A PHARMACOMETRIC-BASED APPROACH TO FACILITATE CRITICALLY NEEDED NEW ANTIBIOTIC DEVELOPMENT

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THE PROBLEM
Regulatory Uncertainty

- Antimicrobial drug development has greatly diminished due to the impact of regulatory uncertainty regarding
  - The ***magnitude of drug effect*** and
  - The ability of contemporary ***clinical trial endpoints to capture drug benefit***
- These elements are critical to statistically power non-inferiority studies
  - The lack of this information undermines the viability of contemporary clinical trial designs

HISTORICAL DATA EXAMINATION

One Solution

- One approach to gain knowledge about the magnitude of treatment effect is through the examination of historical data
- However, there are ***obvious limitations*** to historical data that can introduce potential bias
  - No placebo control,
  - Lack of blinding and randomization,
  - Use of medically dubious interventions, and
  - Inability to authenticate the source data
- Source data verification is an essential component in Good Clinical Practice guidelines

HISTORICAL DATA EXAMINATION

One Solution

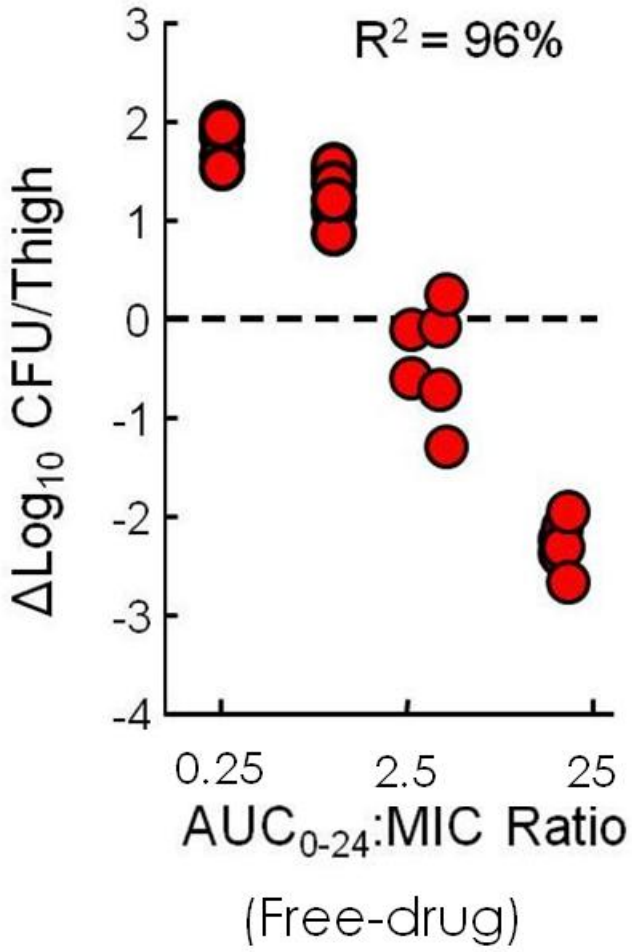
- Using historical data, the US FDA and others have primarily employed a single statistical approach
  - Frequentist inference
- Alternative statistical approaches have not been fully (a nice way of saying “not at all”) considered by the US FDA or others
  - Frequentist inference combined with pharmacometric methods
  - Bayesian inference combined with pharmacometric methods

BAYESIAN VERSUS FREQUENTISTS
The Key Differences

- Frequentist analyses do not incorporate prior information or beliefs
  - In a frequentist analysis, mean is considered to be a real value and only the study data determines numerical results
- In a Bayesian analysis, both prior information and the study data influence the results and conclusion
  - Since the population mean is not considered fixed in a Bayesian analyses, prior information concerning the likelihood of the mean to fall within specified intervals can be quantified and incorporated

A BAYESIAN APPROACH

Three Reasons this is Rational



- First, tigecycline has demonstrated *in vitro* activity against bacteria of clinical interest
- Second, tigecycline was evaluated in animal infection models, where it was effective in bacterial killing
  - Tigecycline exposure, as measured by the $AUC_{0\text{-}24}$:MIC ratio, and outcome were well-described by exposure-response models

van Ogtrop ML, Andes D, Stamstad TJ, Conklin B, Weiss WJ, Craig WA, and Vesga O. In vivo pharmacodynamic activities of two glycylcyclines against Gram-positive and Gram-negative bacteria. *Antimicrob.* Agents Chemother. 2000 44: 943-949.

