DISCLOSURES

Paul G. Ambrose, Pharm.D., FIDSA

- Industry Potential Interest Conflicts
  - *Employer:* Employed by and have equity in ICPD, a company that provides pharmacometric services to industry
  - *Financial Interests or Benefits:* Achaogen, Actelion, AiCuris, Arsanis, Basilea, Cellceutix, Cempra, Cidara, Contrafect, Debiopharm, Geom, GSK, Insmed, Kalya, Medicines Company, Meiji, Melinta, Merck, Nabriva, Nexcida, Northern Antibiotics, Novartis, Paratek, Roche, Spero, Takeda, Theravance, Tetraphase, VenatoRx, Wockhardt, Zavante
  - *Speaker's Bureau:* None
- Government Potential Interest Conflicts
  - *Special Government Employee, FDA:* Anti-infective Advisory Committee, temporary member

ICPD® INSTITUTE for CLINICAL PHARMACODYNAMICS

Pharmacometric Considerations in Unmet Need Programs

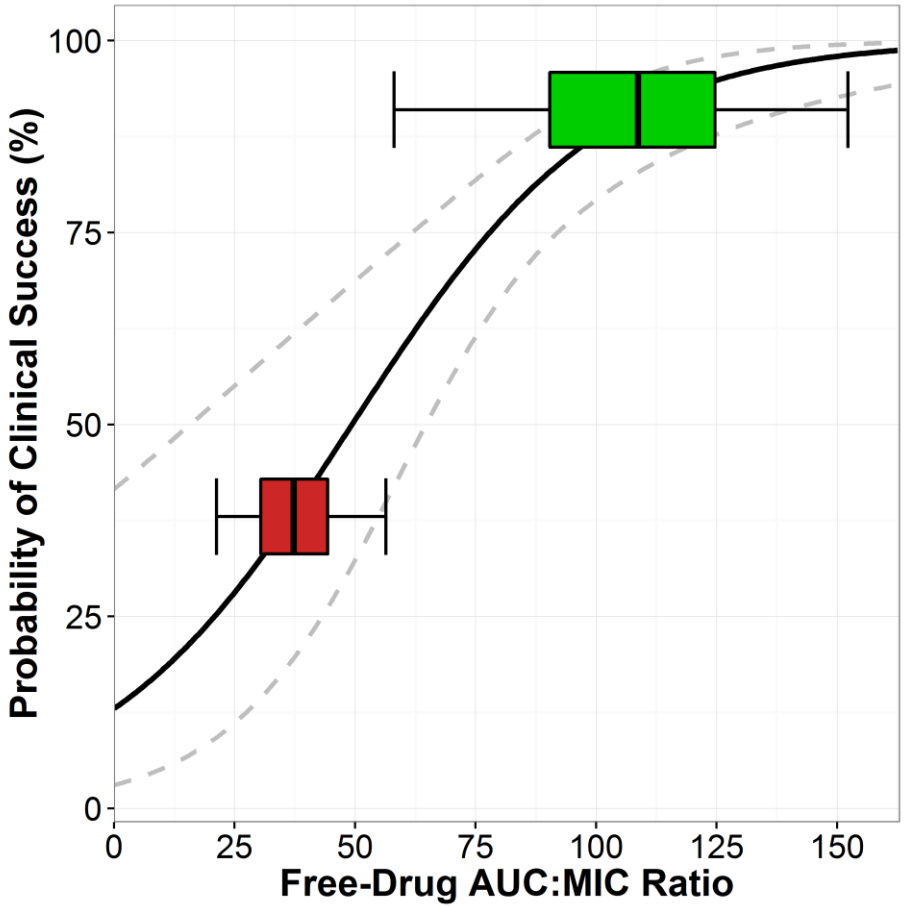
18 July 2016

Paul G. Ambrose, Pharm.D., FIDSA

Institute for Clinical Pharmacodynamics, Inc.
Schenectady, New York

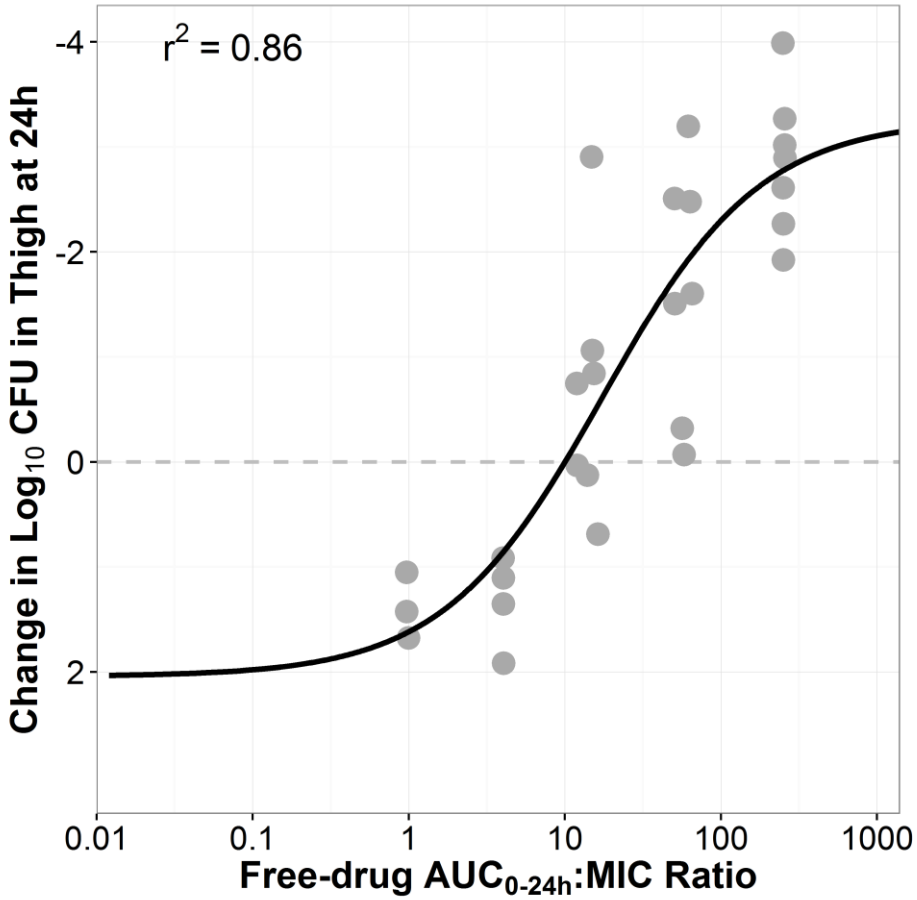
Antibiotic development program failure is less about bad drugs and more about bad decisions

Superiority can be found on an exposure-response function



Could failure have been predicted?

Daptomycin



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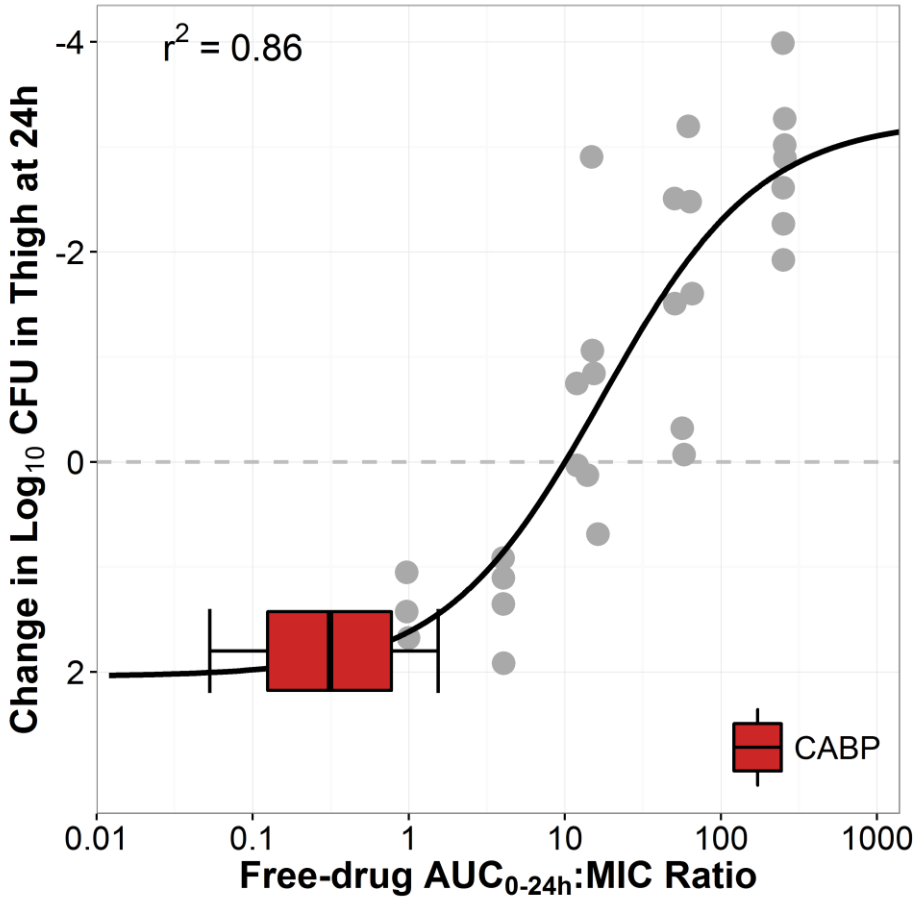
EXPOSURE IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Daptomycin



