PK/PD versus frequentist approaches for drug development

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Three Points

- PK/PD methods good to predict response to drug. RCTs good to assess causal effect of the drug.
- PK/PD methods can be used with RCT data to rigorously assess a causal drug effect where PK/PD predicts one should occur.
- Bayesian Methods good to leverage information. Frequentist methods good to objectively assess evidence.

Cardiovascular World

- Cardiac Arrhythmia Suppression Trial (CAST)
- At baseline, identified patients whose arrhythmias were suppressible by AAD.
- NIH: Randomize the suppressible.

  (some felt trial was immoral)

	Not suppressible *resistant* **to AAD**	**Suppressible** ***susceptible*** **to AAD**
AAD	**Registry**	**Randomize**
Placebo		**Randomize**

CAST Trial & Registry
Death Rates

	Not suppressible *resistant* to AAD	Suppressible *susceptible* to AAD
AAD	***10% - 15%**** ⟷	**7.0%**
Placebo		

Nonrandomized study: Looks like drug works!

* Based on a plausible range of assumptions about who got AADs

CAST Trial & Registry
Death Rates

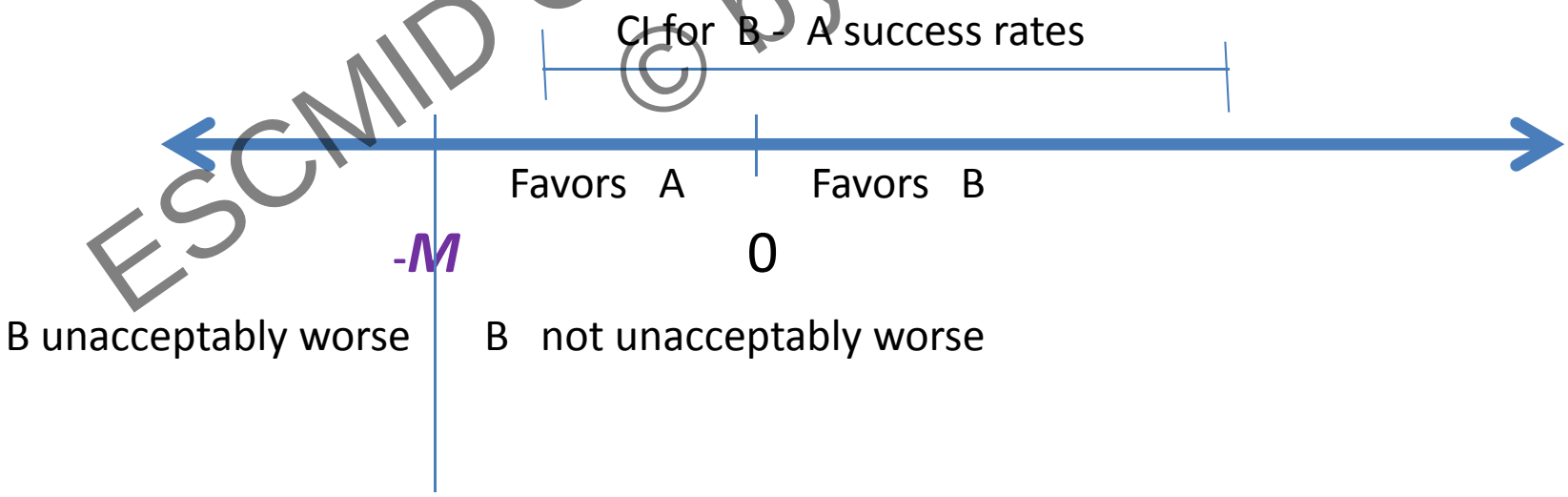
	Not suppressible *resistant* to AAD	Suppressible *susceptible* to AAD
AAD	**10% - 15%***	**7.0%**
Placebo		**4.4%**

RCT: AADs *increased* the death rate in patients with suppressible arrhythmias.

* Based on a plausible range of assumptions about who got AADs

Current Anti-infective Drug Landscape

- Non-inferiority (NI) Trial: New Drug B versus comparator Drug A
- Confidence interval (CI) of difference in success rates needs to exceed a ***margin*** **based on historical data**