A BAYESIAN APPROACH
Three Reasons this is Rational

- Third, tigecycline was studied in patients for whom efficacy was demonstrated and related to $AUC_{0\text{-}24}$:MIC ratio using exposure-response models
- In other words, ***antimicrobial agents*** that enter late-stage clinical development have been effectively ***pre-screened for efficacy***
    - As such, it is highly likely that such agents would be efficacious if appropriate dose regimens are selected for clinical study

OBJECTIVES
A New Approach

- Our objective was to demonstrate the utility of frequentist- and Bayesian-pharmacometric-based logistic regression analyses
  - Determine the magnitude of treatment effect
  - Determine the ability of clinical trial endpoints to capture drug benefit
- A HAP/VAP clinical trial dataset was selected for analysis
  - Contemporary Phase 3 trial involving tigecycline
  - Labeling indications have generated considerable discussions at US FDA and IDSA co-sponsored workshops and in Guidance Documents

METHODS
Statistics

- Logistic regression models
  - The dependent variables were microbiological and clinical success
  - The independent variable in each analysis was the $\log_{10}$ transform of the $AUC_{0\text{-}24}$:MIC ratio
- Frequentisit logistic regression analyses were carried out in the standard fashion based on maximum likelihood estimation

METHODS

Statistics

- Bayesian logistic regression analyses were performed employing a non-informative uniform prior distribution for the intercept parameter

- Bayesian logistic regression analyses were performed employing a normal prior distribution for the slope parameter corresponding to drug exposure

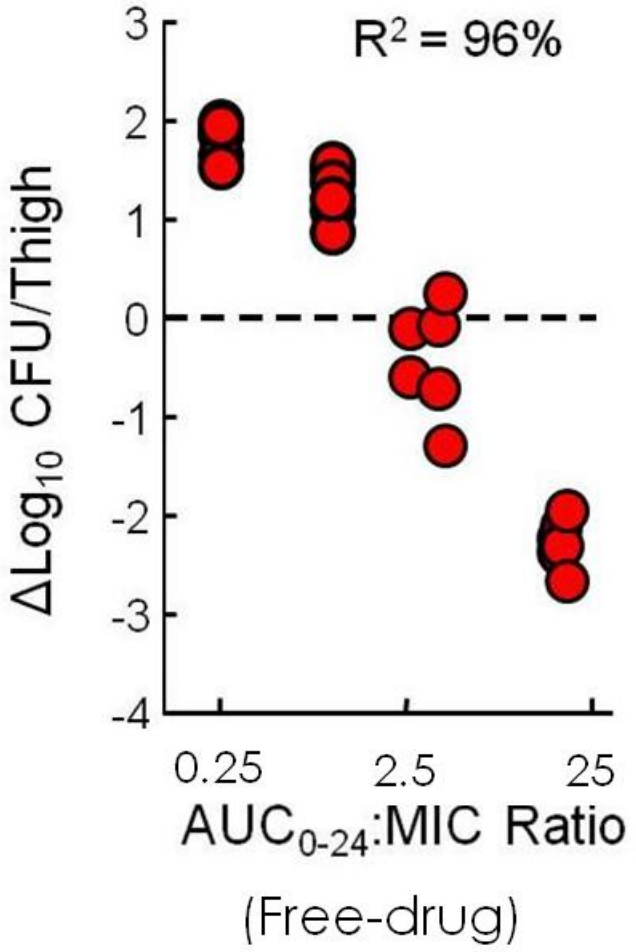
  - Normal prior estimates for the Bayesian analyses were selected to reflect a 99% prior likelihood of treatment effect within an interval of -0.25 to 0.75

    - ✓ Favors a positive treatment effect (drug helps patients)
    - ✓ Allows the possibility of a negative treatment effect (drug hurts patients)

