Activity of Novel β-lactamase Inhibitor QPX7728 Combined with β-lactams Against ST258 *Klebsiella pneumoniae* and ST131 *Escherichia coli* isolates Producing β-lactamases

Mariana Castanheira,[1] Jill Lindley,[1] Tim B. Doyle,[1] Andrew P. Davis,[1] and Olga Lomovskaya[2]

[1] JMI Laboratories, North Liberty, Iowa
[2] Qpex Biopharma, San Diego, California

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Disclosure

Achaogen
Allecra
Allergan
Amplyx
Antabio
Arietis Corp.
Arixa Pharmaceuticals
Astellas Pharma
Athelas
Basilea
Bayer
Boston Pharmaceuticals
Cidara
CorMedix
DePuy Synthes
Destiny Pharma
Discuva Ltd.
Dr. Falk Pharma GmbH
Emery Pharma
Entasis Therapeuticals
Eurofarma Brasil
Fox Chase Chemical Diversity Center, Inc.
Gateway Pharmaceutical
GenePOC Inc.
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Ra Pharmaceuticals
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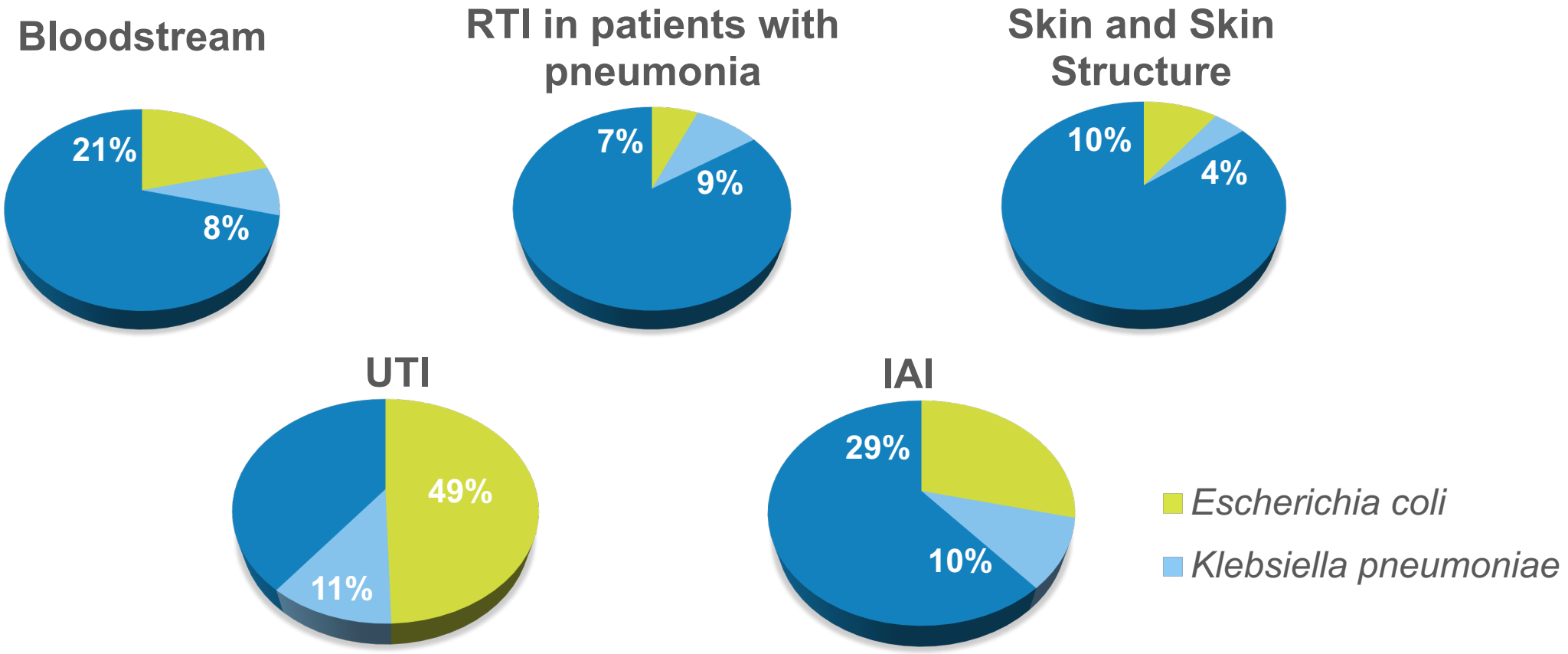
Spero Therapeutics
Summit Pharmaceuticals
Synlogic
Taisho Pharmaceutical
TenNor Therapeutics
Tetraphase
The Medicines Co.
Theravance
VenatoRX
Vyome Therapeutics
Wockhardt
Yukon Pharmaceuticals
Zai Lab
Zavante Therapeutics

SENTRY
ANTIMICROBIAL SURVEILLANCE

Prevalence of *K. pneumoniae* and *E. coli* (2016-2017)



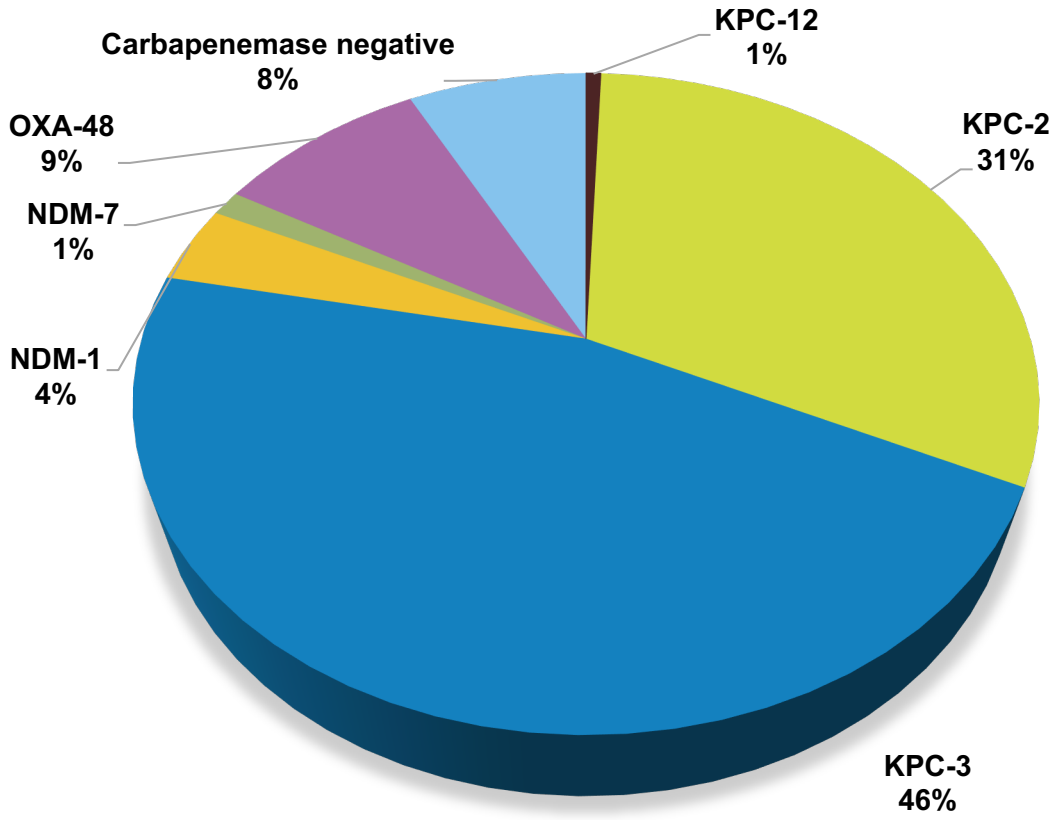
ST131 *E. coli*

- Early isolates in 2003
- ExPEC/Phylogenetic Group B2
- Truly pathogenic
- Carry many but not all virulence genes from phylogenetic group B2
- Carry QRDR mutations leading to fluoroquinolone-resistance and $bla_{\text{CTX-M-15}}$ encoding β-lactam resistance

Nicolas-Chanoine et al., CMR, 2014
Mathers et al., Adv. App. Micro., 2015

ST258 *K. pneumoniae*

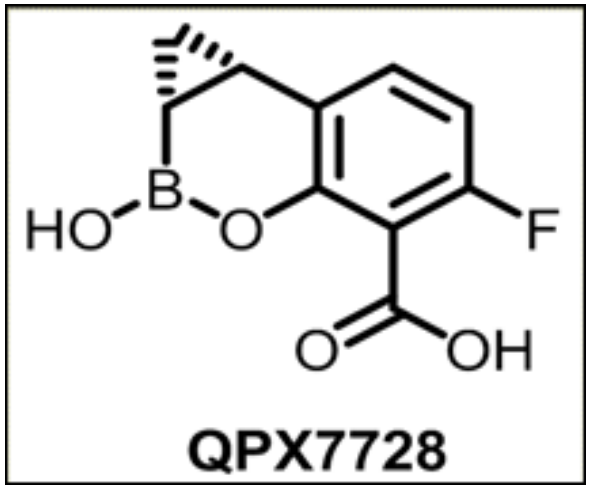
- Responsible for 70% of the KPC-producing isolates in US outbreaks
- Very common in other countries
- 2 genetic clades (I and II)
- ST11 is a SLV that is more common in Asia



Pitout et al., AAC, 2015
Mathers et al., CMR, 2015

QPX7728

- Broad spectrum of inhibition, including class B and class D β-lactamases from *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.
- Not affected by porin modifications and efflux
- Intravenous and oral administration