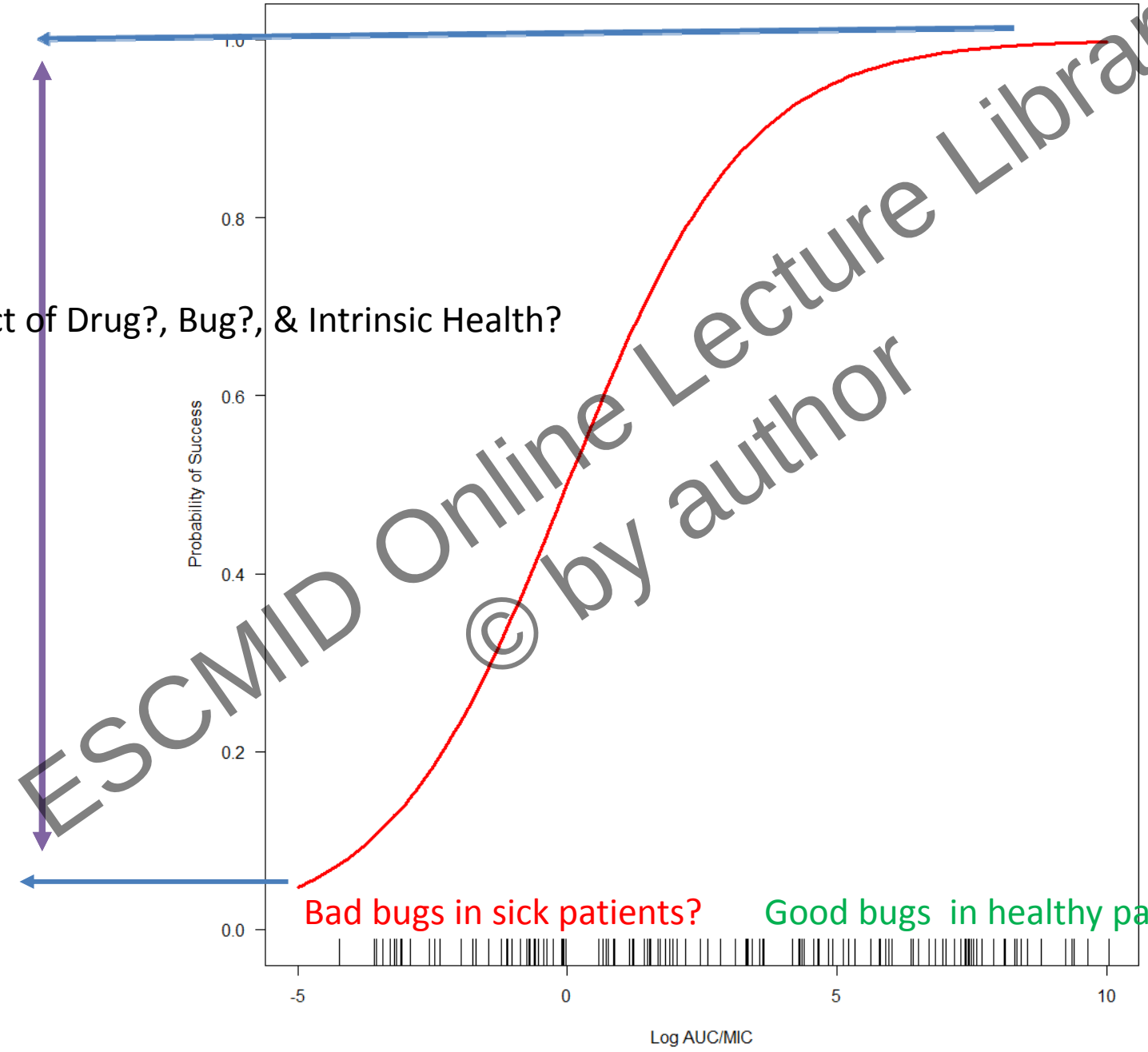


PK/PD modeling for Margin

- In this talk focus on the AUC:MIC ratio
- MIC- minimum inhibitory concentration of drug to kill the bug
- AUC—area under the curve of drug concentration
- Idea
  - Lower MIC --- easier to kill bug with drug
  - Higher AUC --- more drug to better kill bug
- Use AUC:MIC ratio --- bigger is better

Use PK/PD to set a margin?

Log(AUC/MIC) can provide a good prediction of response but drug causality unclear



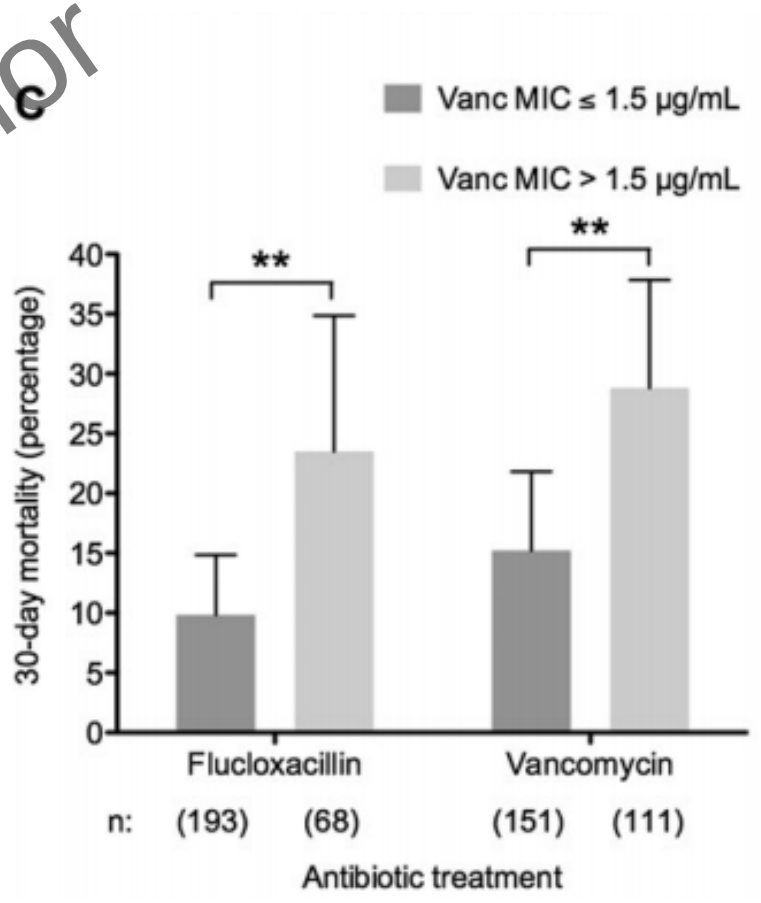
Effect of Drug?, Bug?, & Intrinsic Health?

Bad bugs in sick patients?