METHODS

Statistics

- Treatment effect was defined as the difference in likelihood of success at low and high magnitudes of drug exposure
  - Low and high exposures were fixed at free-drug $AUC_{0\text{-}24}$:MIC ratios of 0.01 and 25, respectively
- 95% lower bounds for treatment effect were obtained using 1,000 bootstrap samples and the bias-correcting acceleration method



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RESULTS

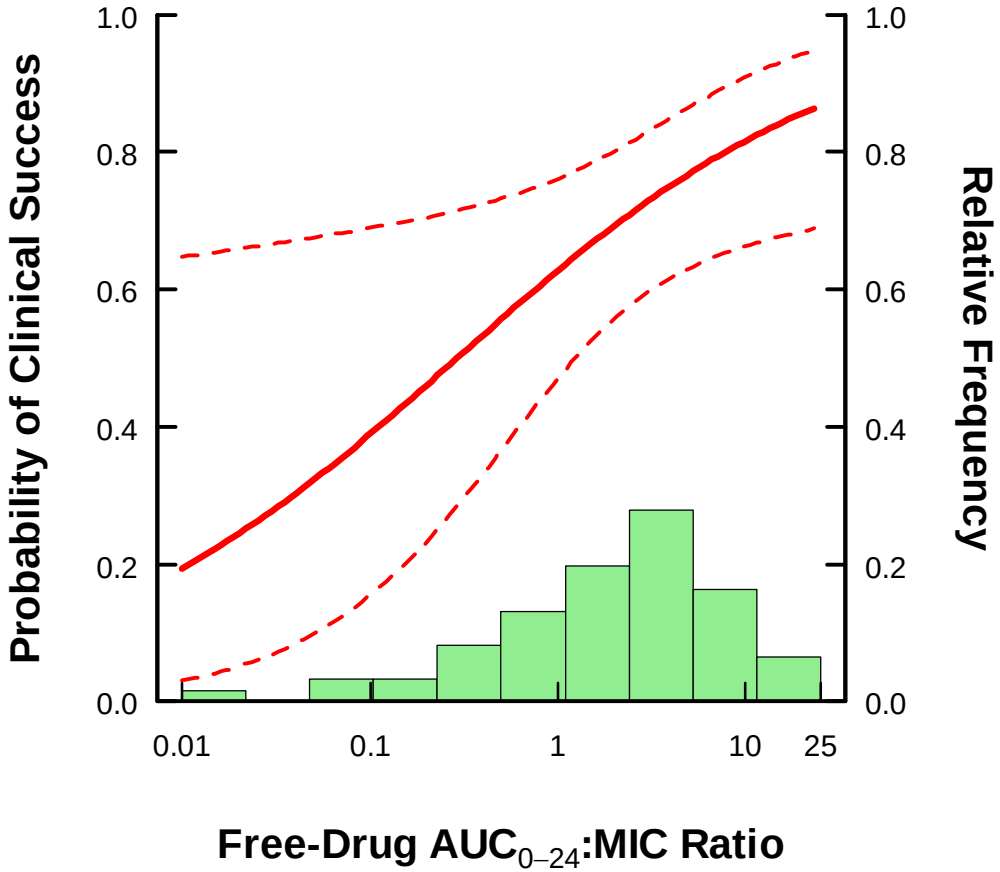
Analysis Population

- 61 patients who were both clinically evaluable and microbiologically evaluable and had sufficient PK data were included in these analyses
- Clinical and microbiological response were highly concordant (95%, 58/61)
  - 42 patients were categorized both as clinical and microbiological successes
  - 16 patients were categorized both as clinical and microbiological failures
  - 2 patients were categorized microbiological but not clinical successes
  - 1 patient was categorized as a clinical but not microbiological success

Bhavnani SM, Rubino CM, Hammel JP, Forrest A, Dartois N, Cooper A, Korth-Bradley J, Ambrose PG. Pharmacological and Patient-Specific Response Determinants in Patients with Hospital-Acquired Pneumonia Treated with Tigecycline. *Antimicrob Agents Chemother.* Awaiting Disposition.