Nelson et al. AAC 2020
Lomovskaya et al. AAC, 2020
Hecker et al. J. Med. Chem. 2020

Objective

To evaluate the activity of β-lactams in combination with QPX7728 against a collection of 118 ST258 *K. pneumoniae* and 92 ST131 *E. coli* collected from a worldwide surveillance study

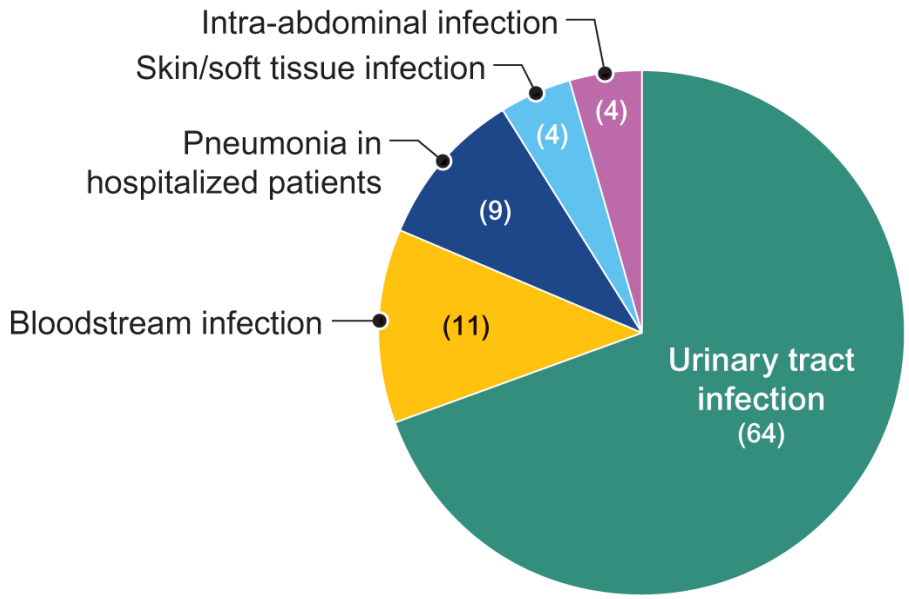
Methods

- A total of 118 ST258 *K. pneumoniae* and 92 ST131 *E. coli* were tested
  - STs and presence of β-lactamases were obtained from whole genome sequencing (WGS) data
  - ST258 and ST131 single loci variants was also included
- Susceptibility testing by reference broth microdilution (CLSI; M07, 2018) against cefepime, ceftibuten, ceftolozane, ertapenem, meropenem, and tebipenem alone or with QPX7728 at 2, 4 or 8 mg/L
  - Quality control (QC) was performed according to CLSI guidelines (M100, 2019)

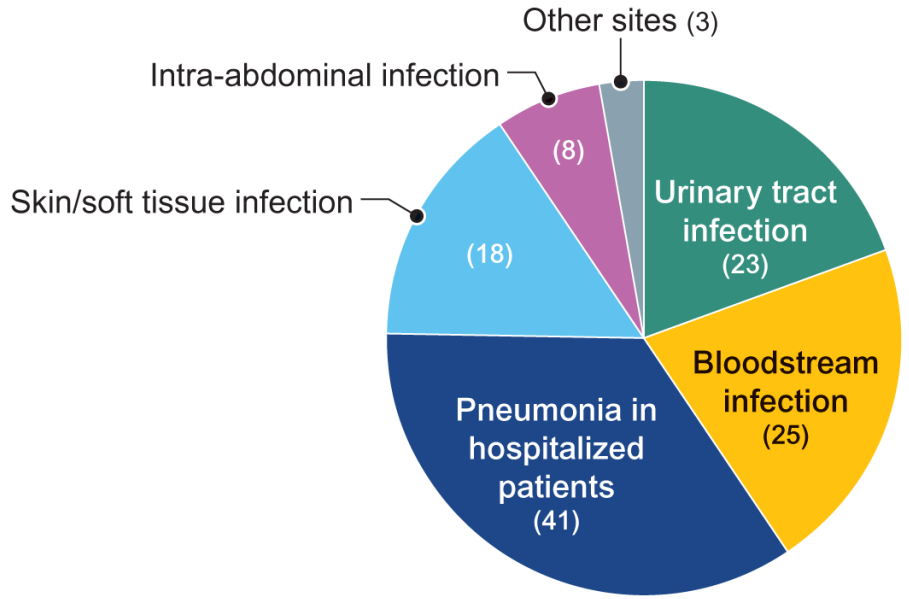
Mendes et al. OFID 2019
CLSI M7Ed10, 2018
CLSI M100Ed29, 2019