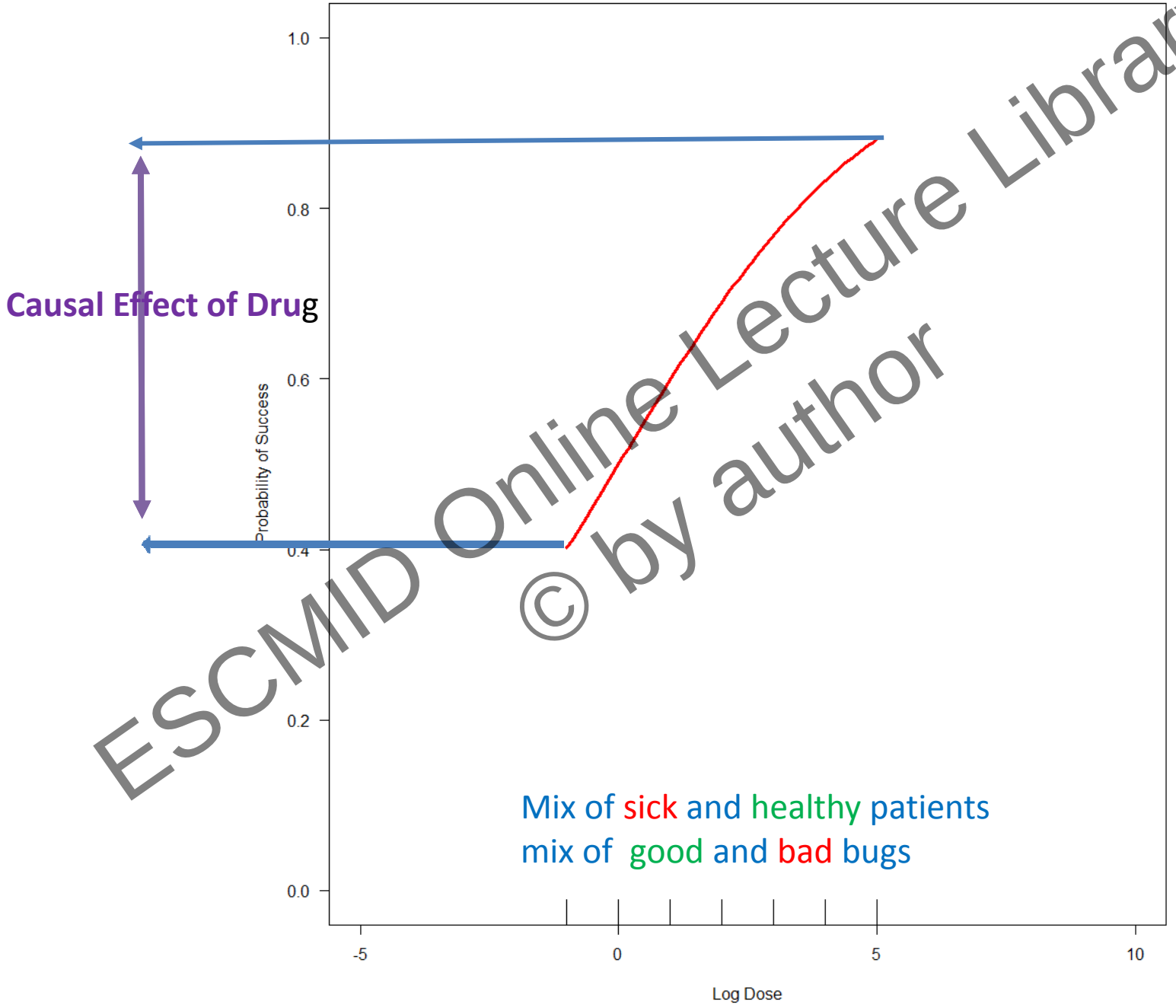
Good bugs in healthy patients?

Holmes et al JID 2011

- Patients with *Staphylococcus aureus* bacteremia treated with vancomycin or flucloxacillin
- Vancomycin MIC predicts death for both vancomycin **&** flucloxacillin treated patient
- MIC-Vanco correlated with pt health, immunity?

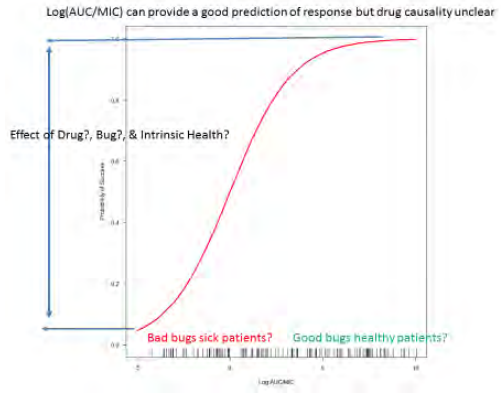


Randomizing to dose allows for a causal conclusion about drug effect



Causal drug conclusion from observational data?