RESULTS

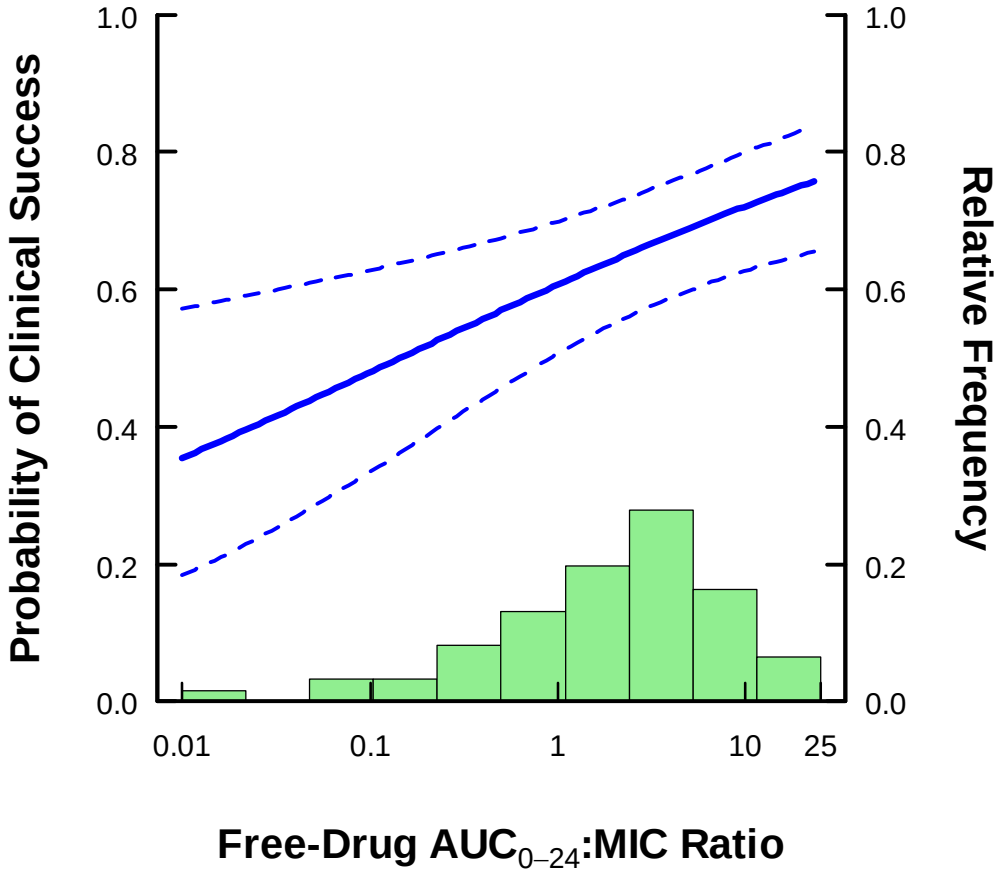
Frequentist Logistic Regression, Clinical Endpoint



Ambrose PG, Hammel JP, Bhavnani SM, Rubino CM, Ellis-Grosse EJ, Drusano GL. A Bayesian Pharmacometric-Based Approach to Facilitate Critically Needed New Antibiotic Development: Overcoming Lies, Damn Lies and Statistics. *Antimicrob Agents Chemother.* Awaiting Disposition.