Results

A. ST131 by infection type

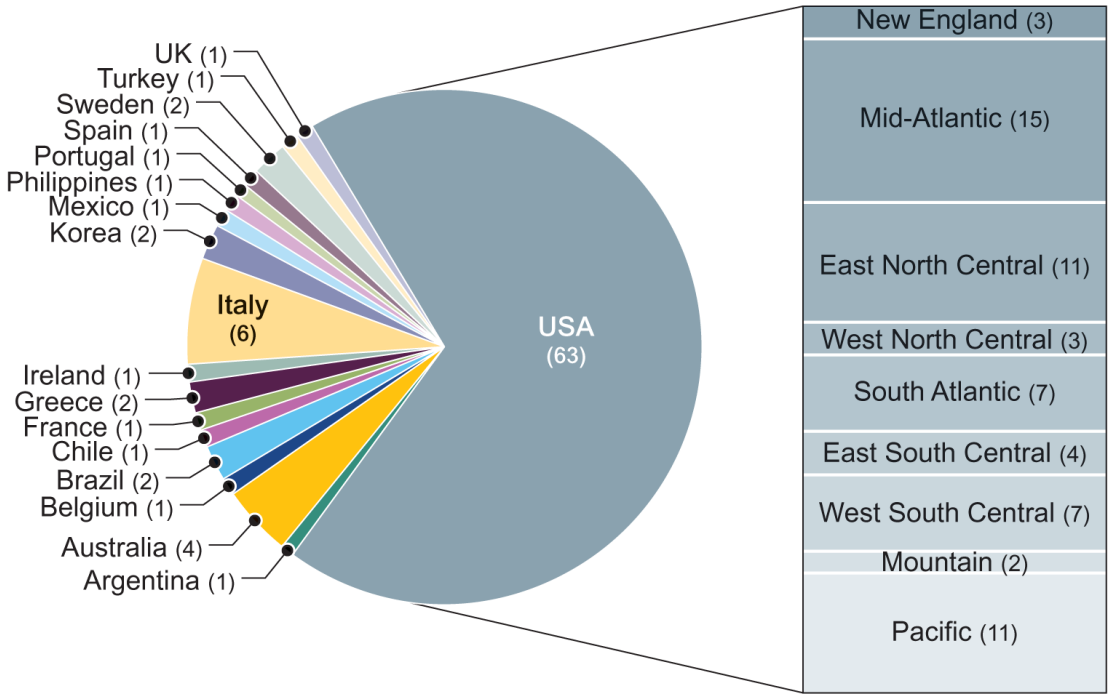


B. ST258 by infection type

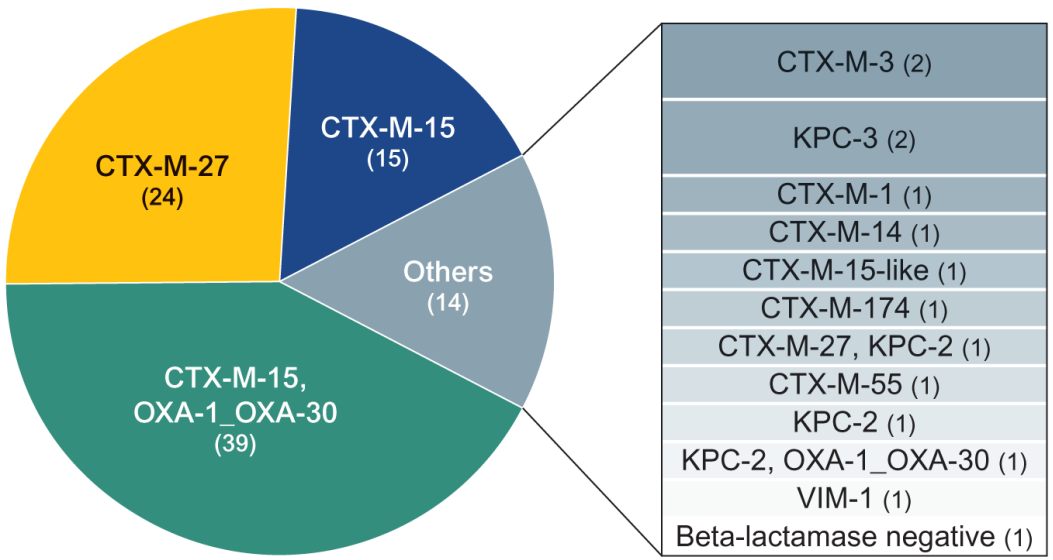


Results

A. ST131 by country/US census division

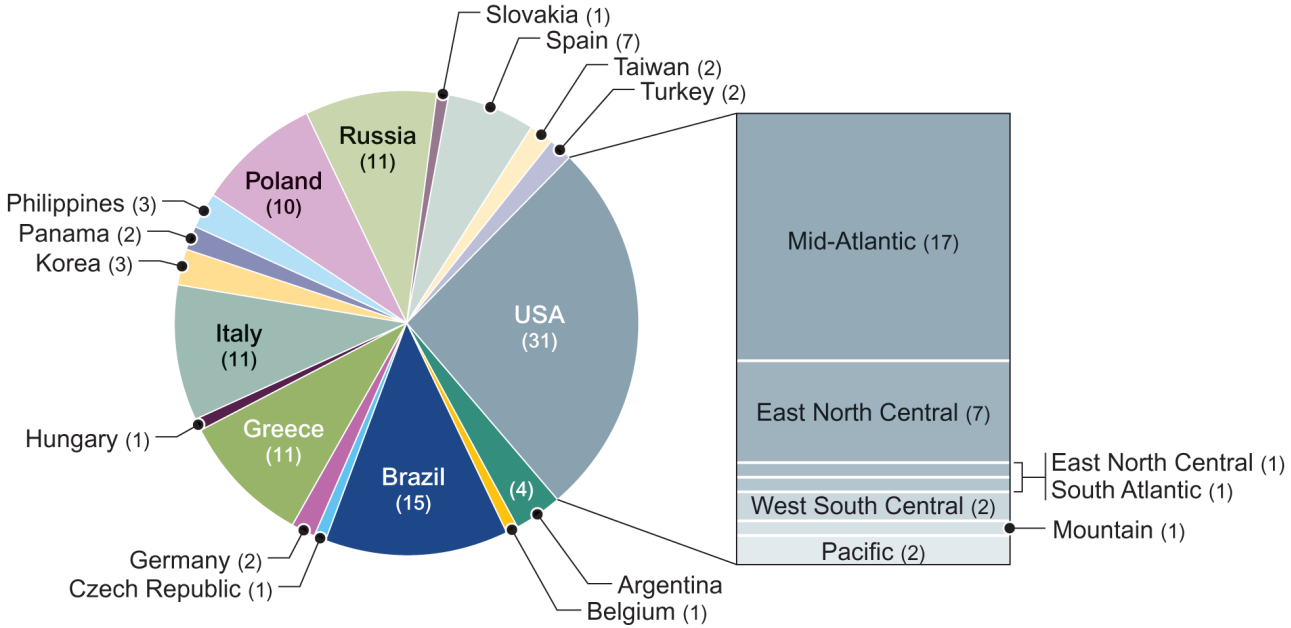


B. ST131 by beta-lactamase

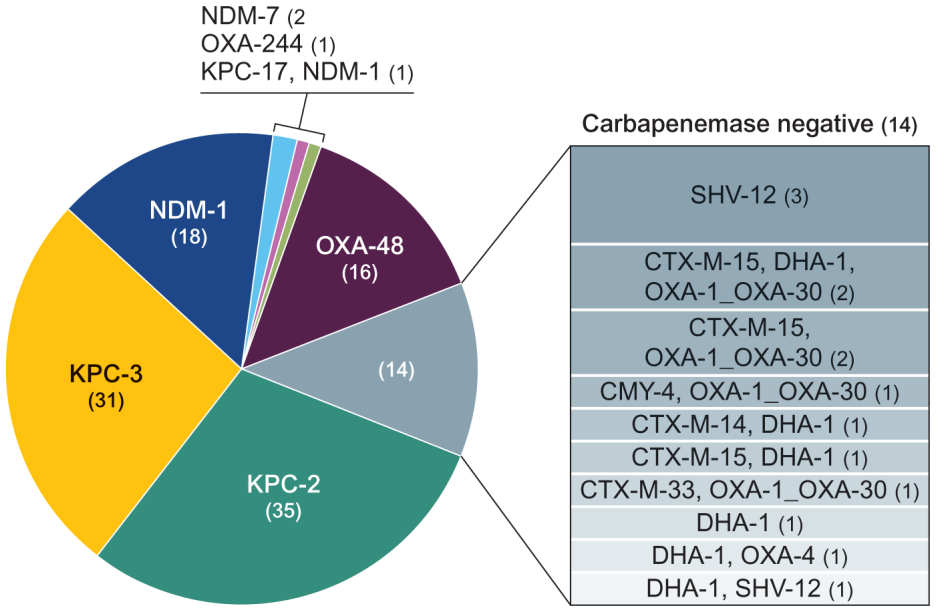


Results

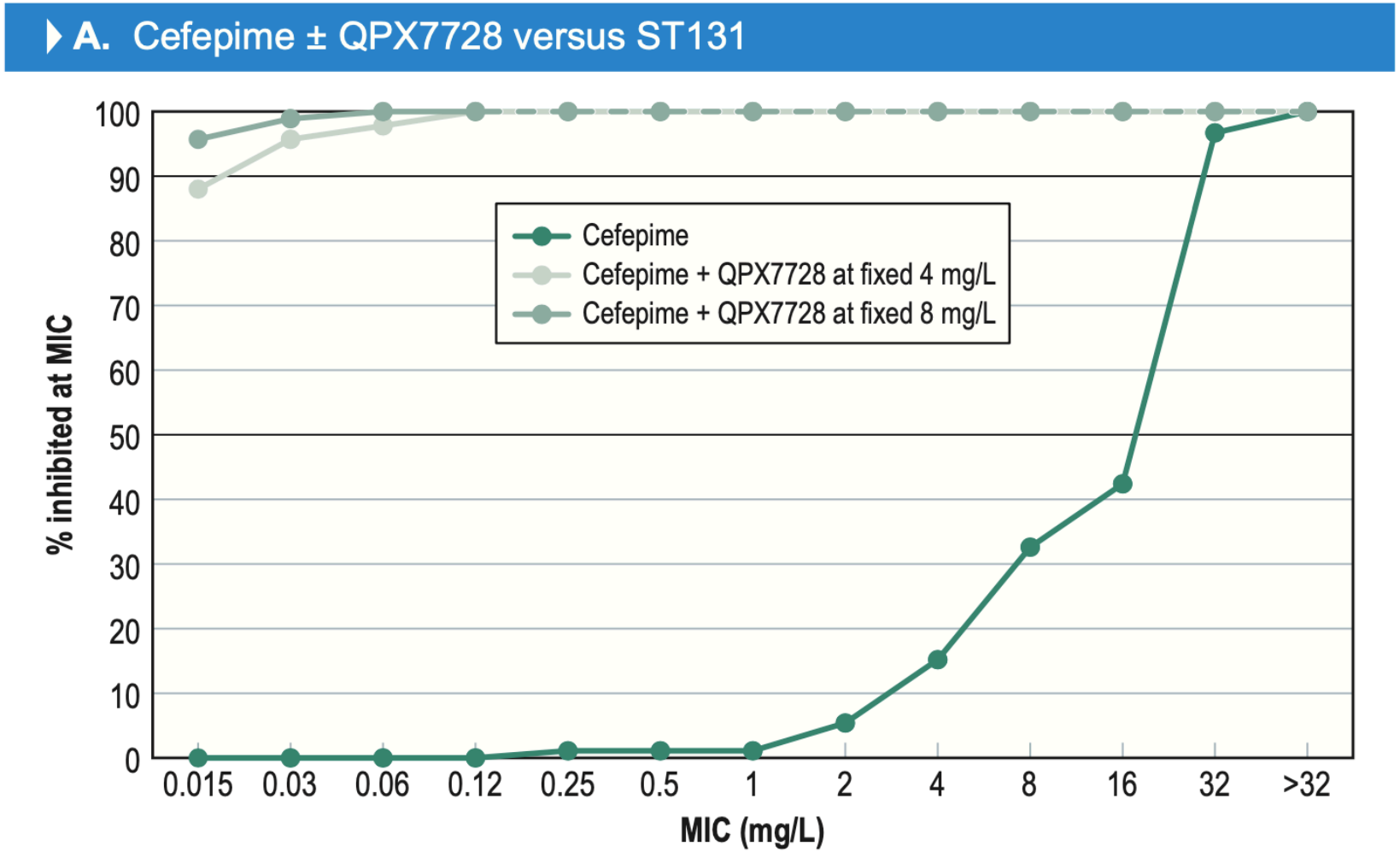