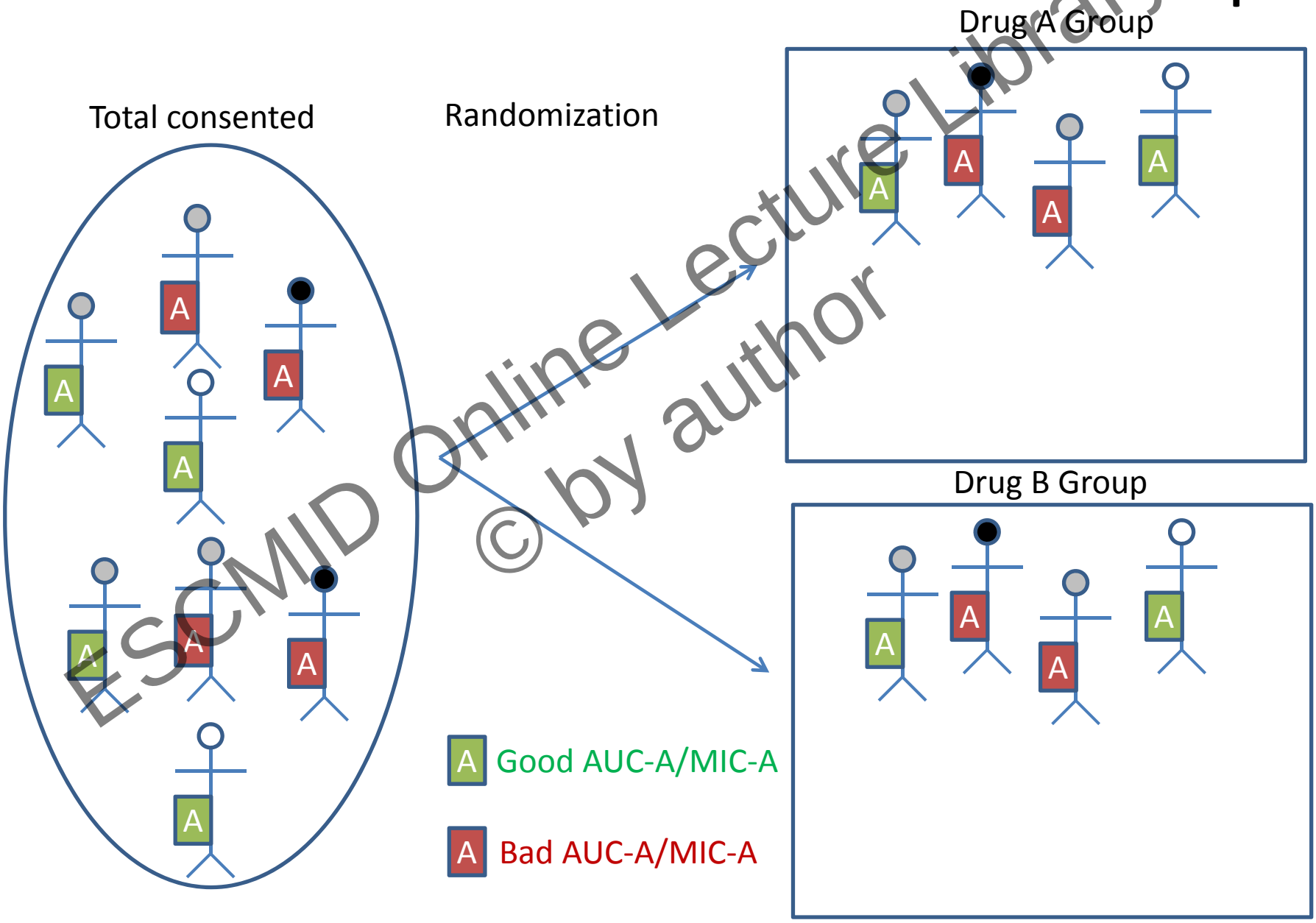
- Make an observational study more like a trial
- Statistically adjust for patient characteristics
  - Comorbidities, age, health, nursing home/hospital
- Statistically adjust for bug characteristics
  - Susceptibility to human immunity
- Hard to know if adjustment creates a valid pseudo-trial



Blending PK/PD with Trial Data

- Do a NI randomized trial of old Drug A versus new Drug B
- Measure MIC-A
- Predict AUC-A based on patient characteristics
  - Form log (pAUC-A/MIC-A)
- See if Drug B beats Drug A in patients with large MIC-A , small pAUC-A
  - RCT quality causal evidence

Randomization Creates Similar Groups



Look for Drug B Effect in Obvious Subgroup

Success Rates by AUC-A:MIC-A ratio

	Bad AUC-A/MIC-A	Good AUC-A/MIC-A
Drug B	.93	.98
Drug A	.52	.98

B beats A !
B has a causal effect!

Analysis of NI UTI trial

- Got data from FDA under a MOU
- NI trial, N=429 patients in UTI subset with complete data & *e coli* sole pathogen
  - can't say much else
- Success rates
  - 92.8% Comparator Drug A
  - 97.1% New Drug B
- p-value .072, not significant for superiority