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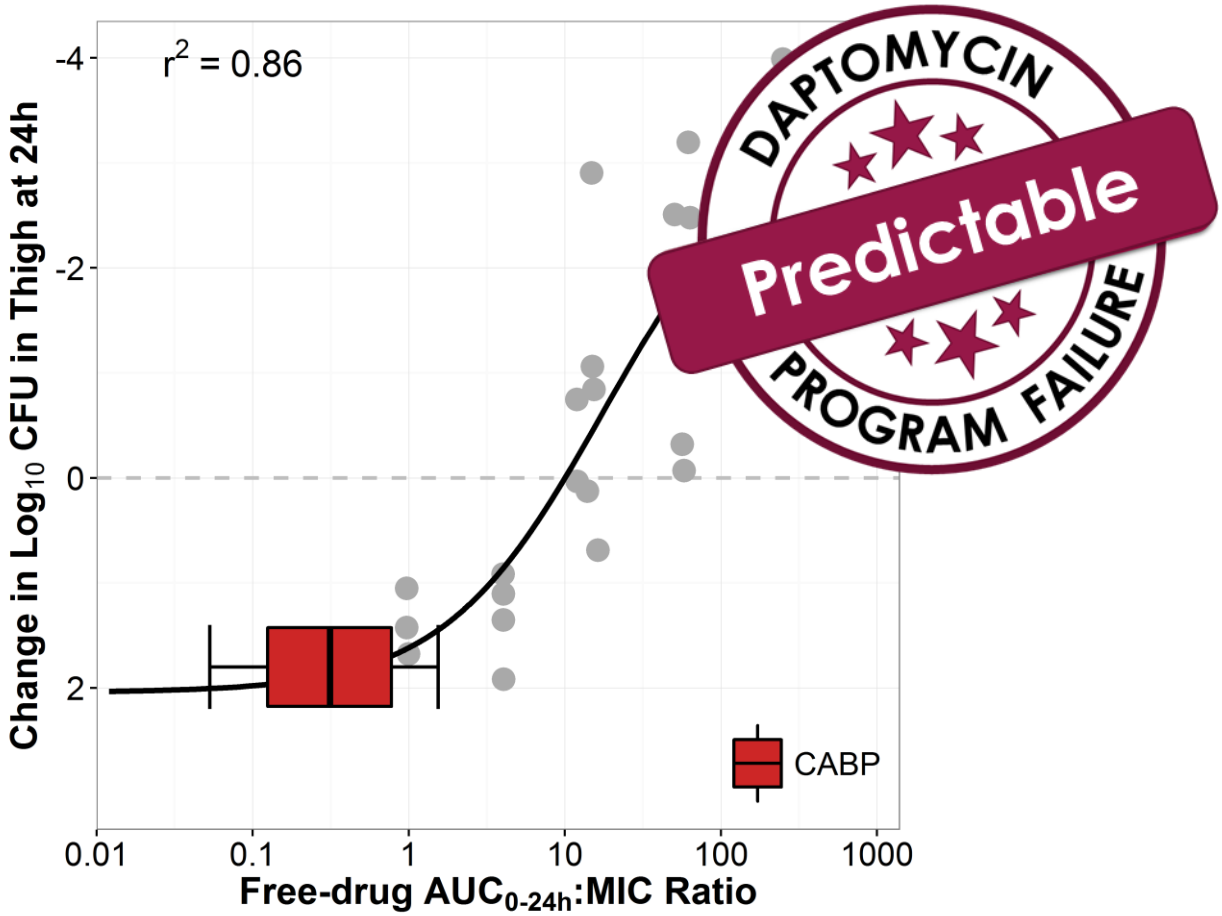
Clinical Data: Merck Sharp & Dohme Corp. Daptopmycin. Package Insert. 2015 November.

FATAL MISTAKE: WRONG ANIMAL MODEL

Daptomycin



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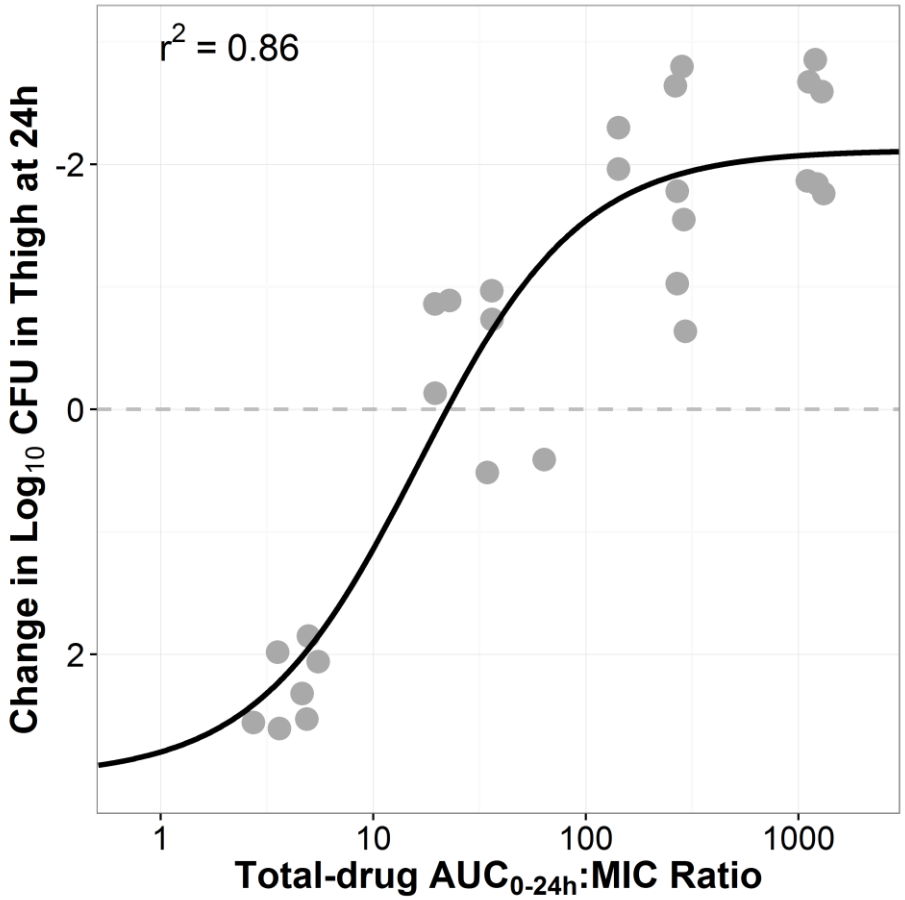
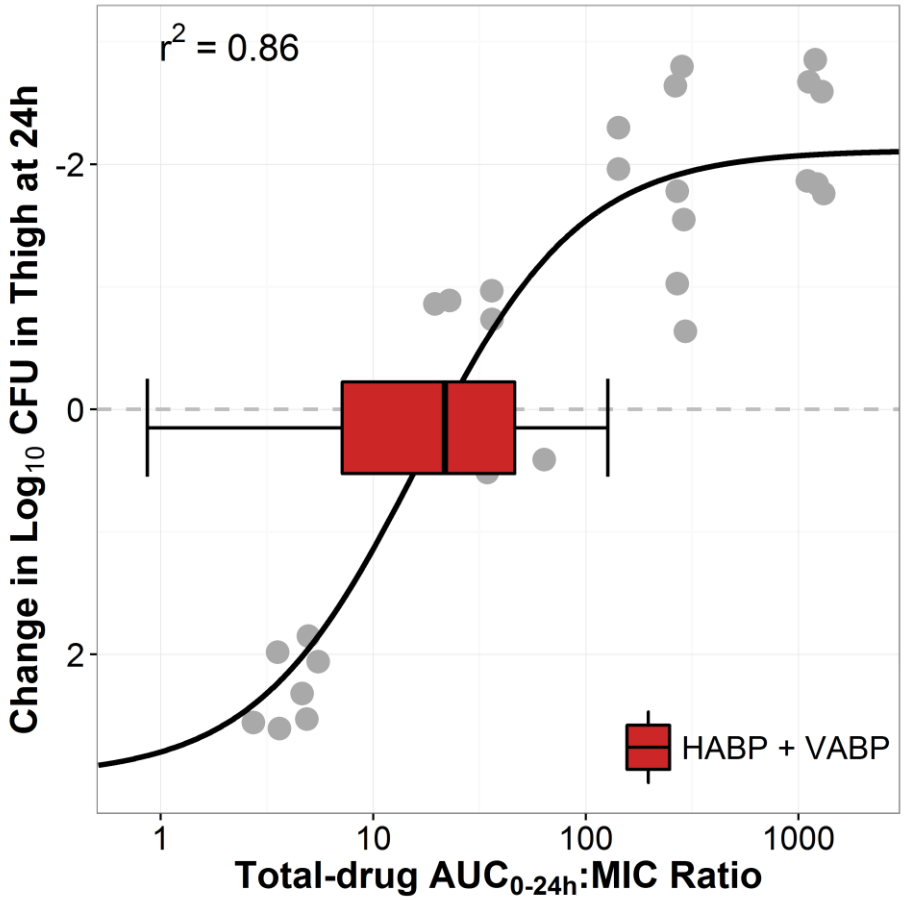
Tigecycline



