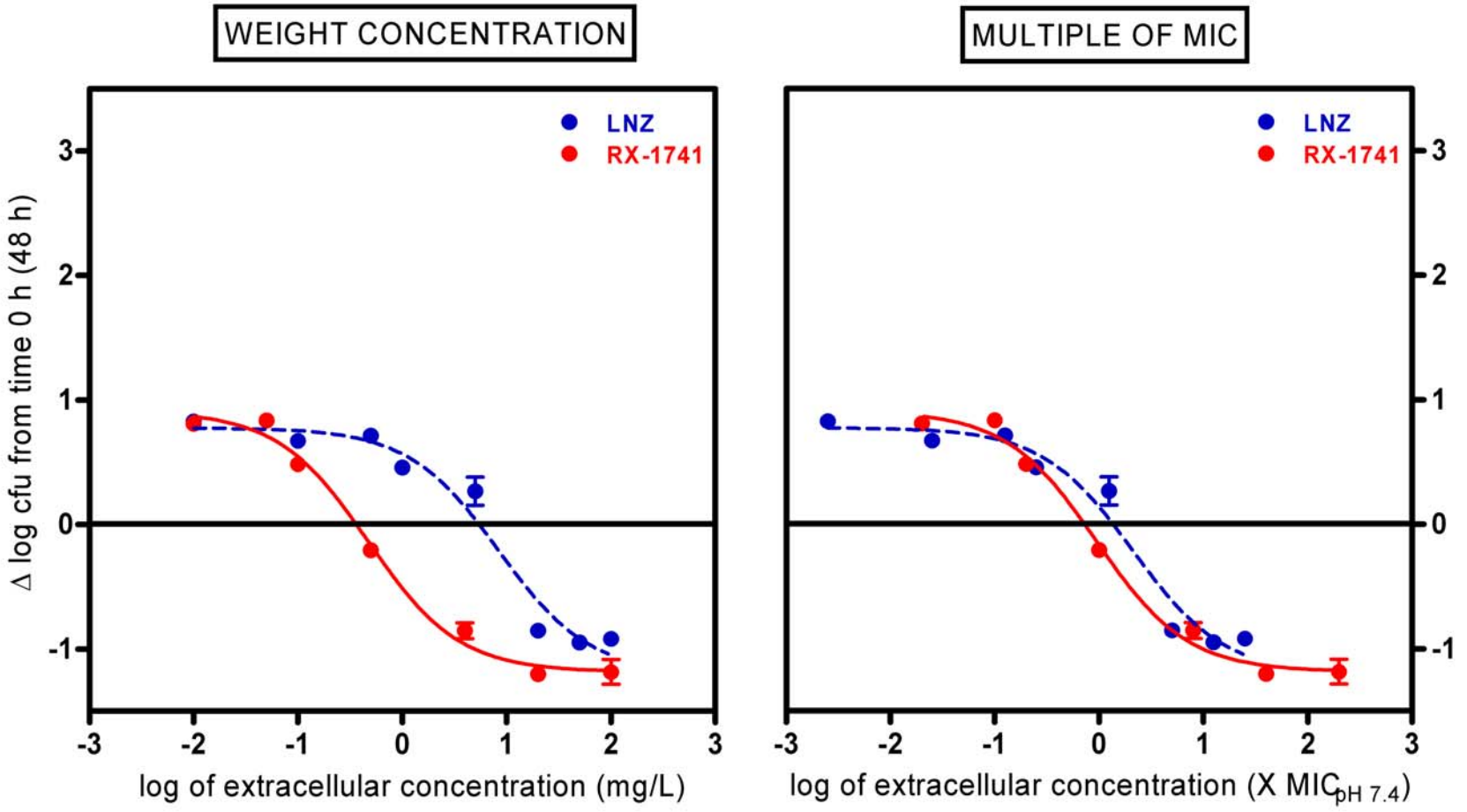
Influence of time



Radezolid reaches its maximal effect against intraphagocytic *S. aureus* after only 3 h drug exposure, while linezolid remained static during this period