pAUC-A:MIC-A ratio

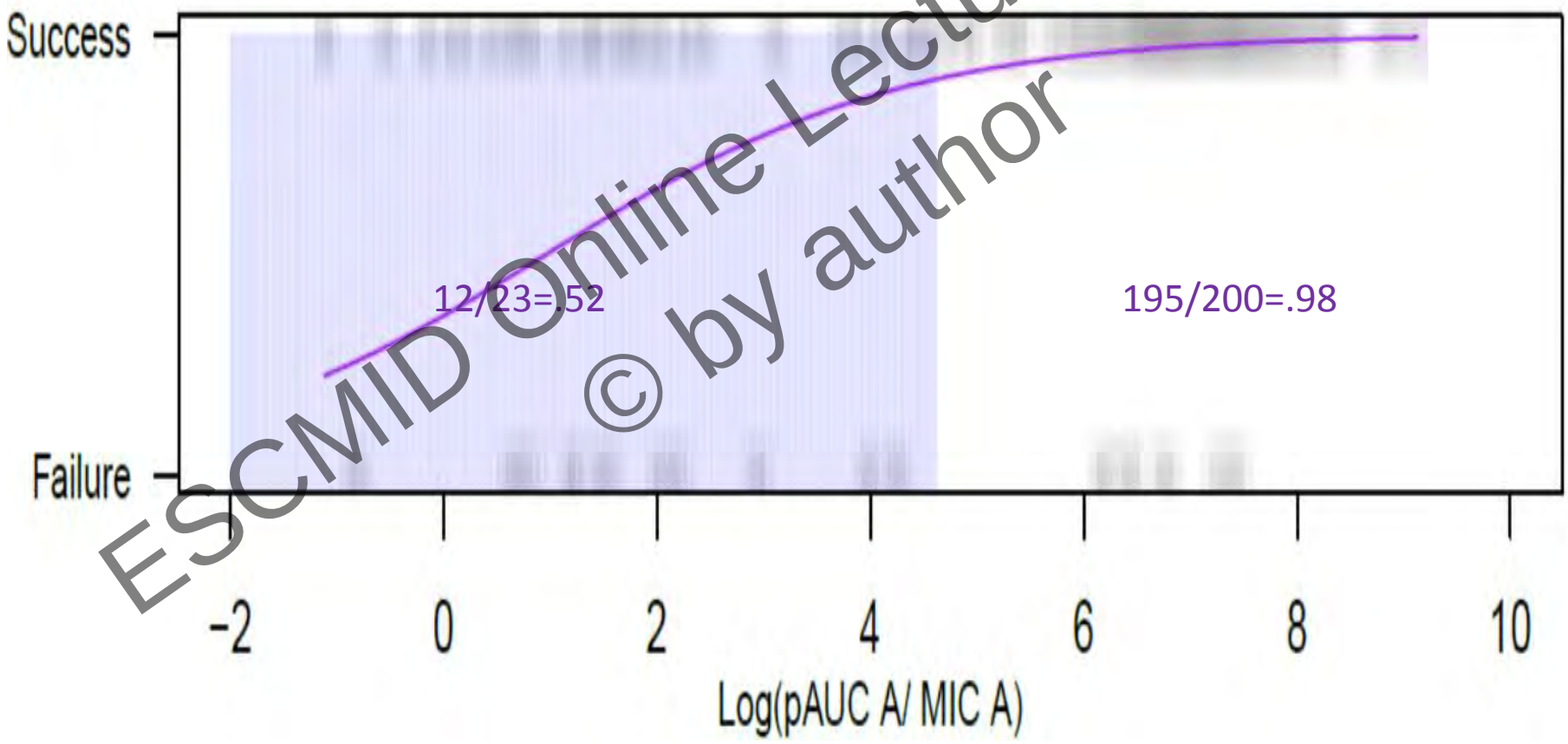
- MIC to drug A from baseline sample
- Predicted AUC to drug A from an equation

  $B_0 + B_1$ CrCl + B_2 Age + Clrace

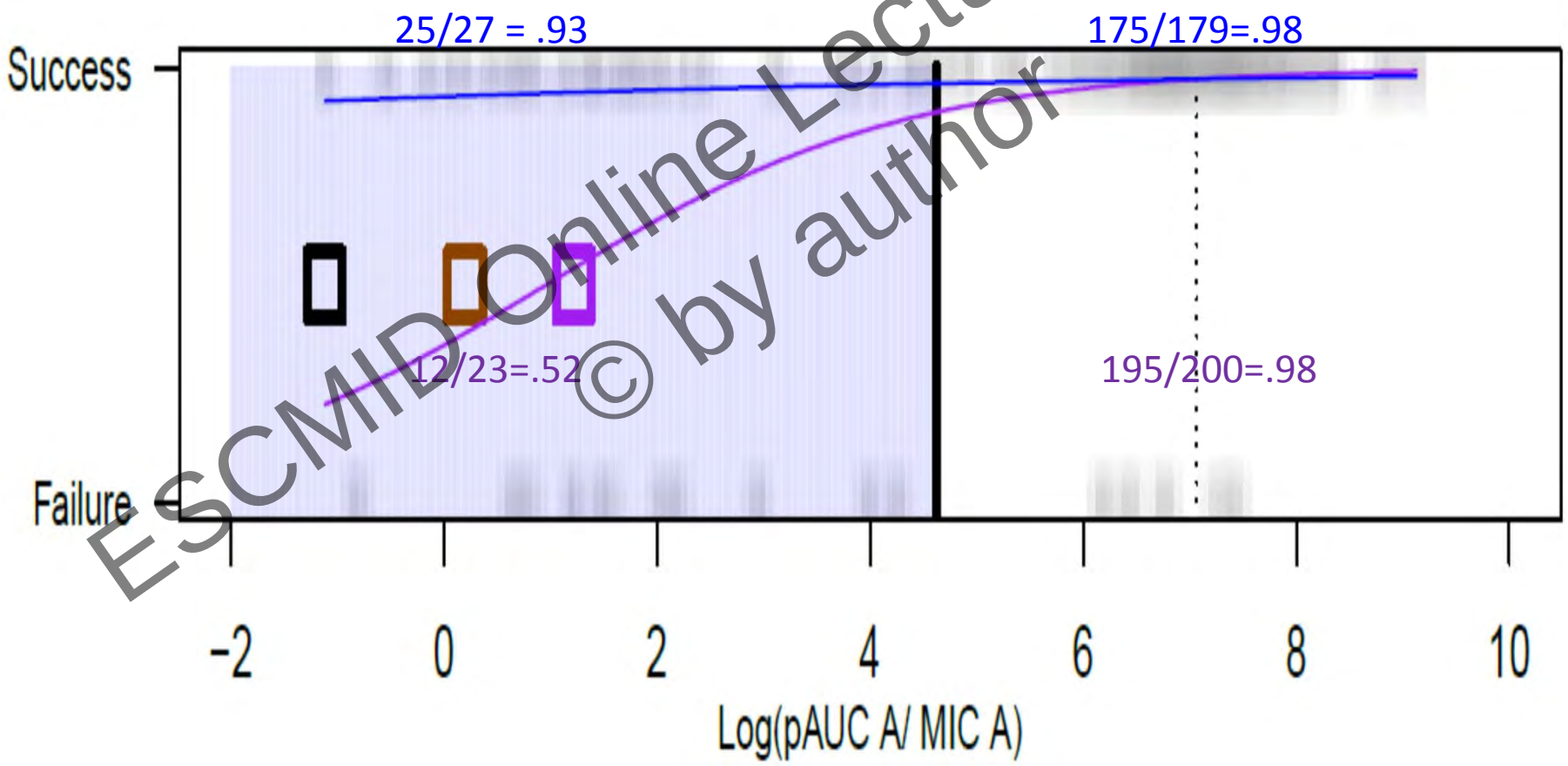
  CLrace=(D1, D2, D3, D4)
- Form LR = log { pAUC-A/MIC-A }