Preclinical data: Courtesy of William A. Craig

EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

Tigecycline



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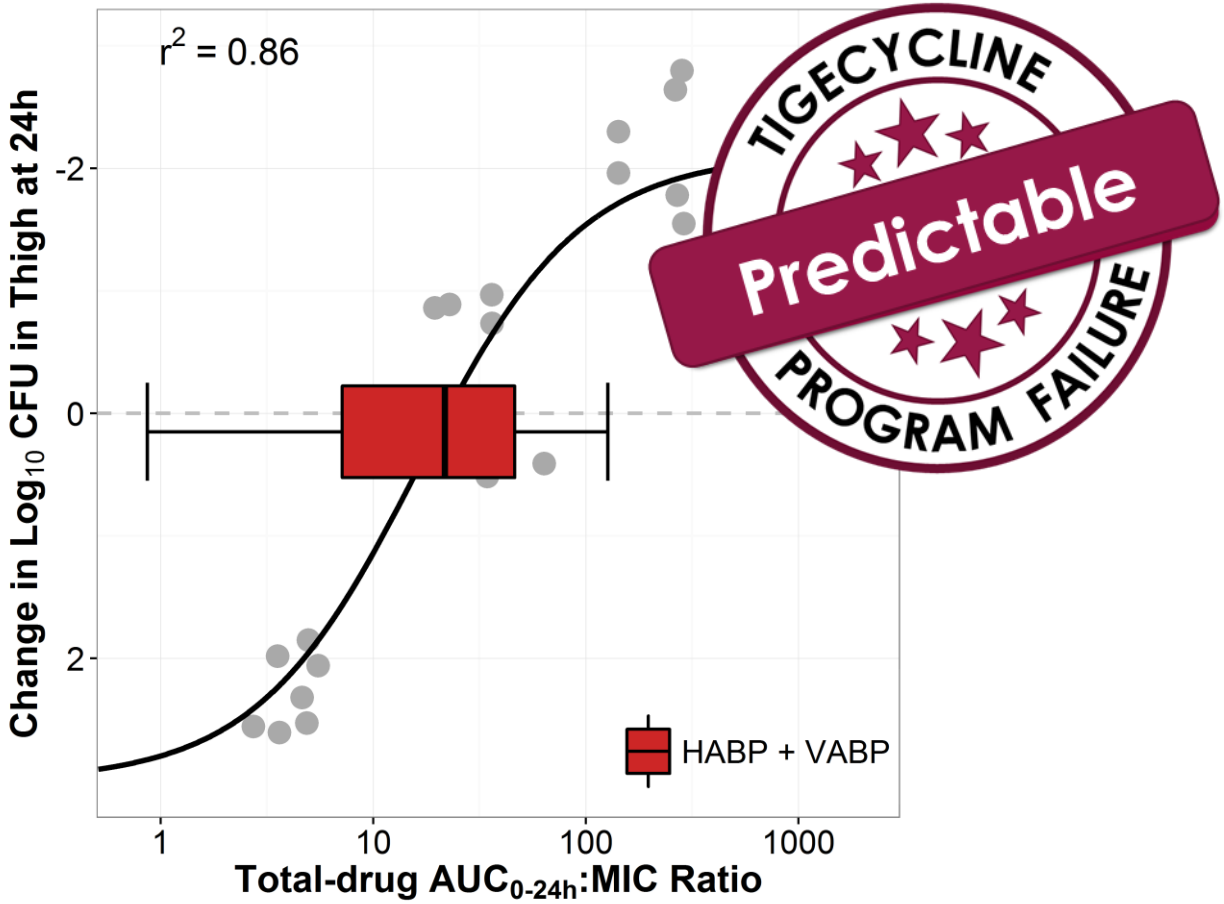
FATAL MISTAKE: MAXIMUM TOLERATED DOSE INSUFFICIENT

Tigecycline



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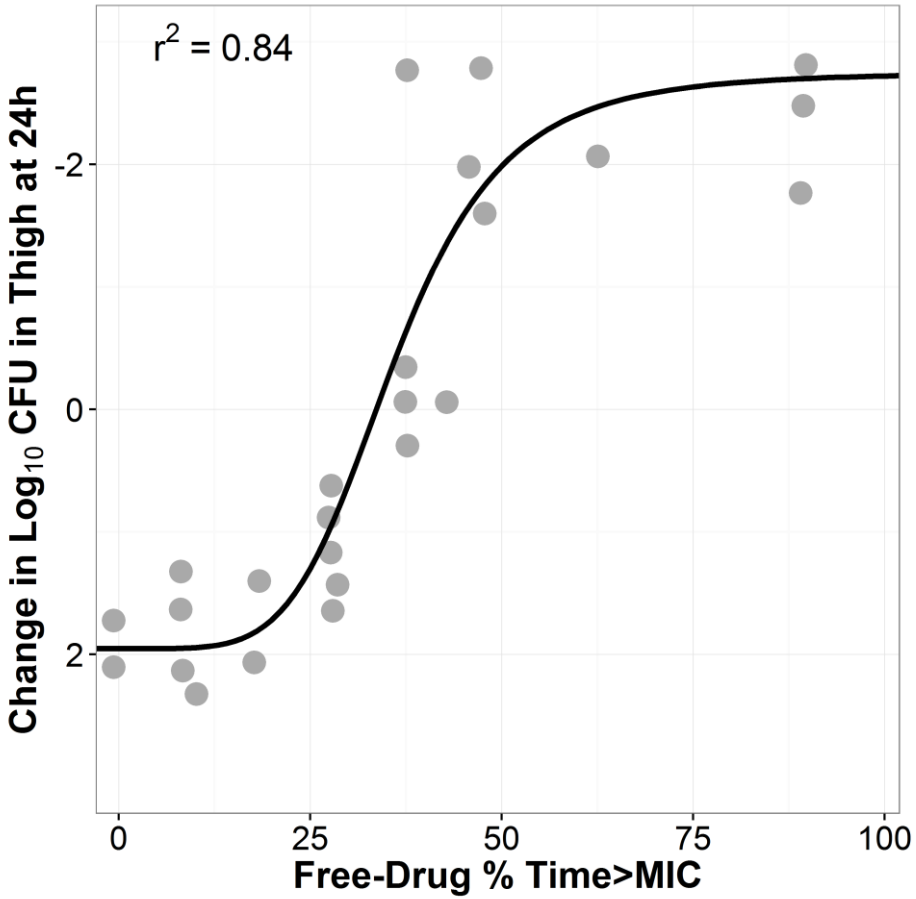
Ceftobiprole



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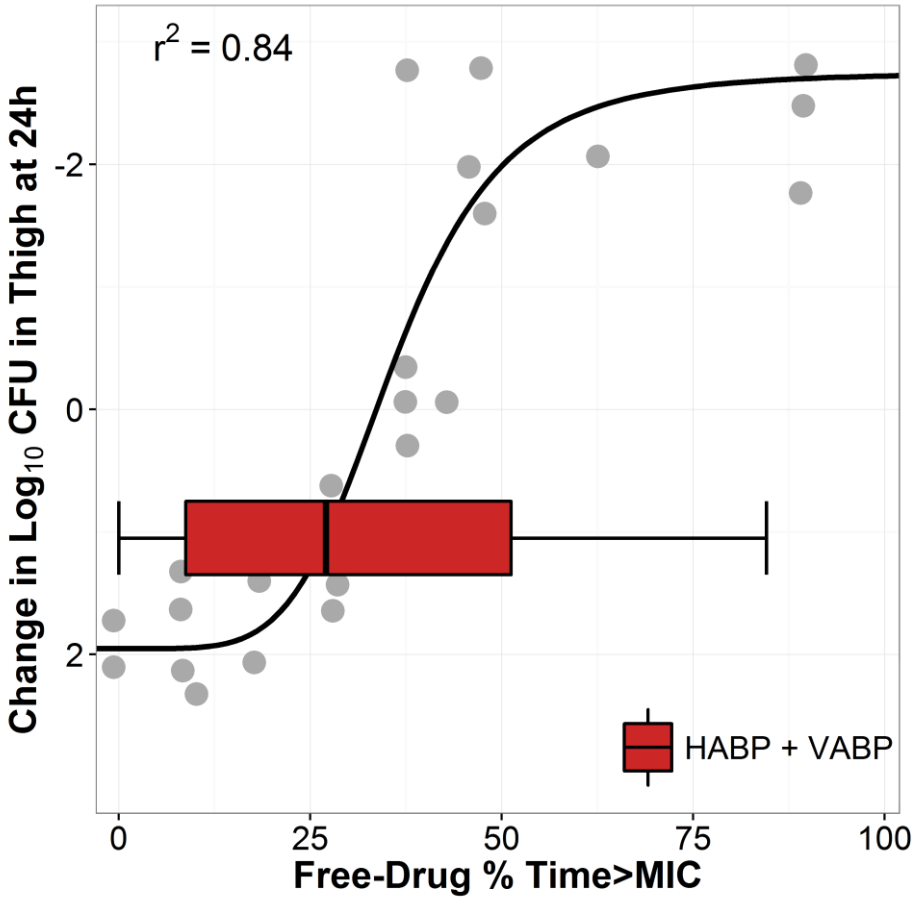
EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

Ceftobiprole



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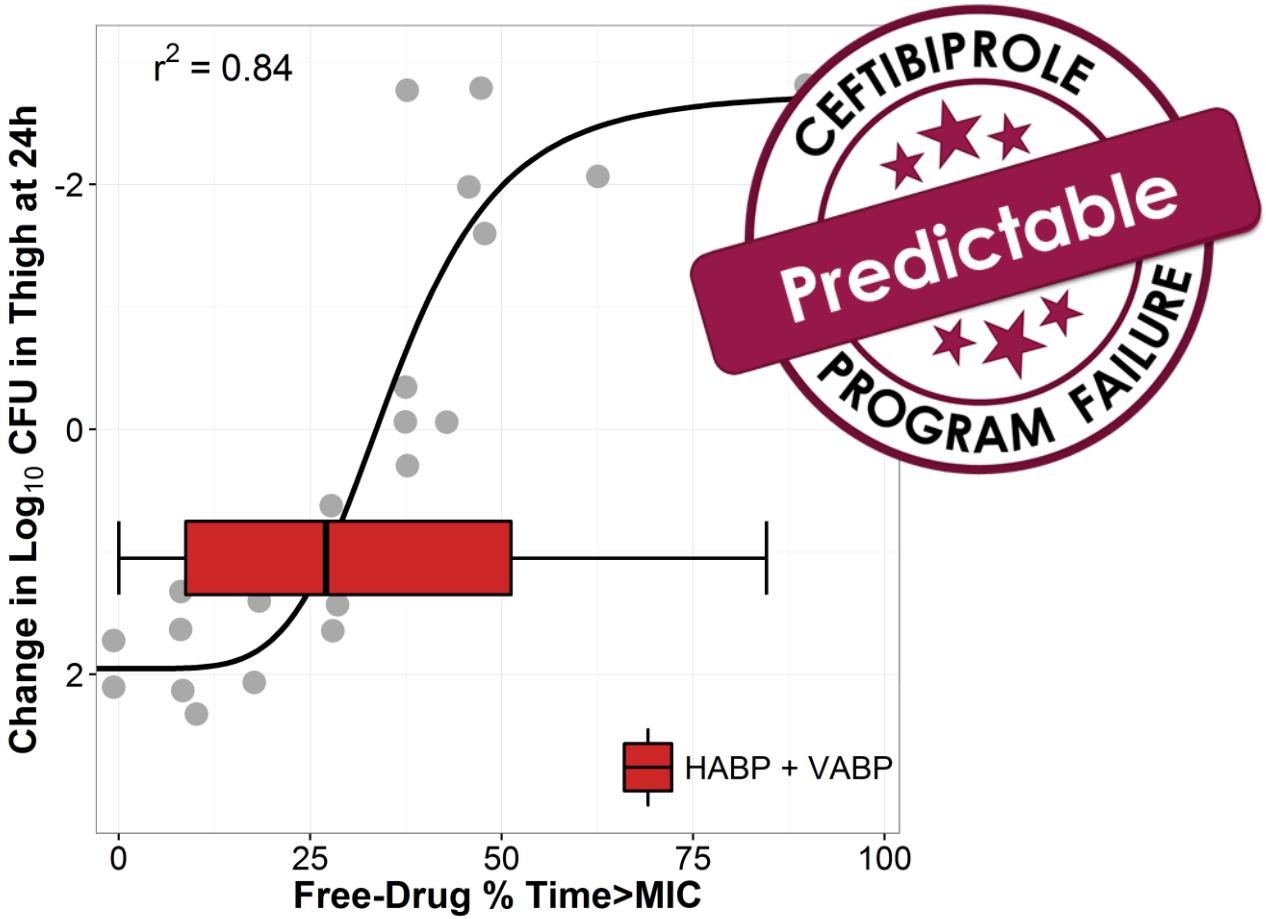
Rodvold KA, Nicolau DP, Lodise TP, Khashab M, Noel GJ, Kahn JB, Gotfried M, Murray SA, Nicholson S, Laohavaeeson, S, Tessier PR. Identifying exposure targets for treatment of staphylococcal pneumonia with ceftobiprole. *Antimicrob Agents Chemotherapy*. 2009 August; *53*(8), 3294-3301.