RESULTS

Bayesian Logistic Regression, Clinical Endpoint



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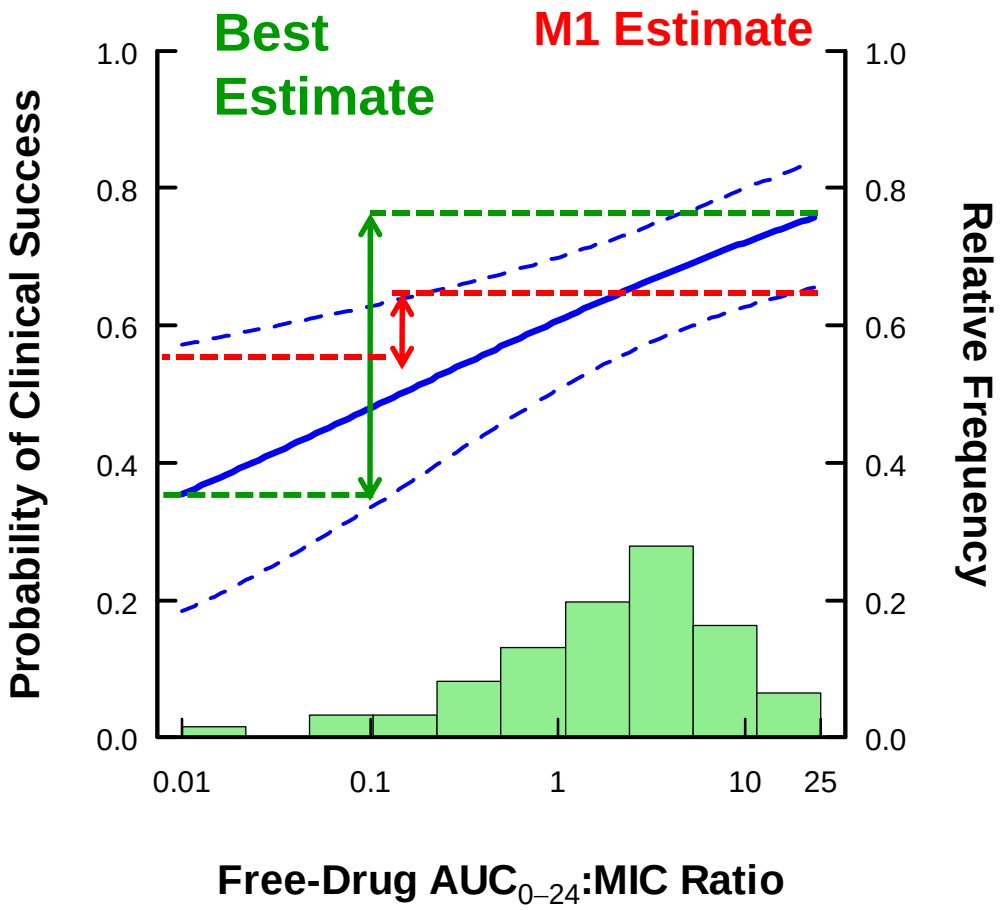
RESULTS

Best Estimates of Treatment effect



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RESULTS

Estimates of Treatment Effect

Method	Endpoint	Estimates of Effect		
		Best	M1	ICPD M1*
Frequentist	Microbiological	0.655	0.004	0.166
	Clinical	0.672	0.043	0.211
Bayesian	Microbiological	0.468	0.074	0.301
	Clinical	0.405	0.085	0.314

* 95% lower bound of treatment effect based upon 1000 bootstrap analysis

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EXPOSURE-RESPONSE ANALYSES
Implications

- The relationships themselves indicate that ***contemporary clinical endpoints*** (e.g. success or failure at the TOC), ***capture a measure of drug effect***

- This observation negates the first of two reasons underpinning the use of historical data to determine the magnitude of treatment effect
  - The perception that data are not available supporting the ability of contemporary endpoints to capture drug effect

- The best estimate of the magnitude of the treatment effect (clinical response) is large for HAP/VAP
  - 0.405 for Bayesian
  - 0.672 for frequentist

EXPOSURE-RESPONSE ANALYSES
Implications

- Frequentist and Bayesian logistic ***regression models provided estimates of the*** response rates as drug exposure approaches zero, supplying an estimate of the ***no-treatment response***

- This observation negates the second reason underpinning the use of historical data

  - The perception that data are not available to provide an estimate of the placebo response rate.

  - It is important to note the magnitudes of treatment effect described above are based upon the difference in drug effect at high and low exposure (rather than placebo).

    - ✓ These magnitudes of the treatment effect are biased low

CONCLUSIONS

A Pharmacometric-Based Approach

- We demonstrated the utility of Bayesian pharmacometric-based analyses for the determination of treatment effect and calculation of NI margins
- Incorporation of bootstrapping to obtain lower bounds for treatment effect improved upon an overly imprecise and arbitrary practice of taking a difference between interval estimates
- We feel that this method integrates contemporary data with pharmacometric-based approaches provides a bridge forward for drug development that is anchored on sounder scientific footings