  All from baseline data

pAUC:MIC predicts Drug A benefit



Drug B beats* Drug A in patients with bad AUC:MIC for Drug A



* p=.01

Consequences

- Superiority in a region obviates need for historical evidence of a margin
  - Use modern endpoints---e.g. patient reported outcomes
- Superiority demonstrates the trial had *assay sensitivity*
- Targeting of proven drugs may be possible
  - Use Drug B in AUC:MIC region of proven superiority
  - Go beyond the overall NI pronouncement
  - Requires timely evaluation of pAUC/MIC

Bayesian Paradigm

Rev. Bayes

- A philosophy of statistics different from the common *frequentis*t view of statistics of p-values and confidence intervals
- Formally allows blending of knowledge or belief with objective collected data
- Requires specification of *intensity of belief* about prior knowledge: a lot, . . . , a little
- In simple cases, intensity of belief is equivalent to a hypothetical number of patients with data

Frequentist Analysis of a Trial

	Success	Failures
Drug A	80	20
Drug B	90	10

Data 100 subjects per arm

80% probability of success on Drug A versus
90% probability of success rate on Drug B

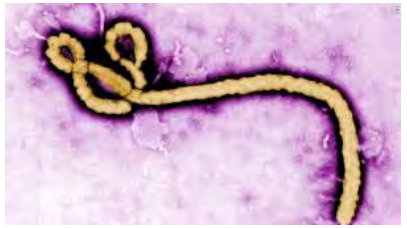
‘Objective’ Bayesian Analysis of a Trial

	Success	Failures
Drug A	80 + 1	20 + 1
Drug B	90 + 1	10 + 1

Data 100 subjects per arm

Prior Belief 50% success rate on A 50% success on B,
each worth 2 patients

79% probability of success on Drug A versus
89% probability of success rate on Drug B



Used in RCT to evaluate Zmapp in patients with Ebola Virus Disease
Adaptive trial with good frequentist statistical behavior

Subjective Bayesian Analysis of a Trial

	Success	Failures
Drug A	80 + 50	20 + 50
Drug B	90 + 95	10 + 5

Data 100 subjects per arm

Prior Belief 50% success rate on Drug 95% success rate on Drug B, each worth 100 patients

65% probability of success on Drug A versus
93% probability of success rate on Drug B

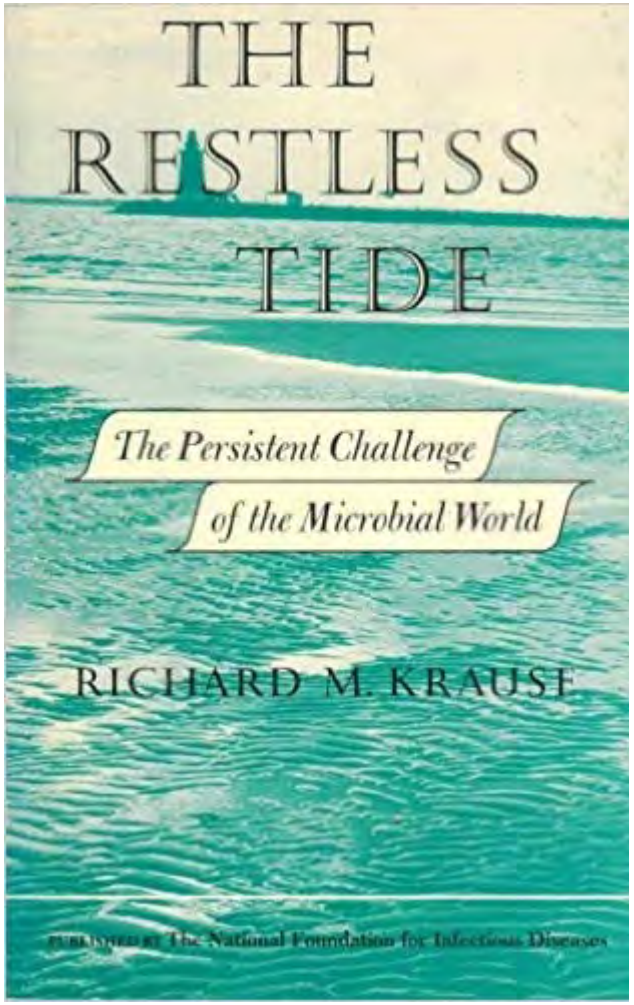
Prior belief as important as the collected data

Bayesian Methods

- If prior beliefs are accurate, leads to better estimation & decisions
- If prior beliefs are not accurate, biased conclusions can be drawn
  - *Not great for objectively assessing evidence*
- Specifying intensity of belief is crucial and often unclear in complex settings.