FATAL MISTAKE:
ELF PENETRATION NOT ACCOUNTED FOR

Ceftobiprole



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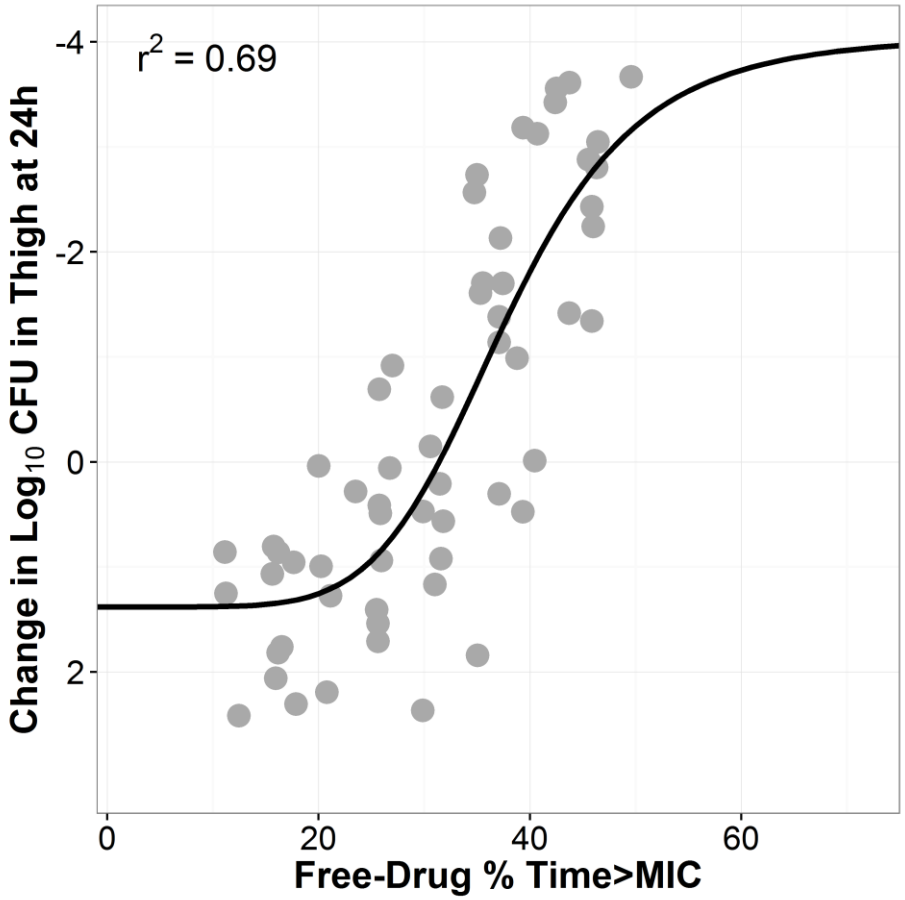
Doripenem



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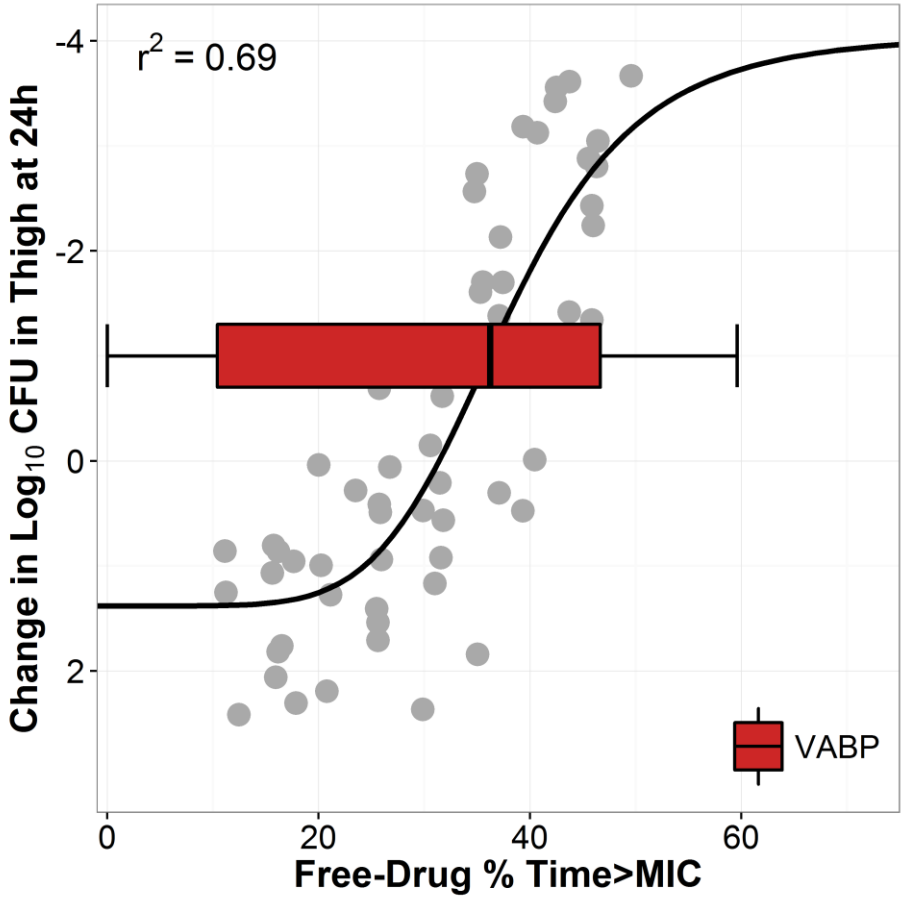
EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

Doripenem



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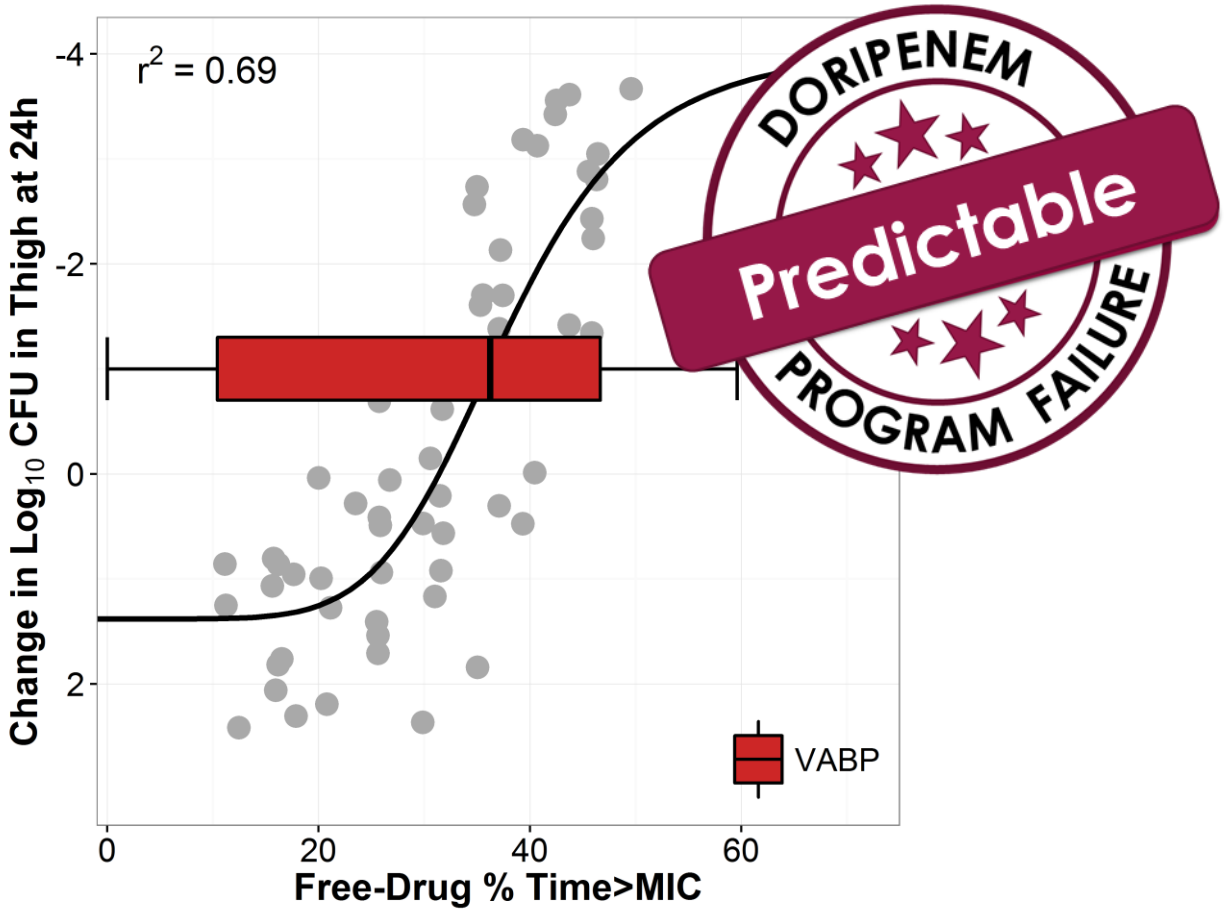
Justo J, Gotfried MH, Roles JJ, Deyo K, Fischer P, Danzinger LH, Rodvold KA. Doripenem intrapulmonary pharmacokinetics in healthy adult subjects [A1-1748]. 51st *Interscience Conference on Antimicrobial Agents and Chemotherapy.* Chicago, IL, 2011 September 17-20.