A. ST258 by country/US census division



B. ST258 by beta-lactamase

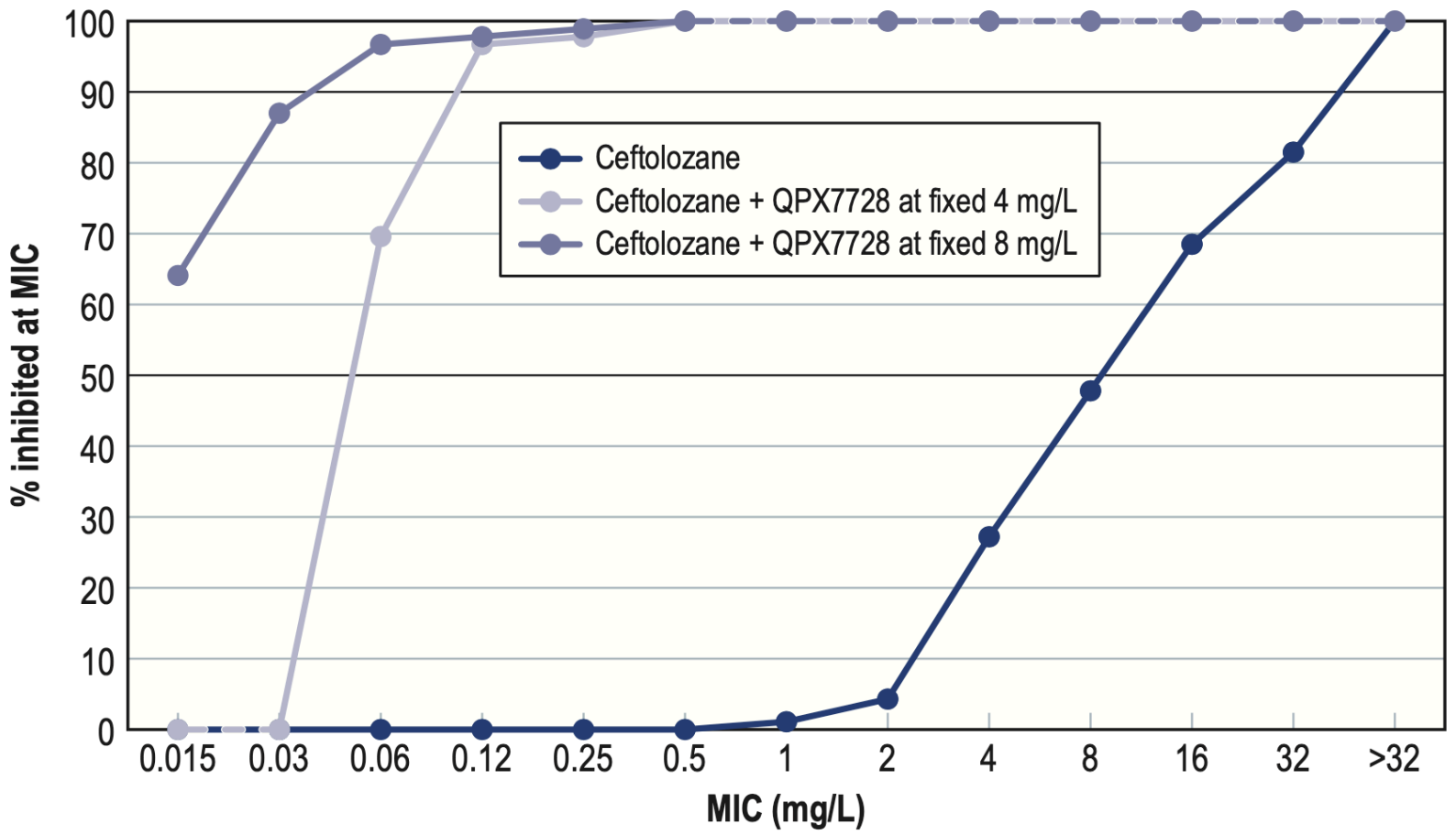


ST131


A. Cefepime ± QPX7728 versus ST131
% inhibited at MIC
100
90
80
70
60
50
40
30
20
10
0
Cefepime
Cefepime + QPX7728 at fixed 4 mg/L
Cefepime + QPX7728 at fixed 8 mg/L
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
>32
MIC (mg/L)