S. A. (MHB)	LNZ	RX-1741
MICs (mg/L)	2	0.25-0.5

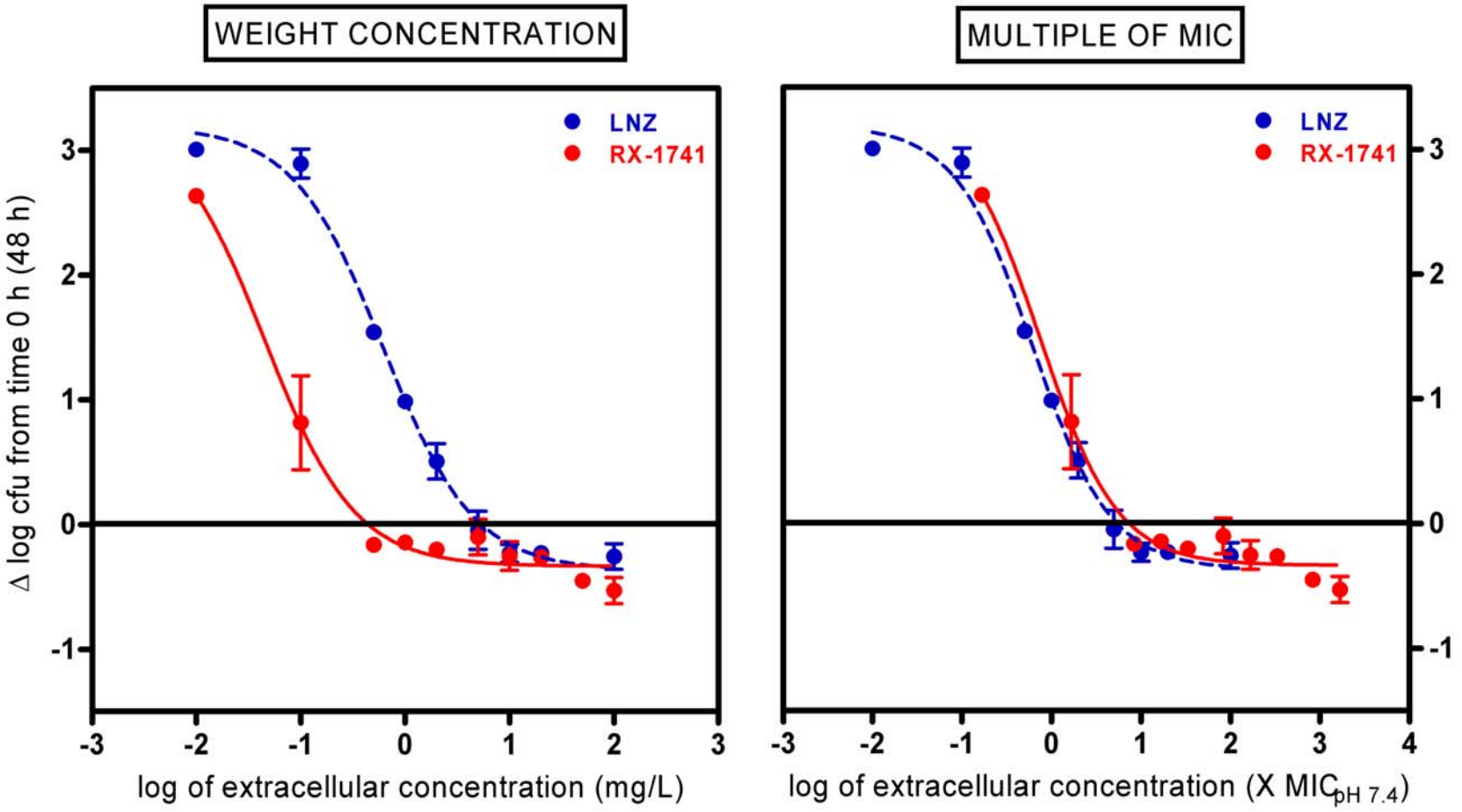
Intracellular *L. pneumophila* (ATCC 33153)



Against phagosomal *L. pneumophila*,
radezolid shows higher intracellular potency (in mg/L)
compared to linezolid