FATAL MISTAKE: DRUG CLEARANCE IN VAP PATIENTS NOT ACCOUNTED FOR

Doripenem



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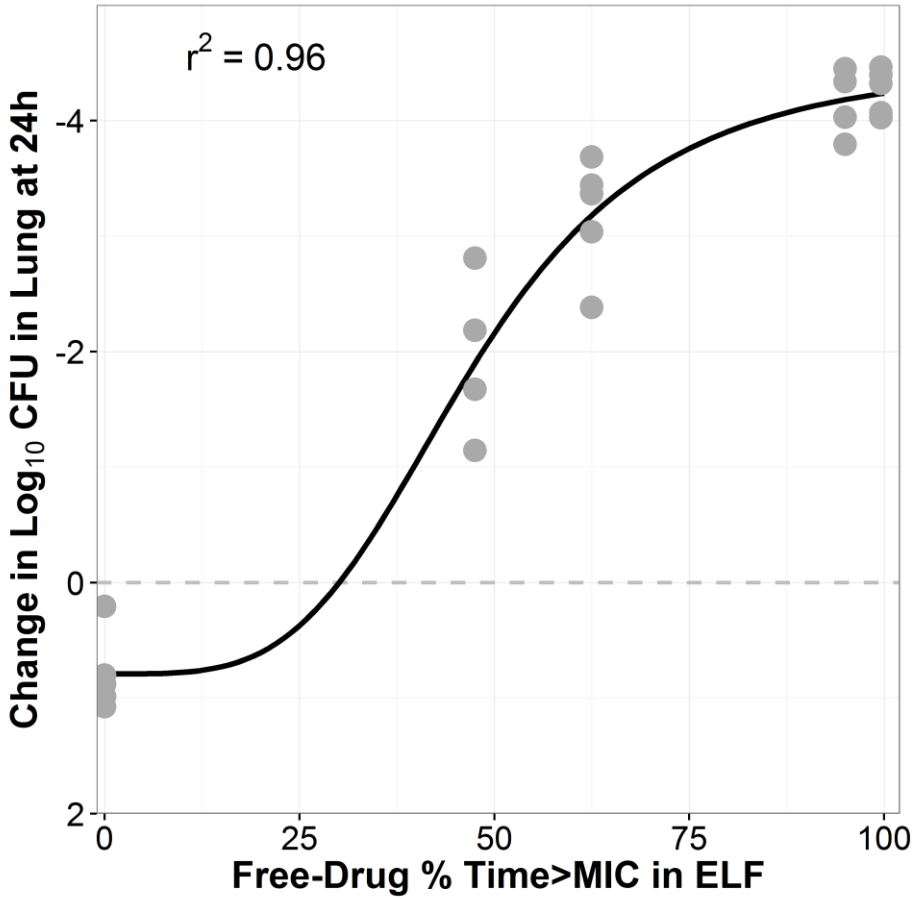
Meropenem



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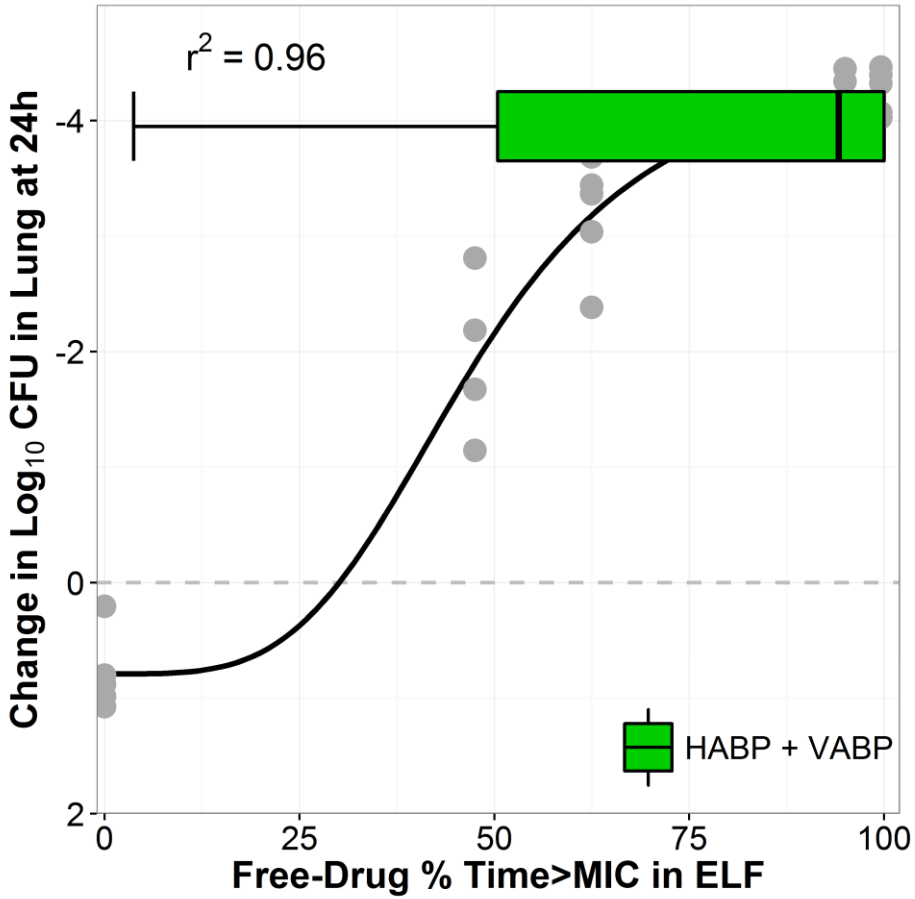
EXPOSURE IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

Meropenem



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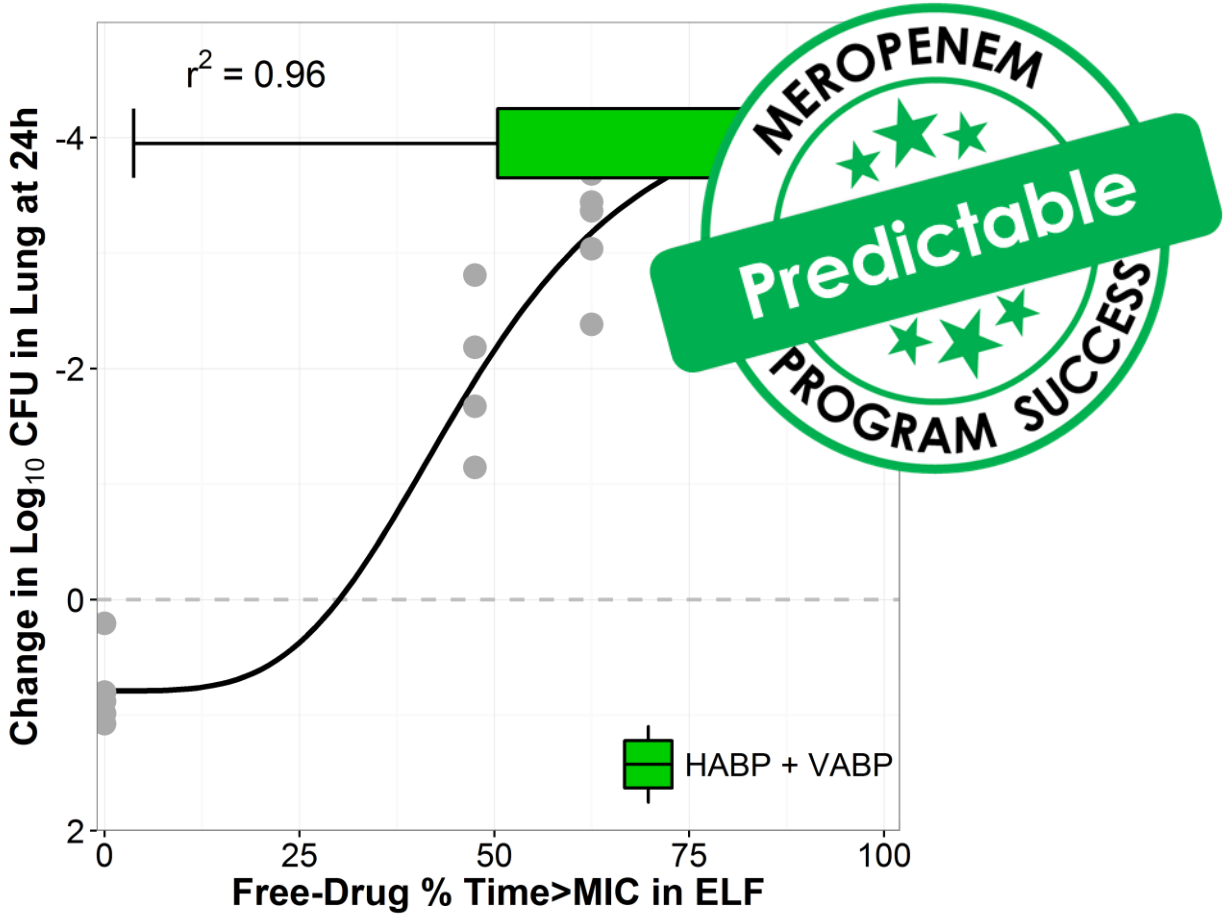
Meropenem