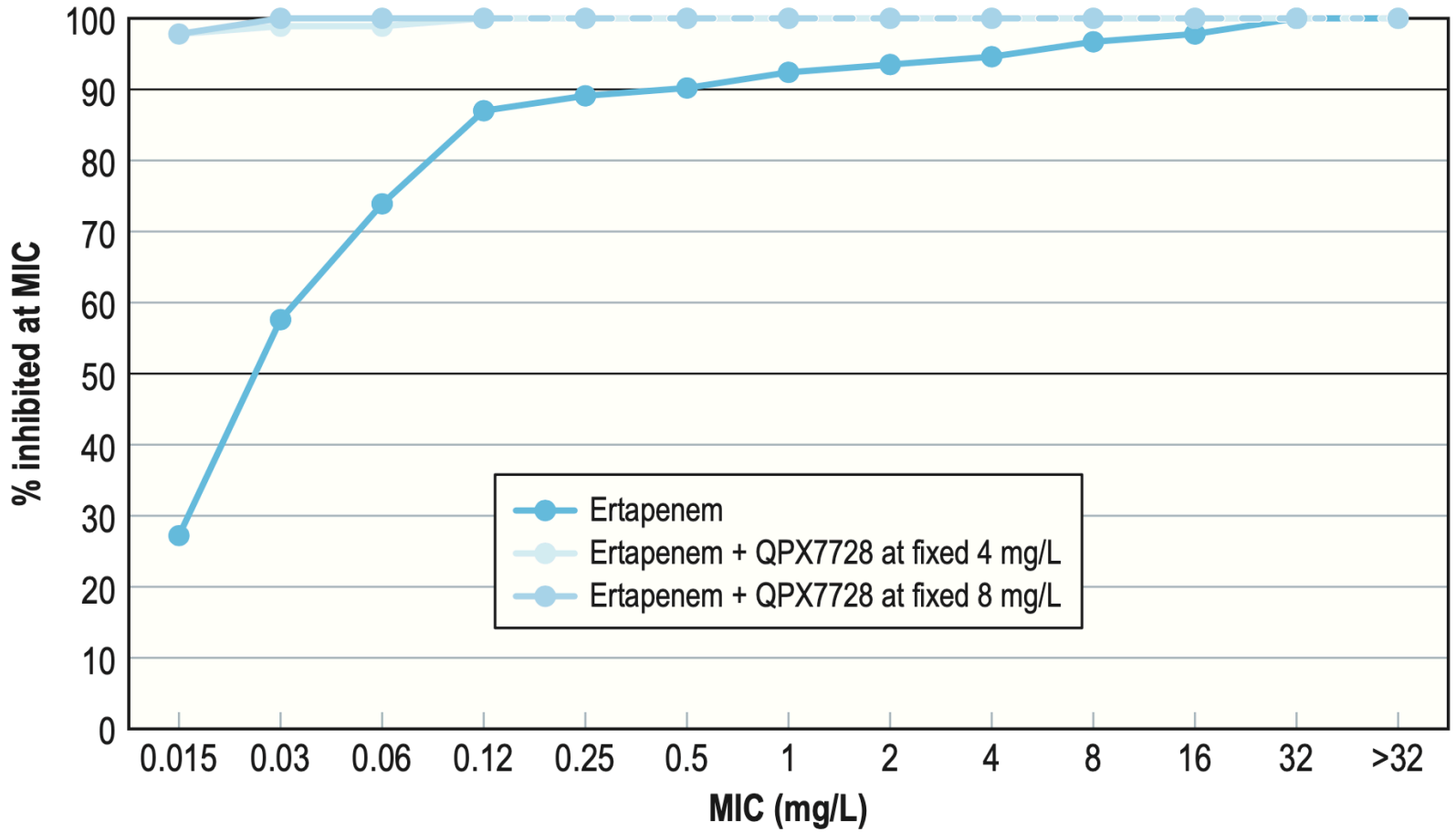
ST131

C. Ceftolozane ± QPX7728 versus ST131



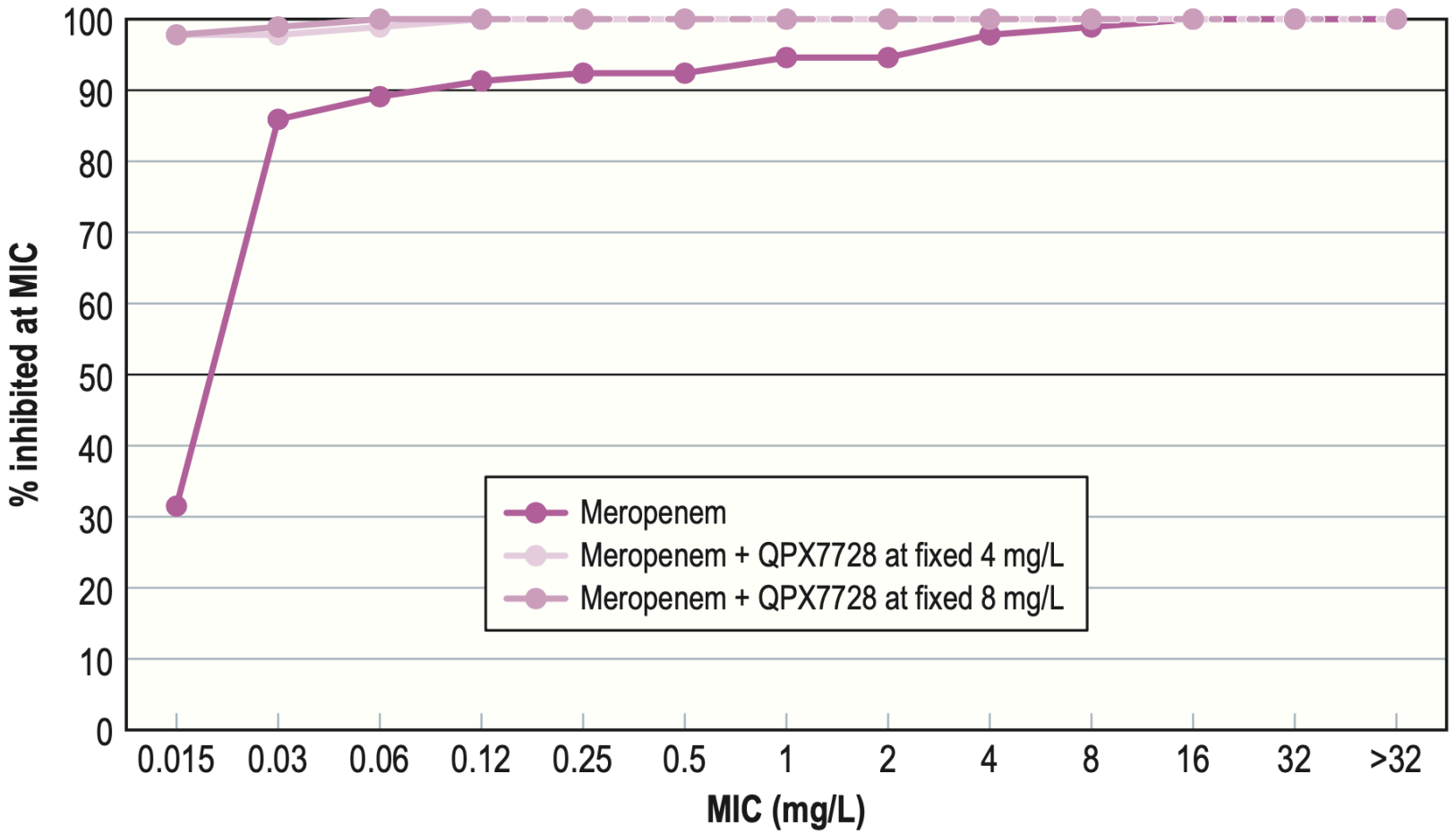
ST131

D. Ertapenem ± QPX7728 versus ST131

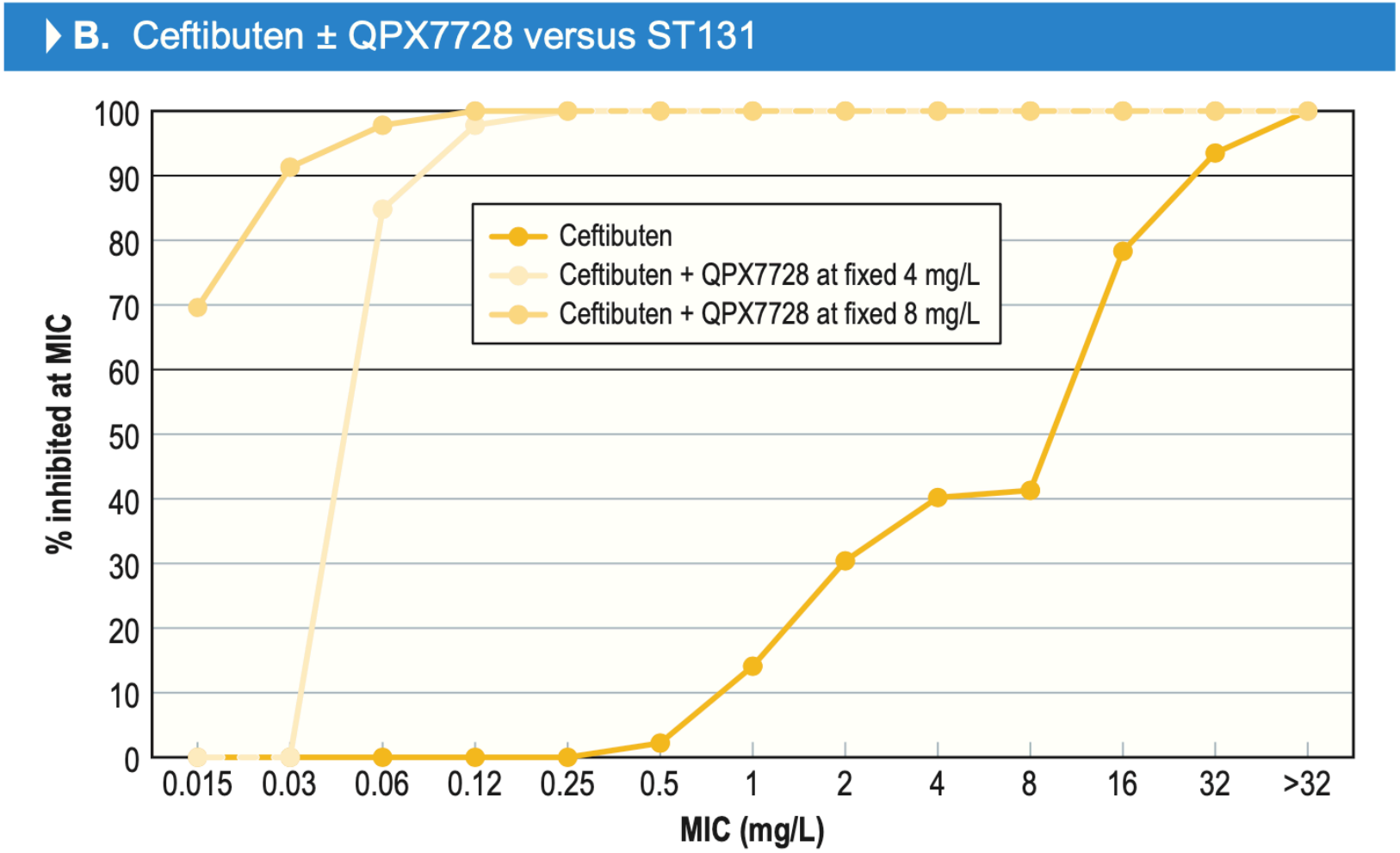


ST131

E. Meropenem ± QPX7728 versus ST131

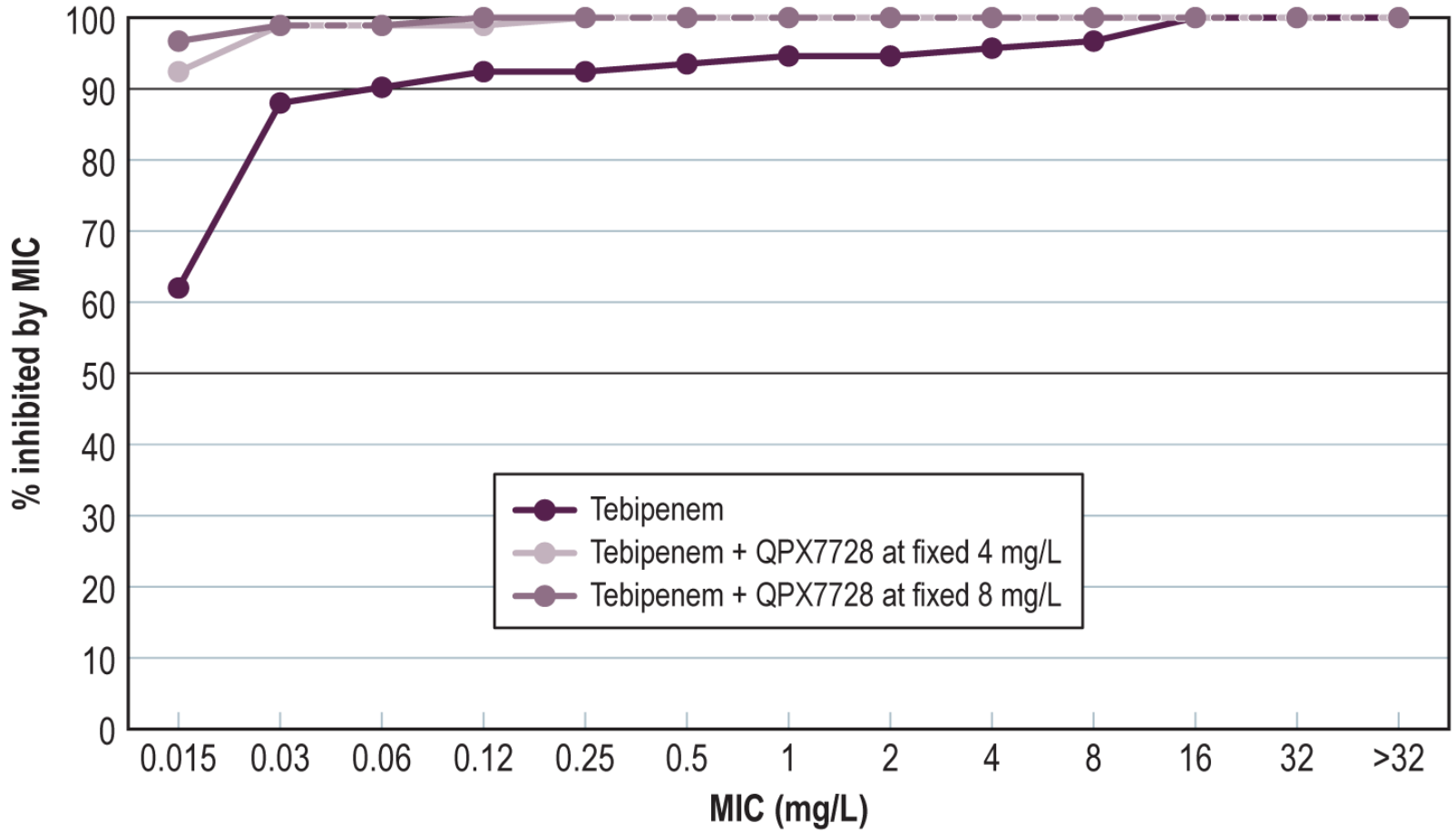


ST131


B. Ceftibuten ± QPX7728 versus ST131
% inhibited at MIC
100
90
80
70
60
50
40
30
20
10
0
Ceftibuten
Ceftibuten + QPX7728 at fixed 4 mg/L
Ceftibuten + QPX7728 at fixed 8 mg/L
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
>32
MIC (mg/L)