L.P. (BYEα)	LNZ	**RX-1741**
MICs (mg/L)	4-8	**0.5-1**

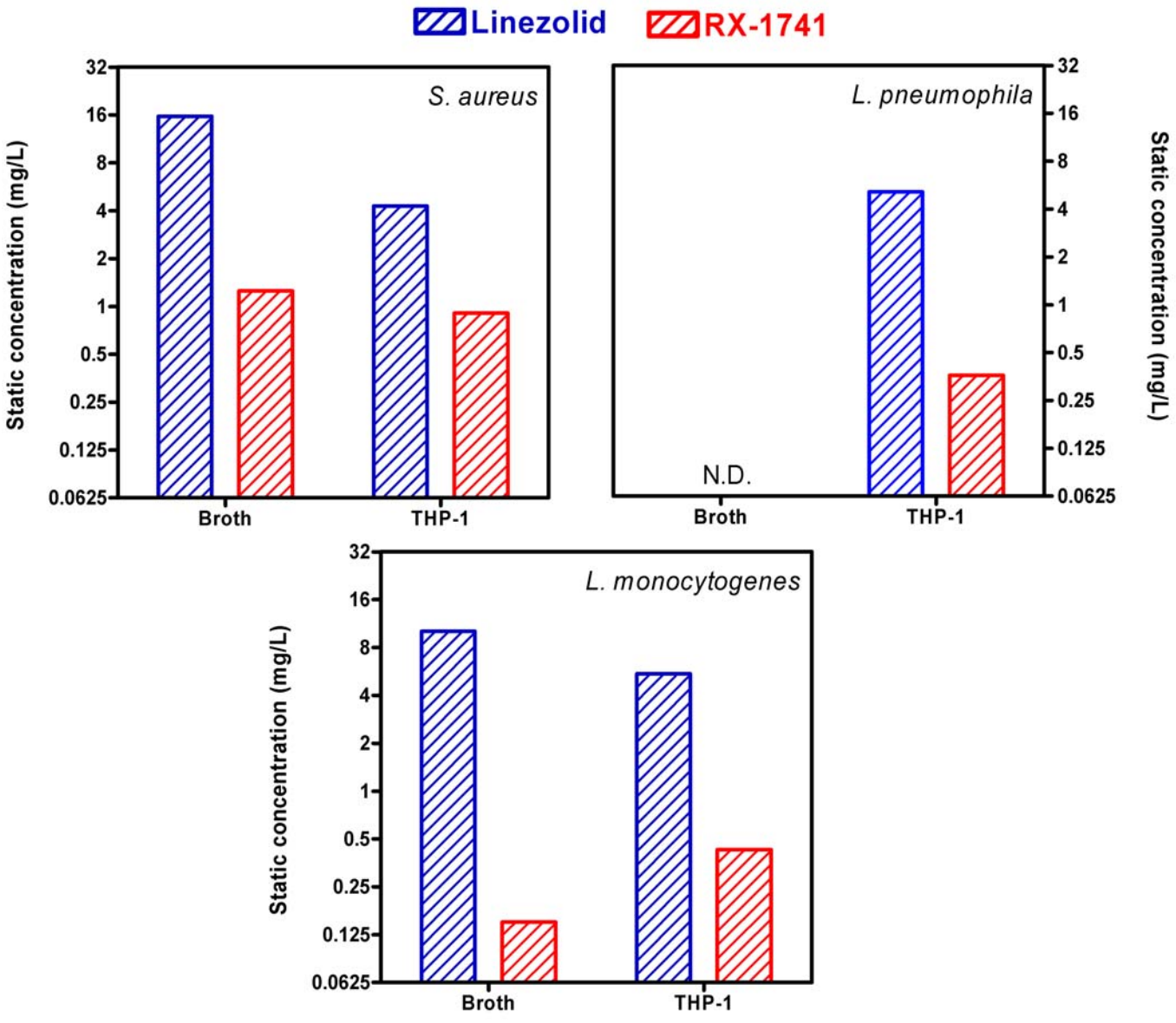
Intracellular *L. monocytogenes* (strain EGD)



Against cytosolic *L. monocytogenes*, radezolid shows higher intracellular potency (in mg/L) compared to linezolid

L.M. (TSB)	LNZ	RX-1741
MICs (mg/L)	1-2	**0.03-0.06**

Comparative static concentrations



In all cases, the concentration of radezolid required to inhibit bacterial growth is lower than linezolid

Conclusions

- Compared to the linezolid, radezolid (RX-1741) shows increased potency towards both extracellular and intracellular S*. aureus*, *L. pneumophila* and *L. monocytogenes*

→

The higher intracellular activity of radezolid is probably due to :

- its higher intrinsic activity (lower MICs values)
- its higher cellular accumulation as compared to linezolid