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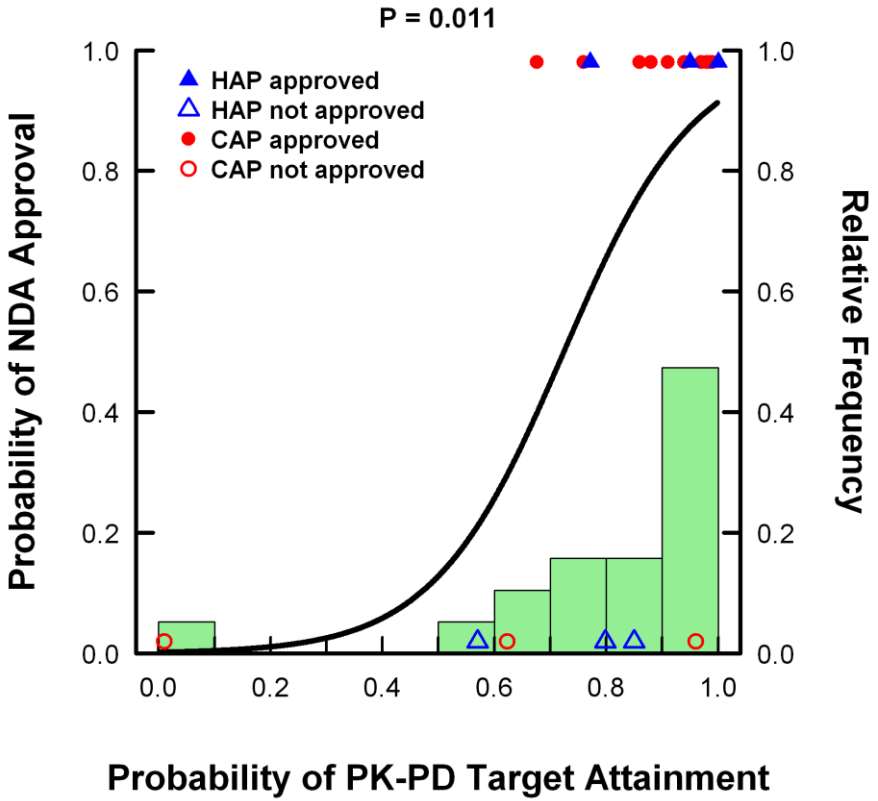
New Drug Applications



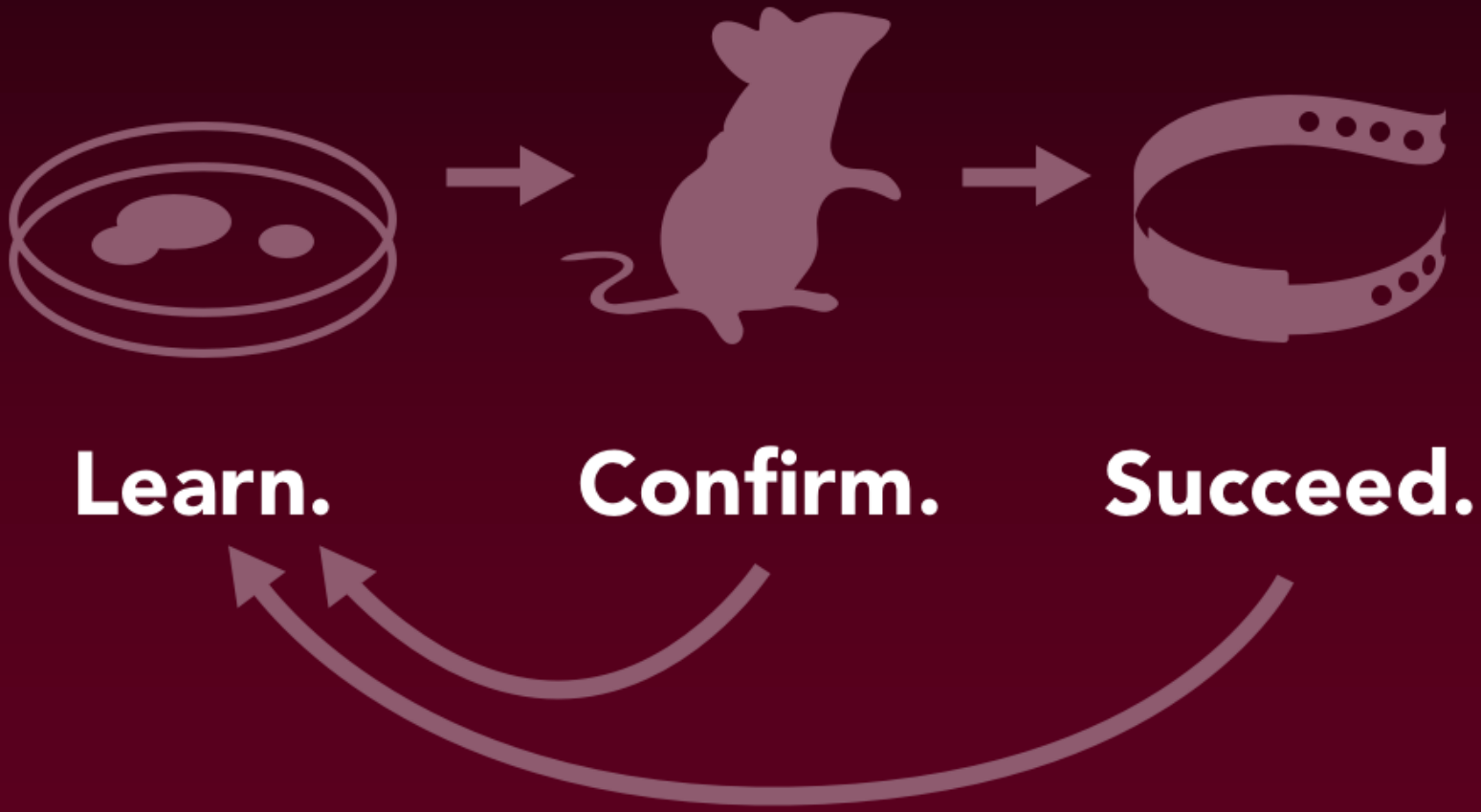
Quartile	Target Attainment Median (Range)	% NDA Approval (n/N)
1	0.62 (0.01-0.76)	40% (2/5)
2	0.85 (0.77-0.88)	60% (3/5)
3	0.94 (0.88-0.96)	80% (4/5)
4	0.985 (0.97-0.99)	100 % (5/5)

20 pneumonia programs; 17 antibiotics in total, with 14 regulatory approvals and 6 failures

Bulik CC, Bhavnani SM, Hammel JP, Forrest A, Dudley MN, Ellis-Grosse EJ, Drusano GL, Ambrose PG. Evaluation of the Probability of Regulatory Approval Based on Pre-Clinical PK-PD Target Attainment For Community-Acquired and Hospital-Acquired Pneumonia. A-295. 53rd InterScience Conference on Antimicrobial Agents and Chemotherapy. September 10-13, 2013, Denver CO.

How to keep the NDA on the tracks?

A Proven Approach



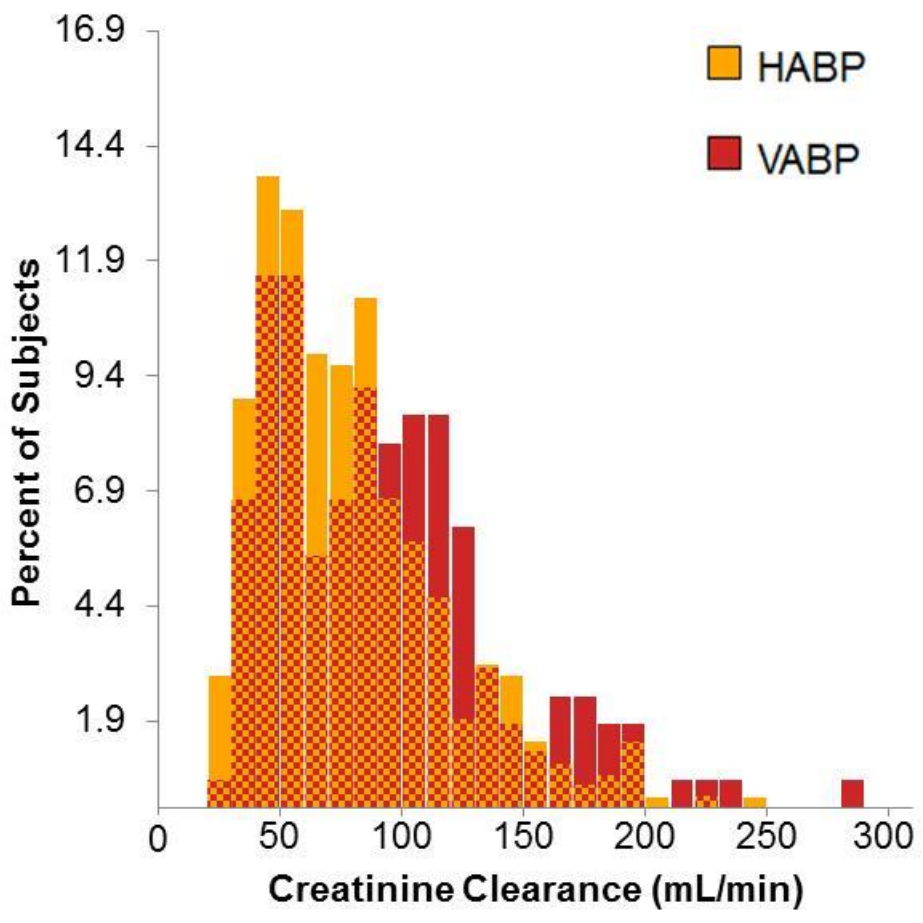
Pathogen susceptibility: Patient population matters

Antimicrobial Agent	Percent Susceptible, HABP/VABP			
	Pseudomonas aeruginosa	*Klebsiella* species	*Acinetobacter* species	*Enterobacter* species
Gentamicin	**72/66**	**82/71**	**25/18**	**87/81**
Levofloxacin	60/58	**84/76**	**16/11**	88/89
Cefepime	**70/65**	**87/78**	**27/20**	93/91
Ceftazidime	**68/63**	**77/68**	12/10	62/64
Meropenem	**72/66**	99/99	**58/46**	100/99
Piperacillin-tazobactam	**76/71**	**76/71**	**19/11**	71/70

Note. HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; Boldface indicate ≥5% decrease is susceptibility for VABP isolates relative to HABP isolates (SENTRY 2004-2008).