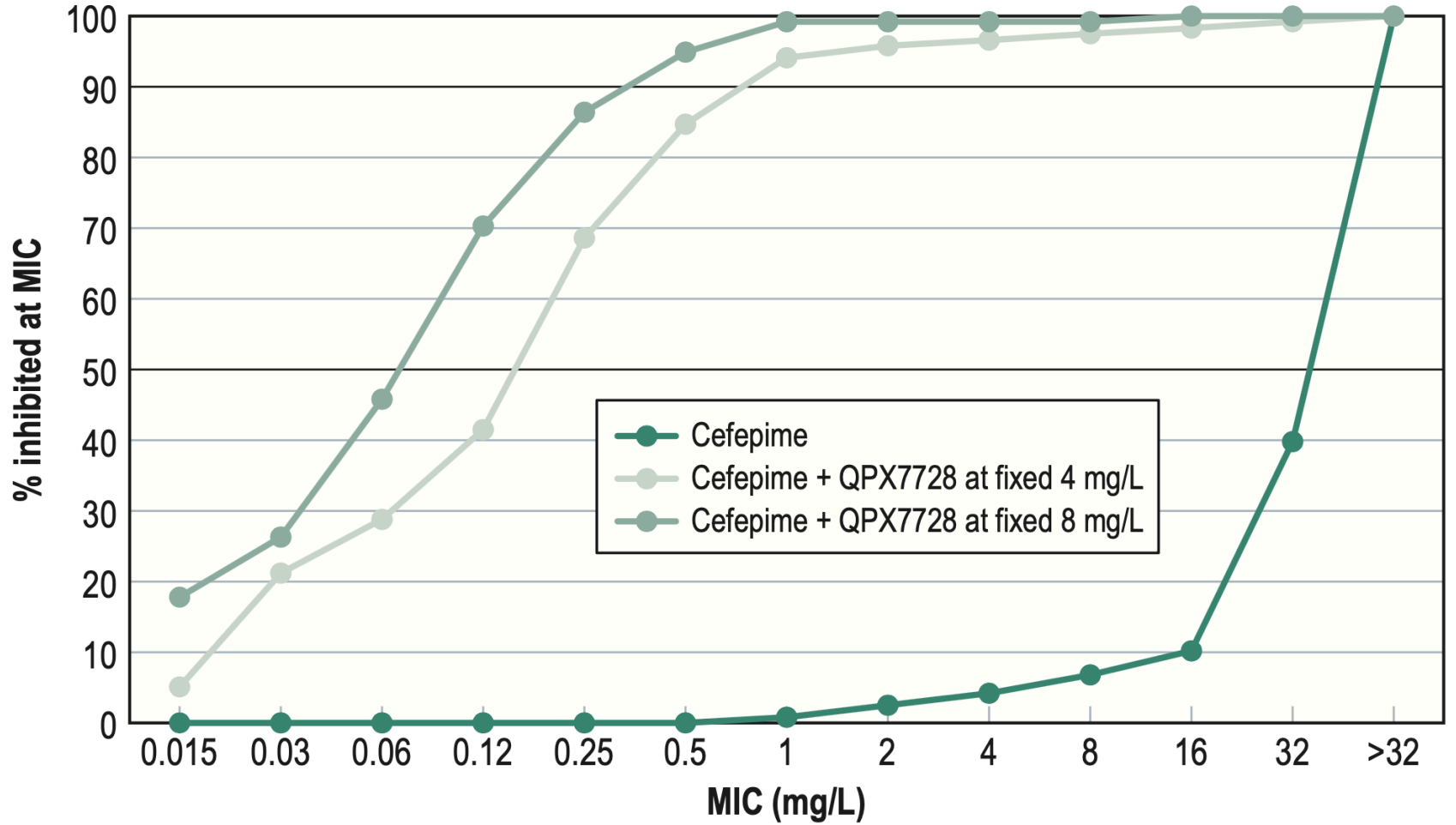
ST131

F. Tebipenem ± QPX7728 concentration of inhibitor



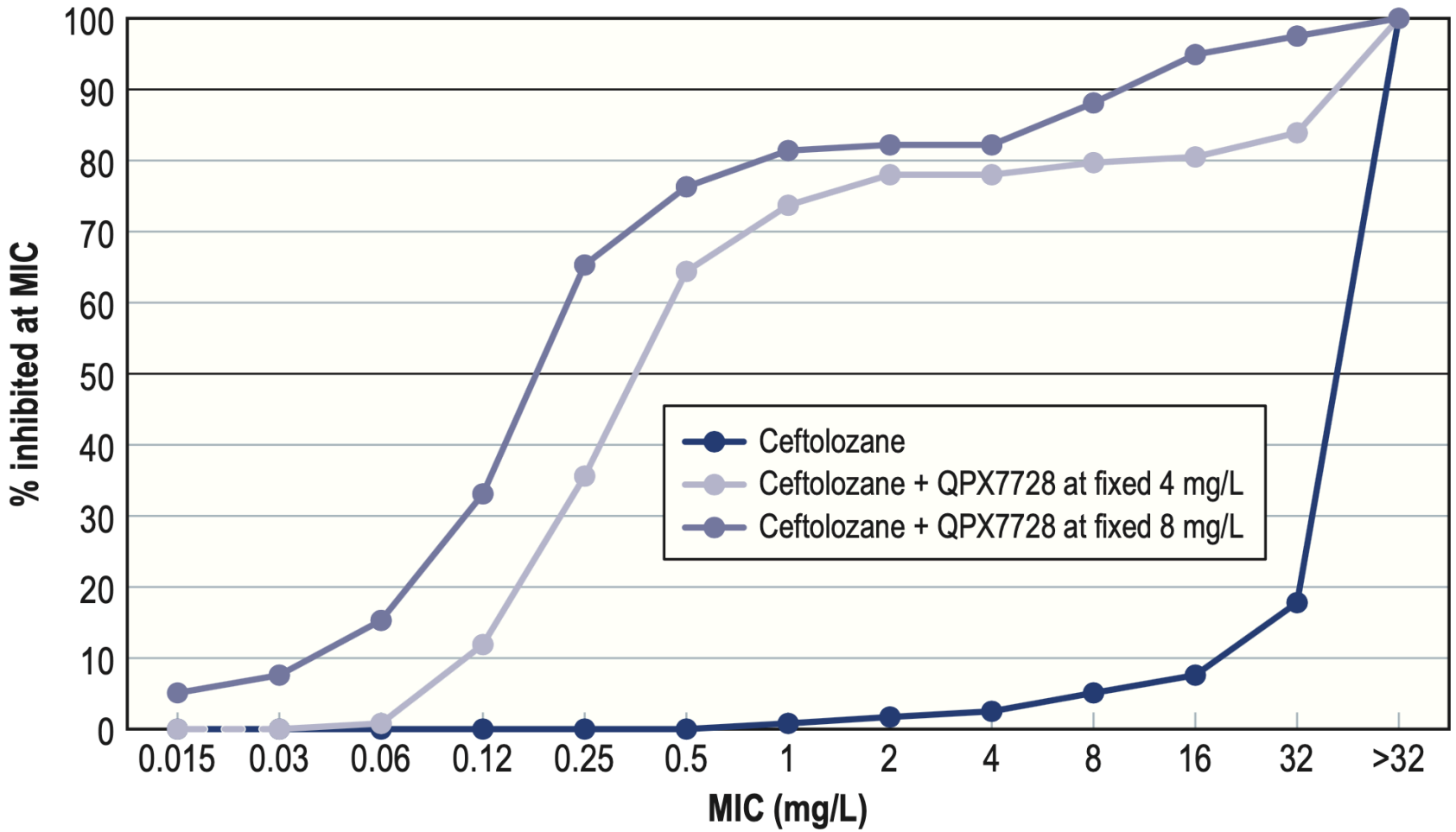
ST258

A. Cefepime ± QPX7728 versus ST258



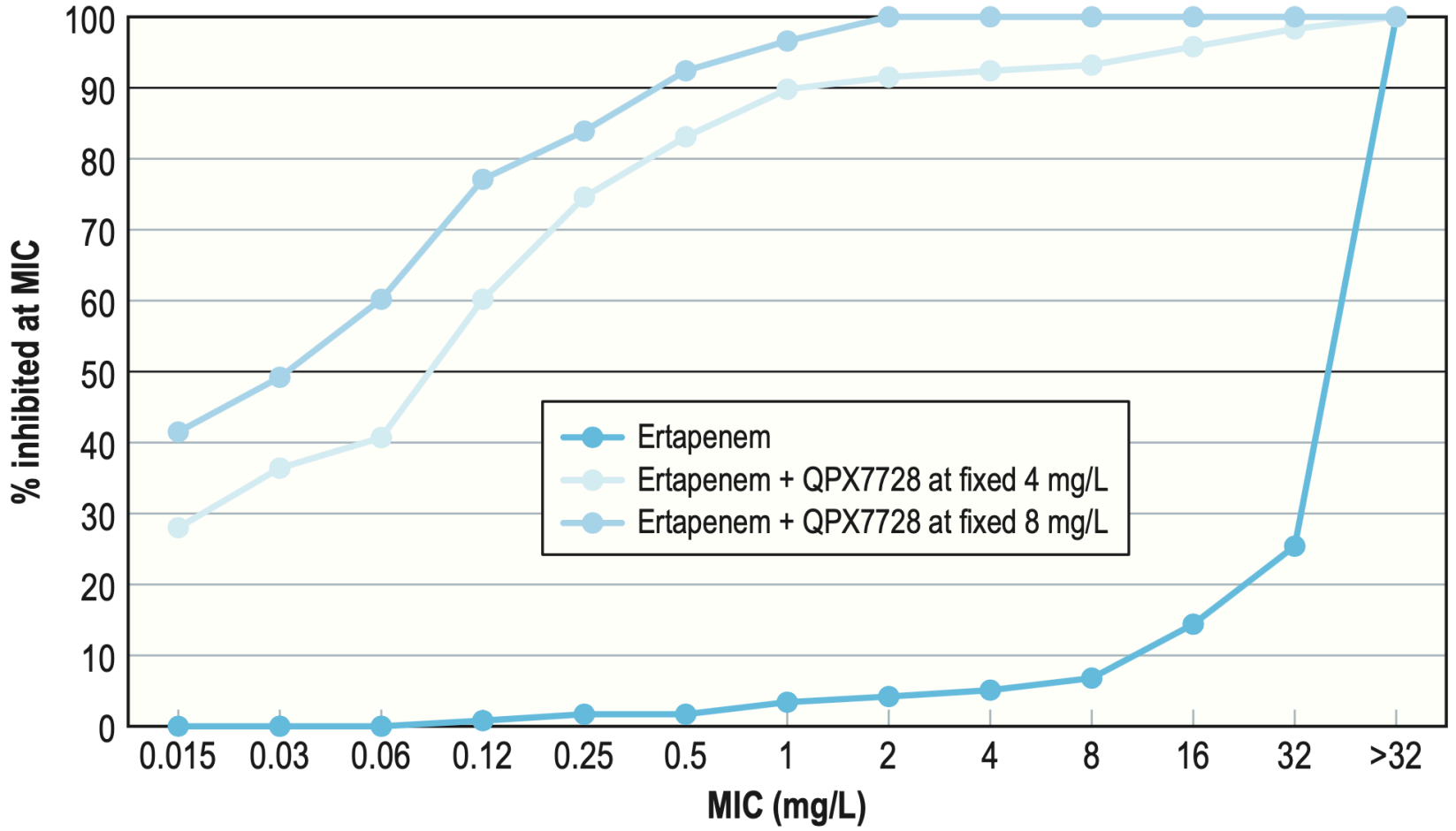
ST258

C. Ceftolozane ± QPX7728 versus ST258



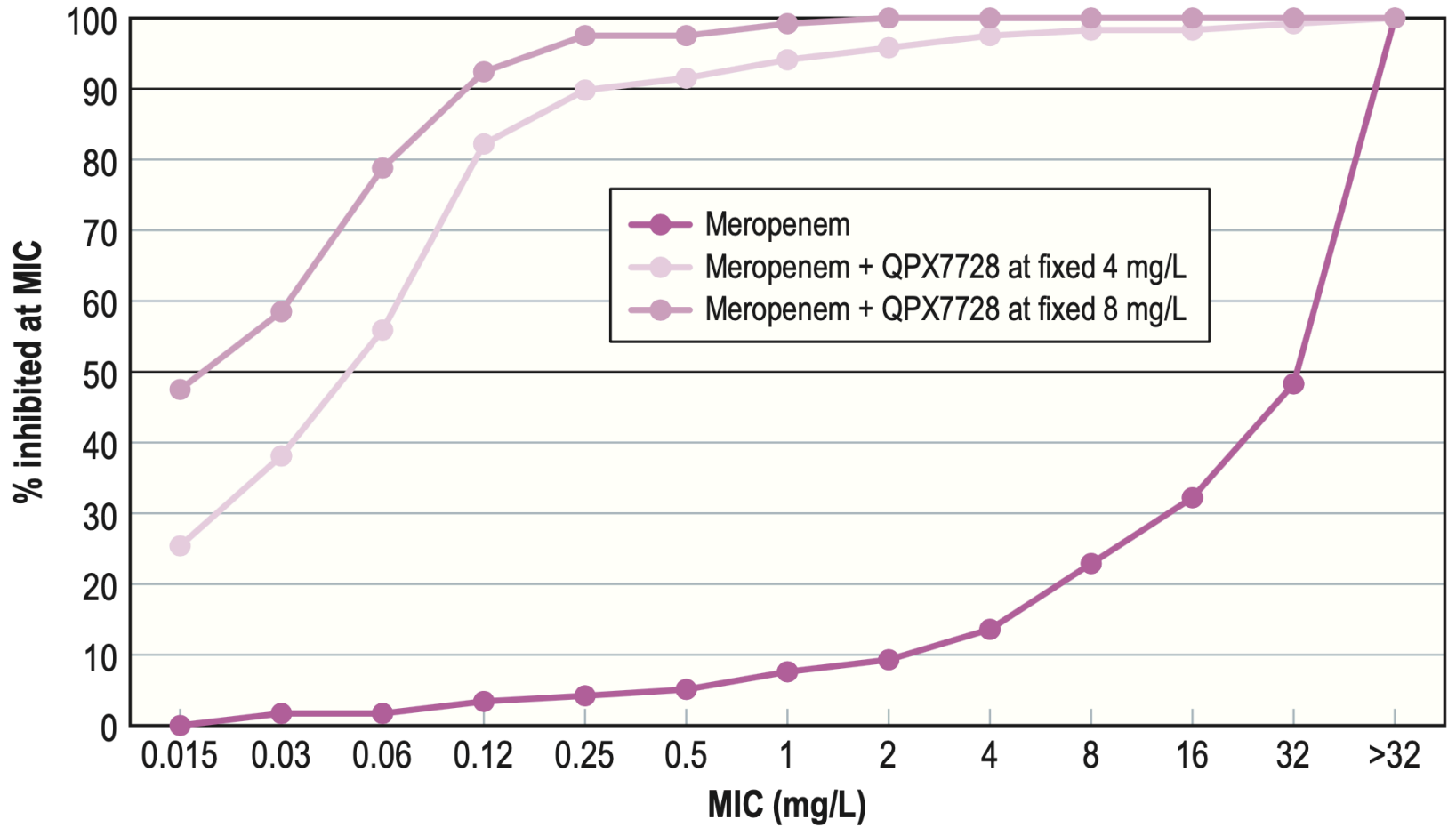
ST258

D. Ertapenem ± QPX7728 versus ST258

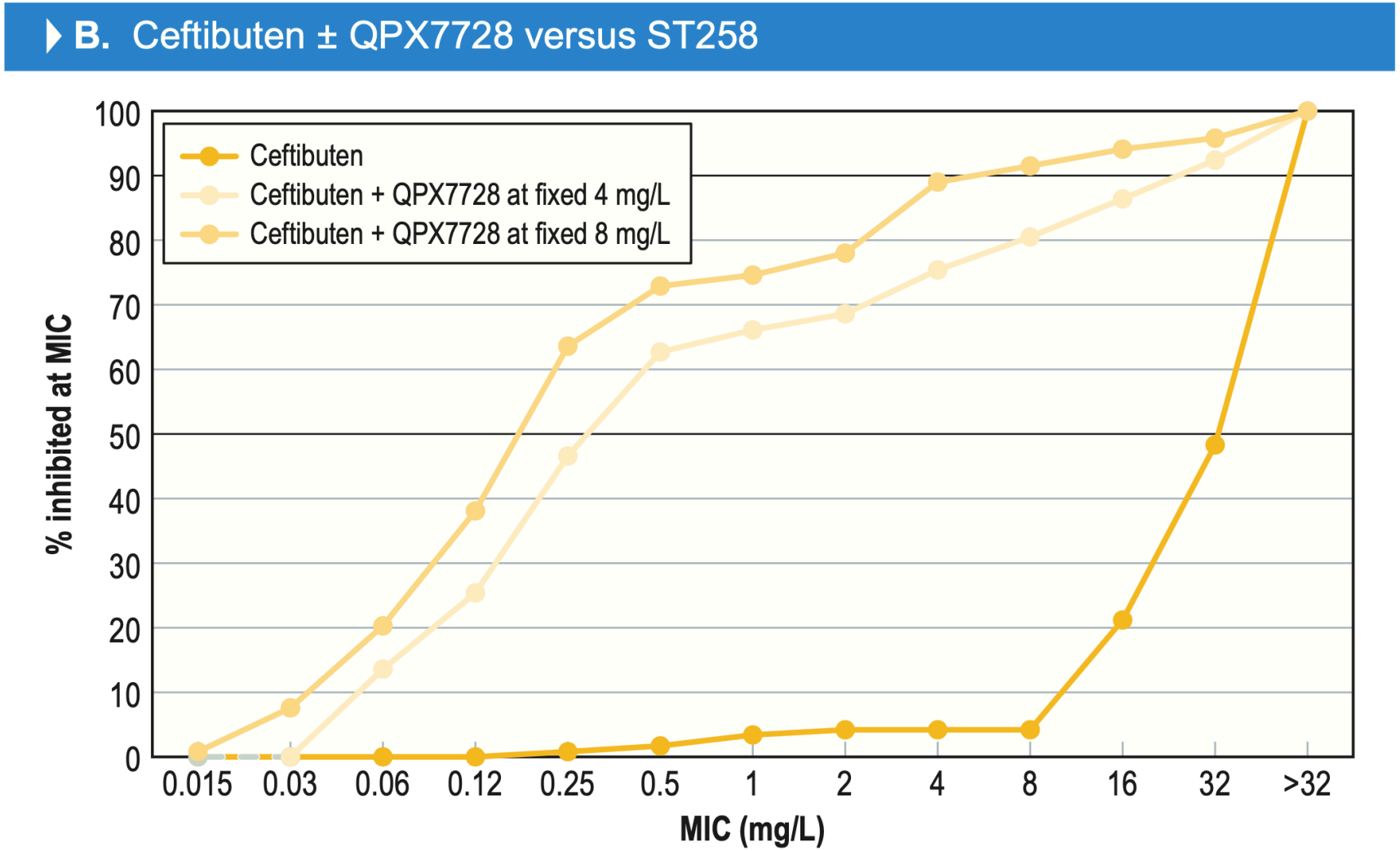


ST258

E. Meropenem ± QPX7728 versus ST258

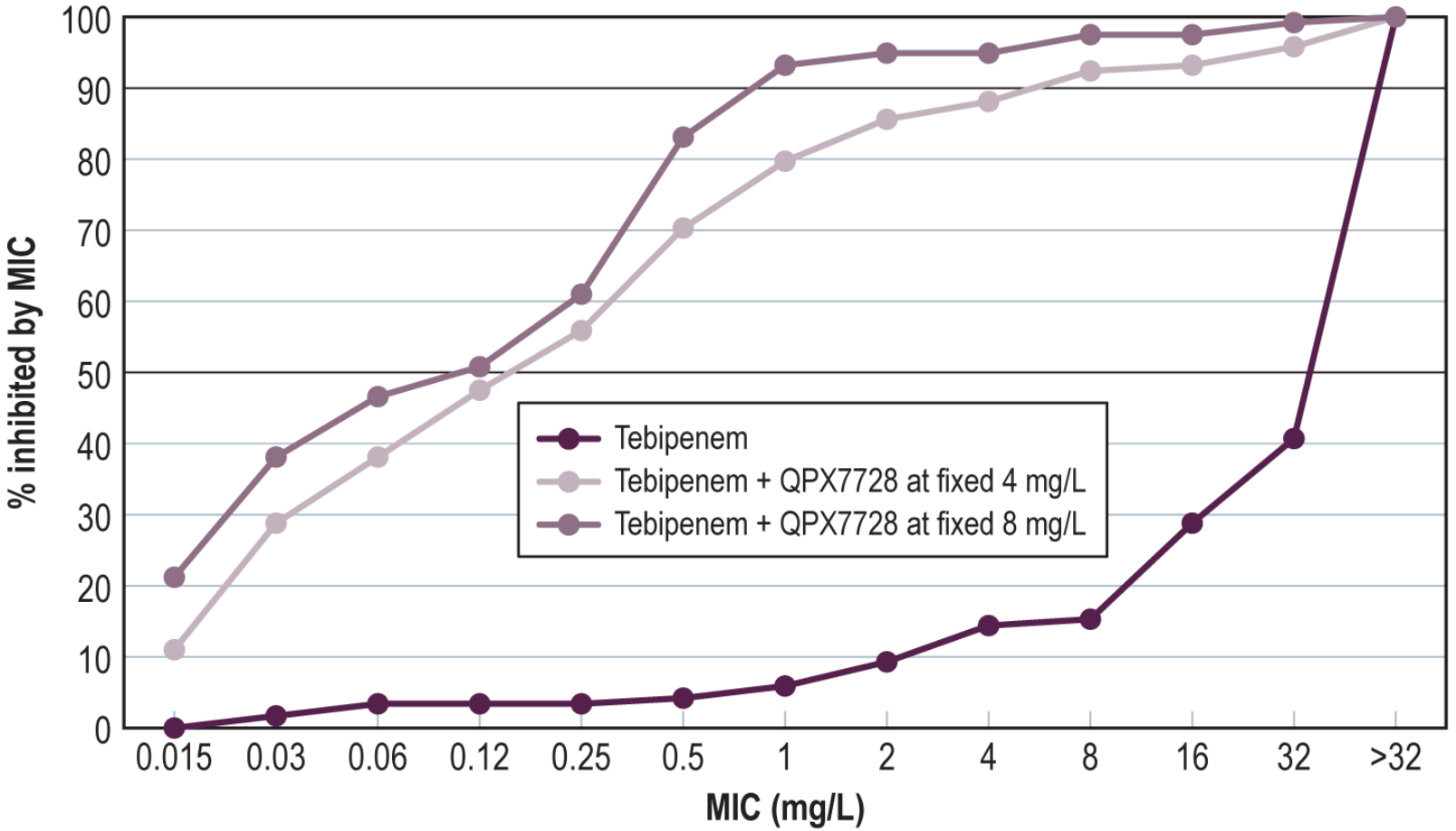


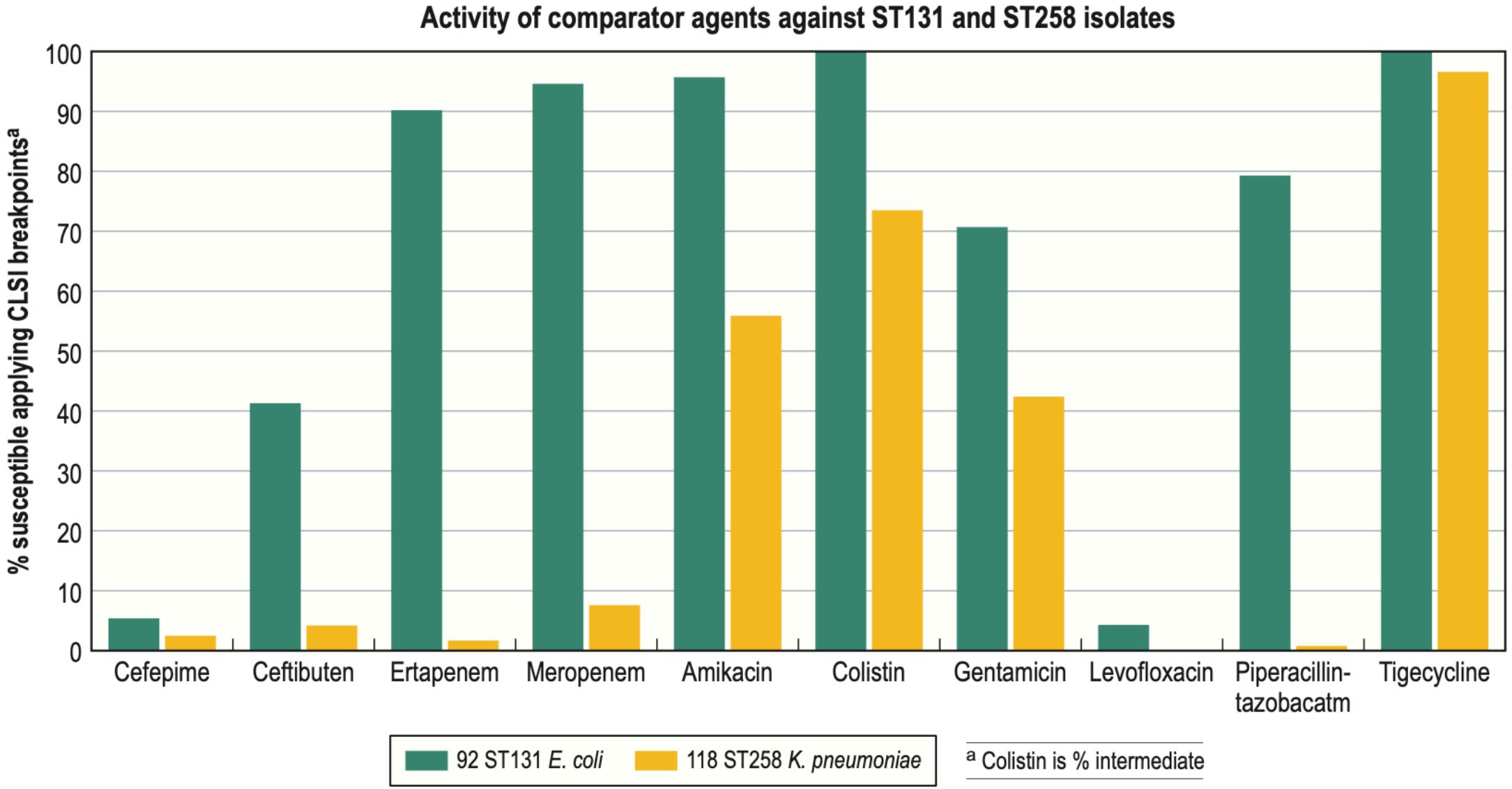
ST258


B. Ceftibuten ± QPX7728 versus ST258
Ceftibuten
Ceftibuten + QPX7728 at fixed 4 mg/L
Ceftibuten + QPX7728 at fixed 8 mg/L