Final Points

- Development of anti-microbial resistance is ceaseless
- PK/PD & Bayesian methods
  are essential for efficient
  drug discovery & development
- RCTs ideal way to prove
  drugs are clinically effective



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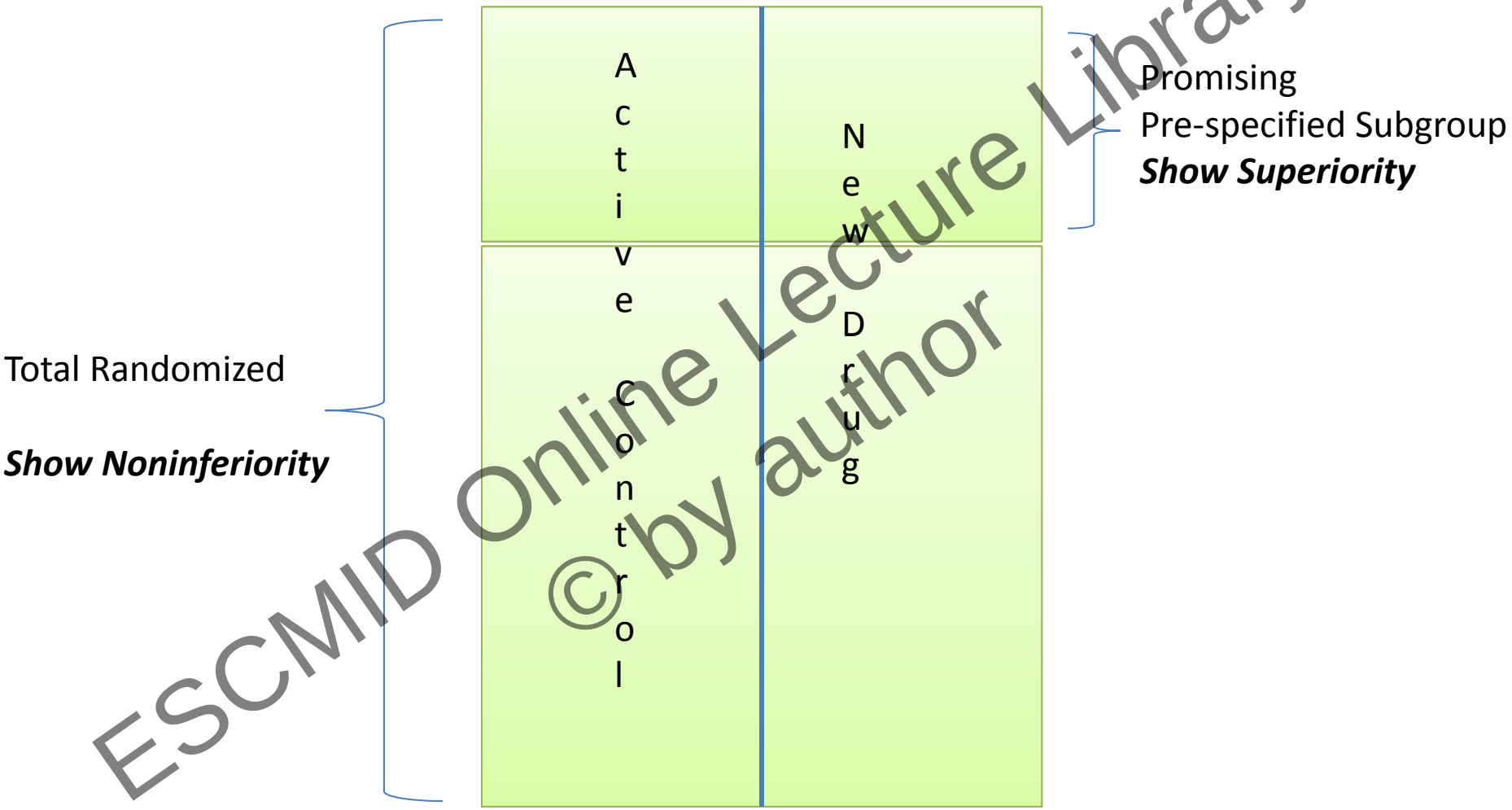
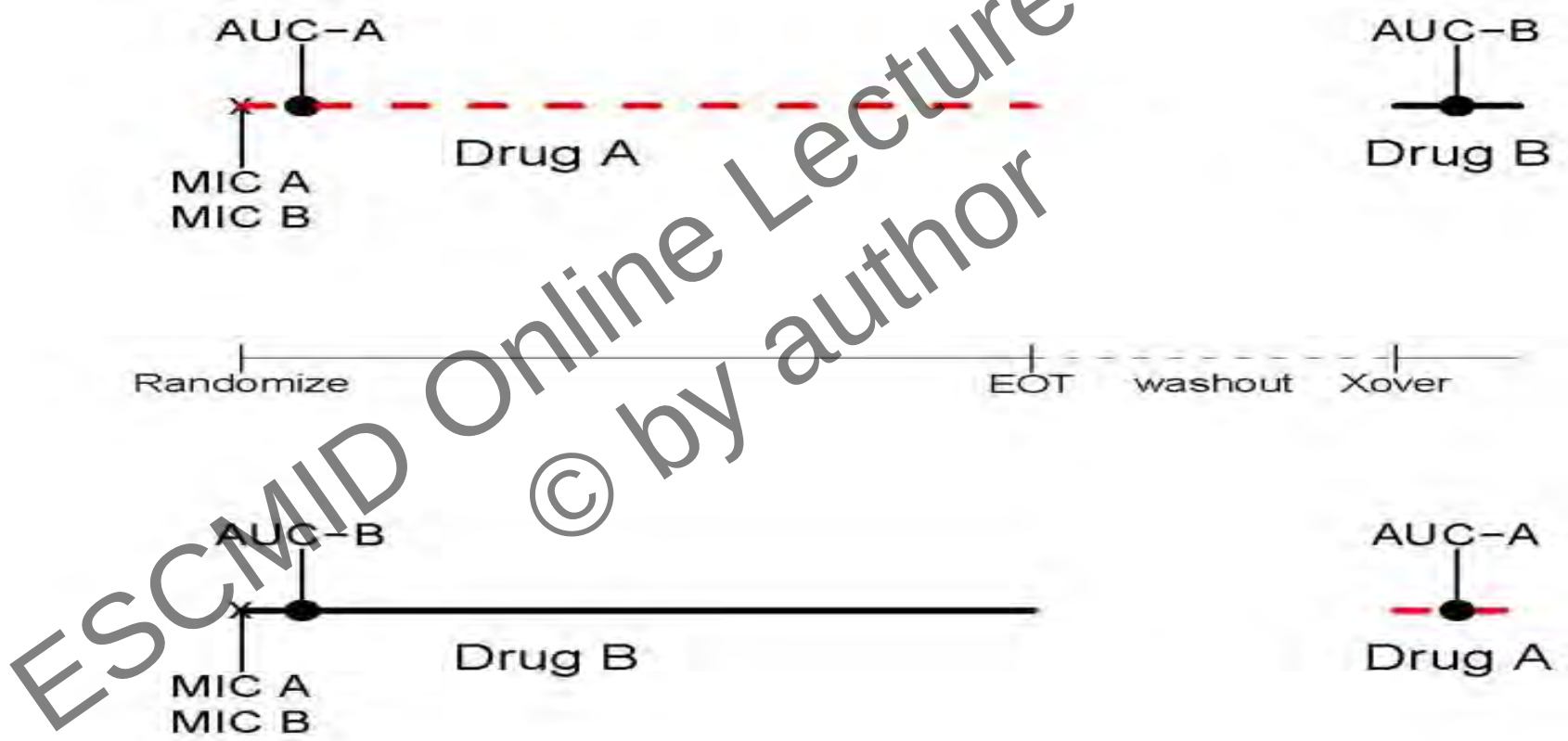