Ronald N. Jones *Clin Infect Dis.* 2010;51:S81-S87

Pharmacokinetics: Patient population matters

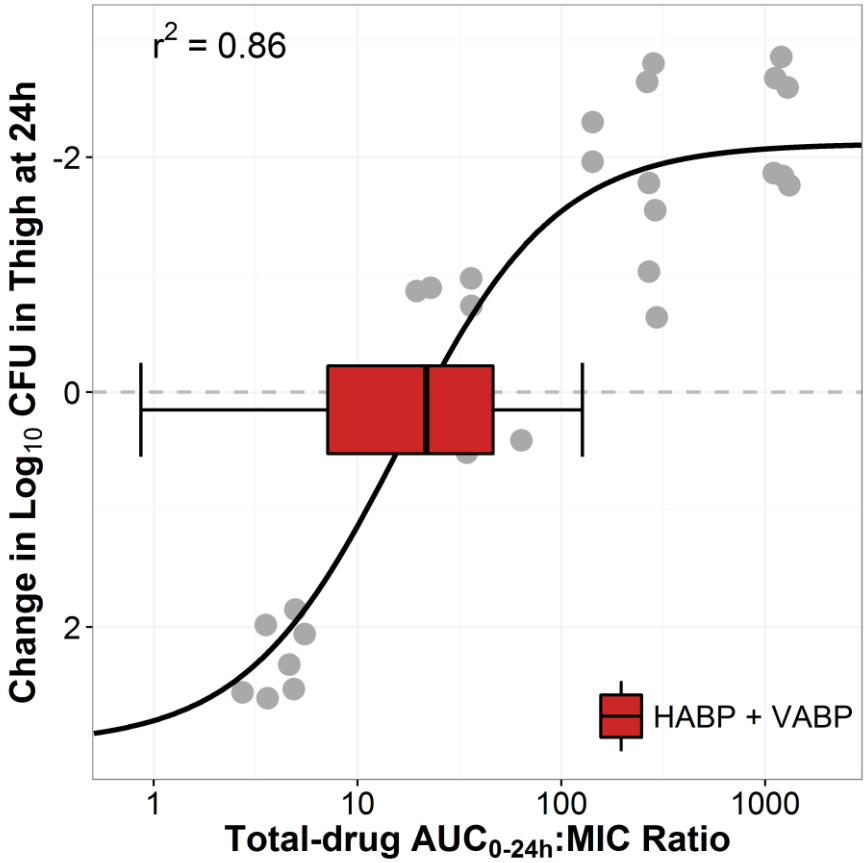


	HABP	VABP
N	415	164
Mean	79.3	94.4
SD	39.1	47.0
Min	20.5	26.8
Max	241.0	283.6

Kruskal-Wallis One-Way Analysis of Variance, P = 0.0003

Ambrose PG, Bhavnani SM, Ellis-Grosse EJ, Drusano GL. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: Look before you leap! *Clin Infect Dis* 2010; 51 (suppl 1):S103-S110.

Impact of increased clearance and MIC in VABP *vs.* HABP



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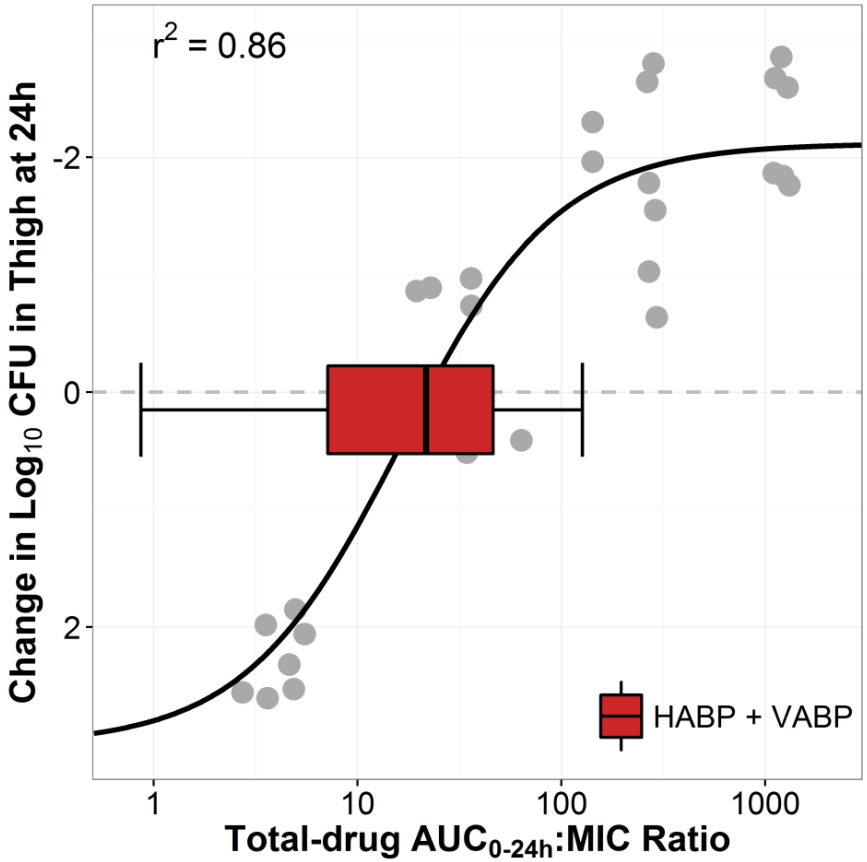