% inhibited at MIC
100
90
80
70
60
50
40
30
20
10
0
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
>32
MIC (mg/L)

ST258

F. Tebipenem ± QPX7728 concentration of inhibitor




Activity of comparator agents against ST131 and ST258 isolates
% susceptible applying CLSI breakpoints[a]
100
90
80
70
60
50
40
30
20
10
0
Cefepime
Ceftibuten
Ertapenem
Meropenem
Amikacin
Colistin
Gentamicin
Levofloxacin
Piperacillin-tazobacatm
Tigecycline
92 ST131 E. coli
118 ST258 K. pneumoniae
[a] Colistin is % intermediate

Conclusions

- ST131 *E. coli* and ST258 *K. pneumoniae* display high level resistance to many clinically available agents
- Resistance mechanisms carried by these isolates include β-lactams since these isolates harbor β-lactamase genes active against broad-spectrum cephalosporins and carbapenems
- QPX7728 restored the activity of all β-lactam agents tested at concentrations of 2, 4 or 8 mg/L

Conclusions

- Beyond serine enzymes that are inhibited by newer β-lactamase inhibitors, QPX7728 lowered MIC values for isolates carrying metallo-β-lactamases and oxacillinases
- QPX7728 is an important addition to the armamentarium to treat infection caused by multidrug resistant organisms, including ST131 *E. coli* and ST258 *K. pneumoniae*

Acknowledgements

- This study was sponsored by Qpex Biopharma


JMI LABS