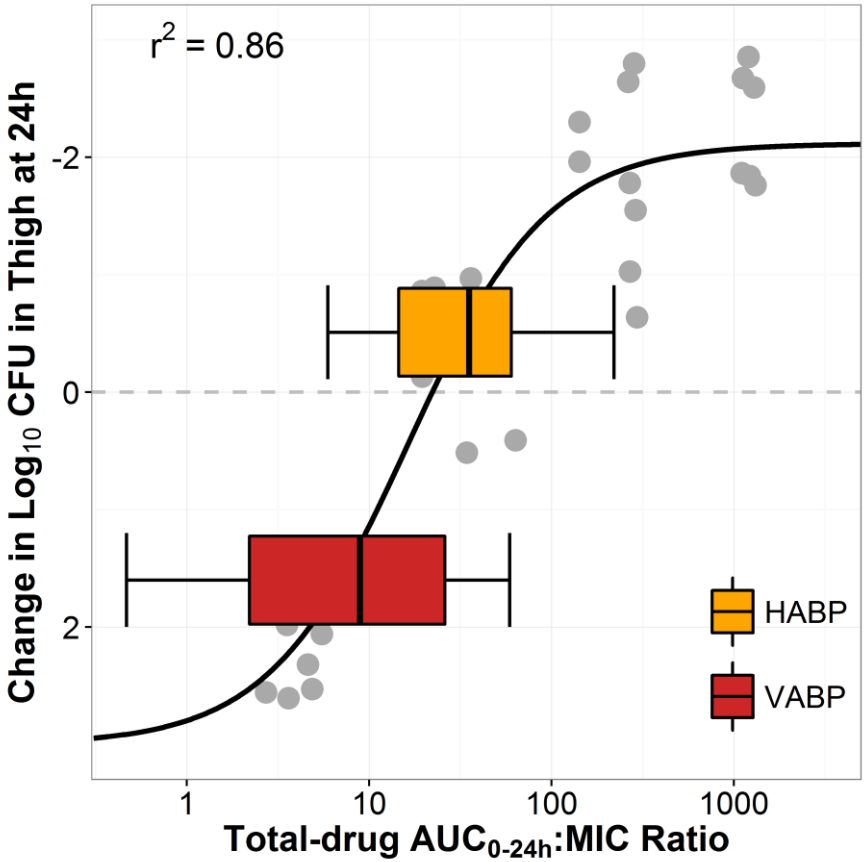

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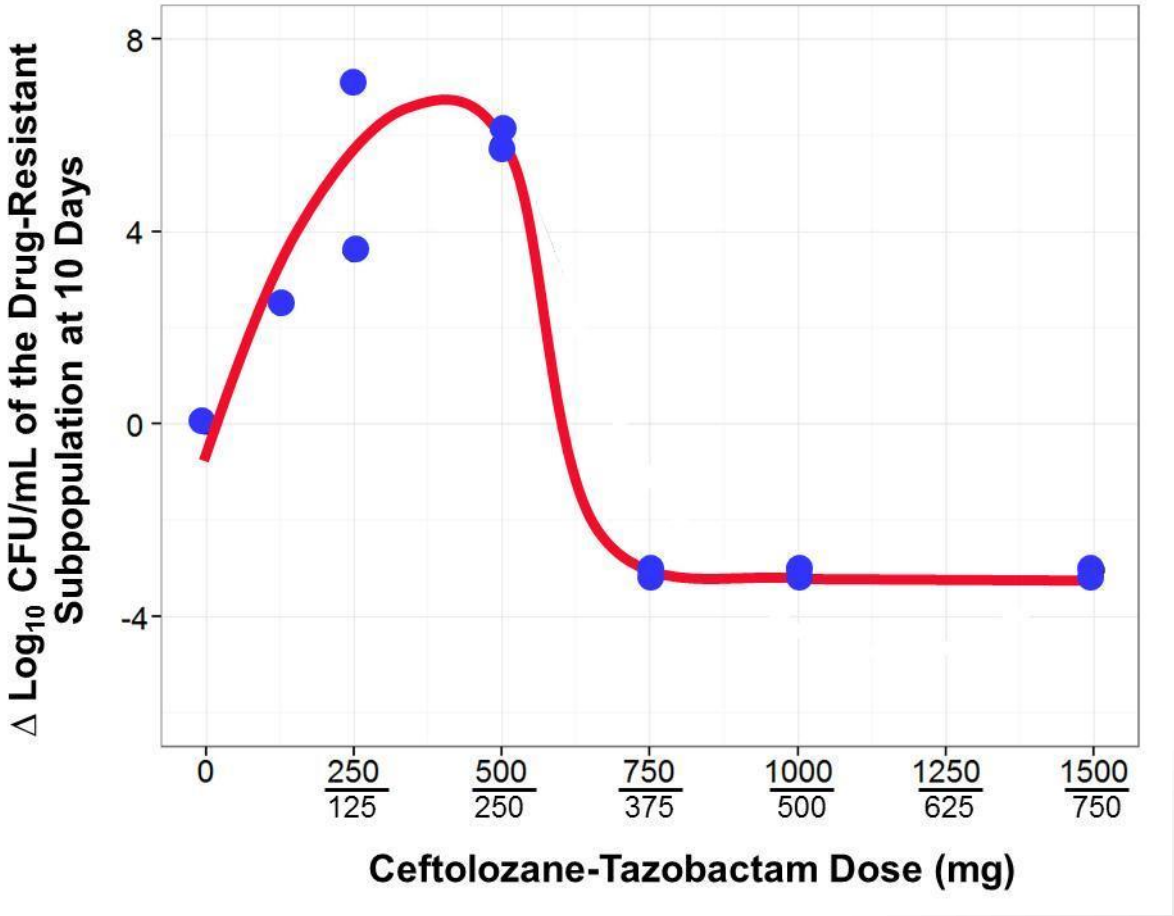
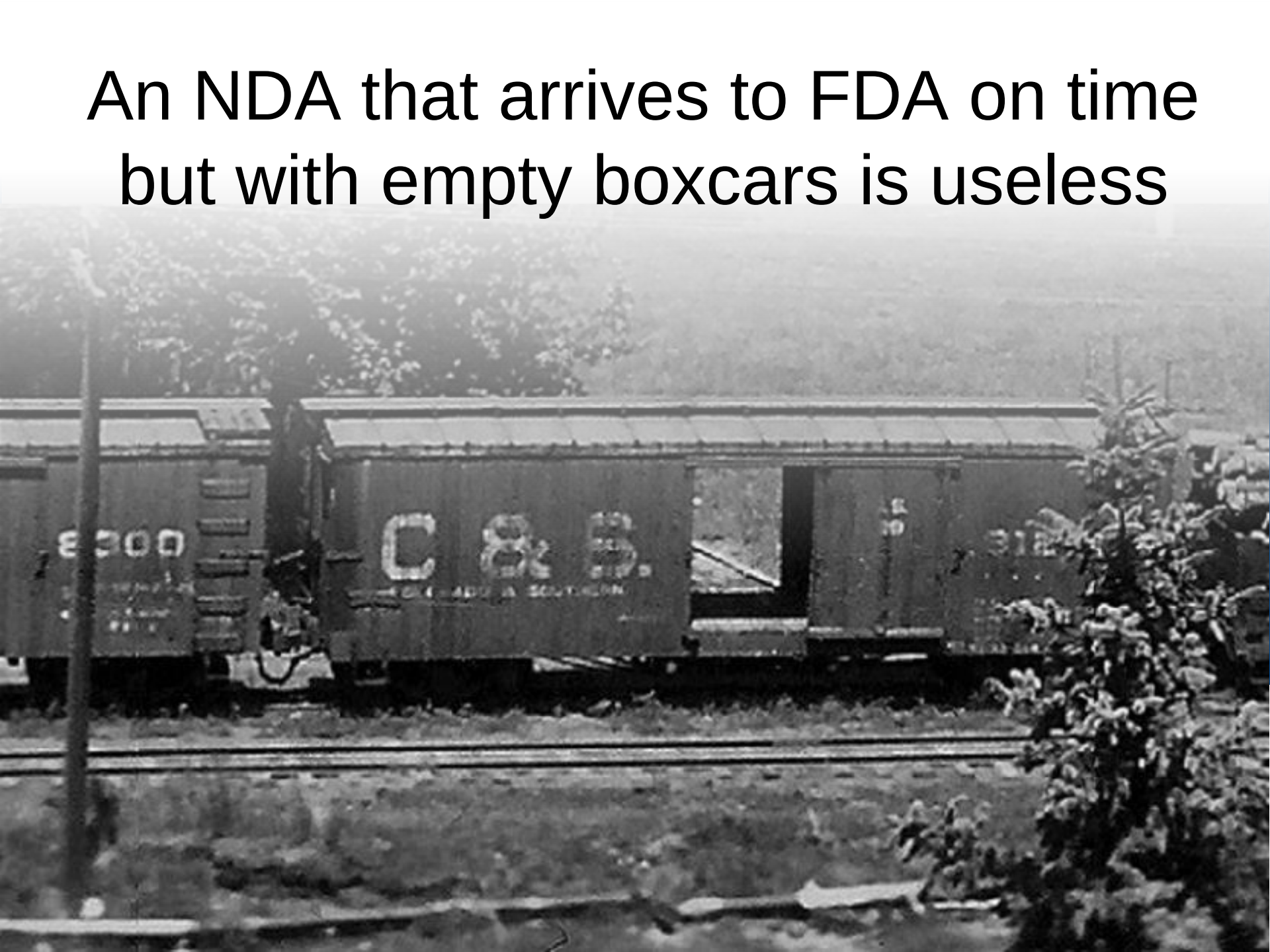
Pressure test dosing regimens



Strain	*E. coli* JMI 11103	
Enzyme		CTX-M-15
MIC (mg/L)	Ceftolozane	16
	Ceftolozane-Tazobactam	0.25
Hydrolytic Activity		120
qRT-PCR		8.3

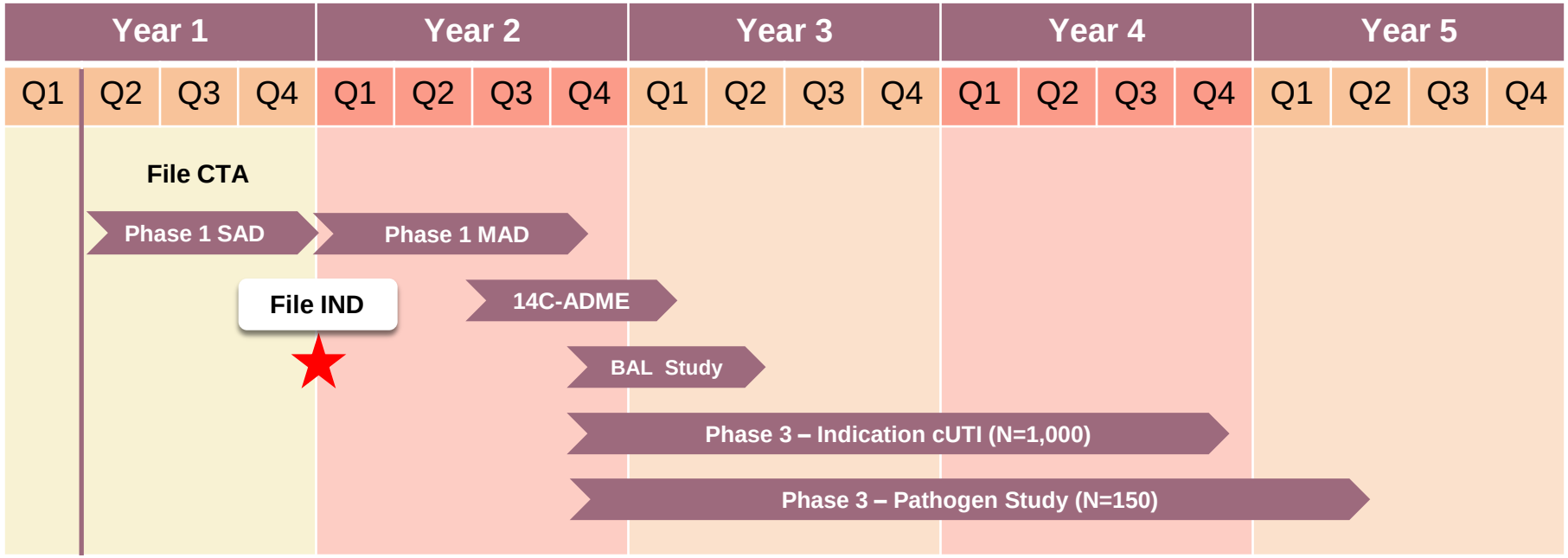
VanScoy B, Mendes RE, Castanherira M, McCauley J, Bhavnani SM, Forrest A, Okusanya OO, Jones RN, Friedrich LV, Steenbergen JN, Ambrose PG. Relationship between ceftolozane/tazobactam exposure and drug-resistance amplification in a hollow-fiber infection model. *Antimicrob. Agents Chemother*. 2013; 57:4134-4138.

An NDA that arrives to FDA on time but with empty boxcars is useless



Risky Study Sequence Without Time for Thought

Accelerated clinical development timeline



Develop the drug you have and not the one you wish you had

ACKNOWLEDGMENTS

Many Thanks to those that continue to inform my thinking!

DAVID ANDES, M.D.
University of Wisconsin

WILLIAM A. CRAIG, M.D.
University of Wisconsin

MICHAEL N. DUDLEY, PHARM.D.
The Medicines Company

GEORGE L. DRUSANO, M.D.
University of Florida

JAMES KAHN, M.D.
JBK Strategic Consultations

JUSTIN BADER, PHARM.D.
Institute for Clinical Pharmacodynamics

SUJATA M. BHAVNANI, PHARM.D, MS
Institute for Clinical Pharmacodynamics

ALAN FOREST, PHARM.D.
Institute for Clinical Pharmacodynamics

ELIZABETH LAKOTA, PHARM.D.
Institute for Clinical Pharmacodynamics

CHRISTOPHER M. RUBINO, PHARM.D.
Institute for Clinical Pharmacodynamics

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Thank you for your attention.