Use AUC instead of pAUC?

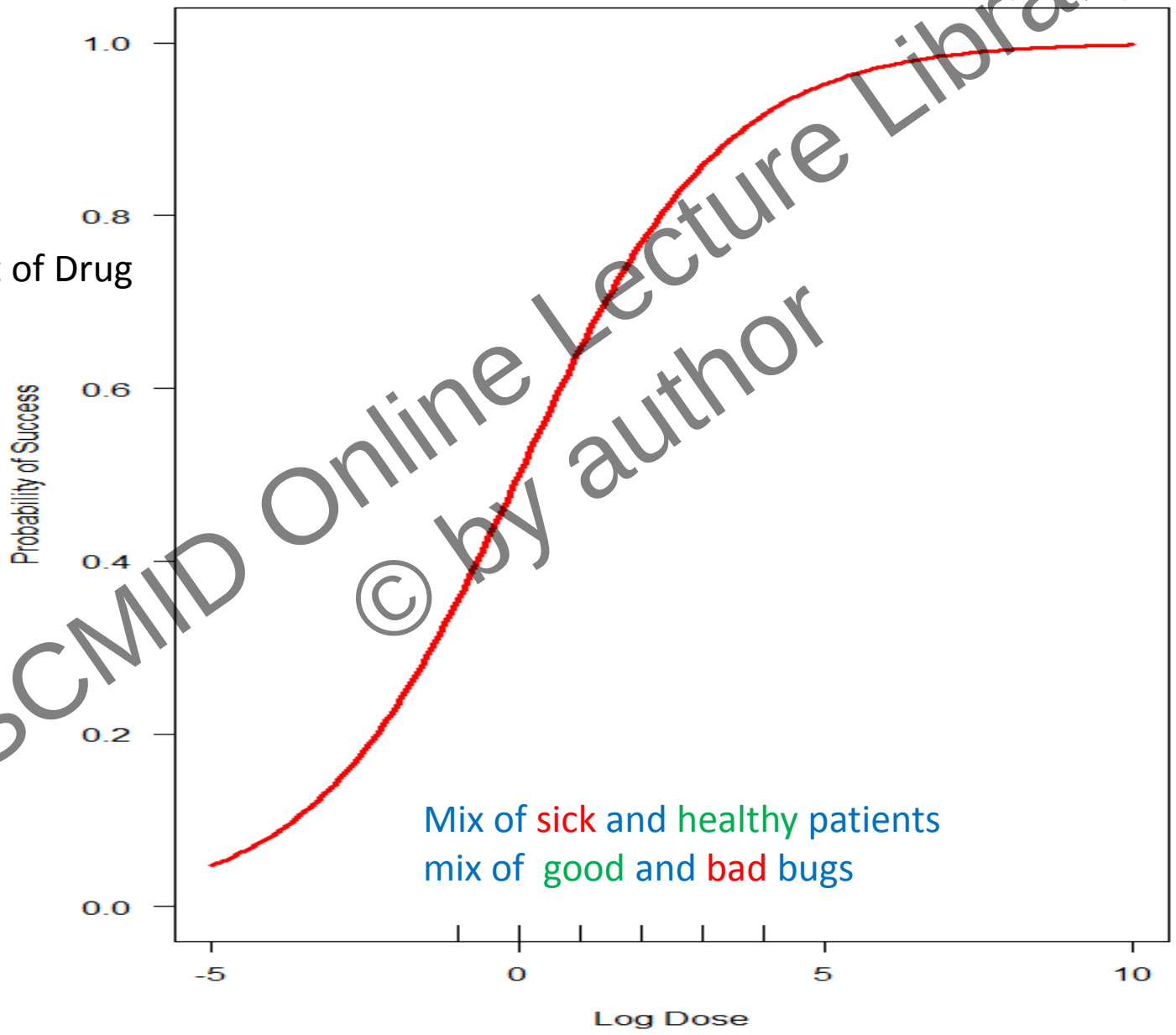


Summary

- Tempting to use PK/PD data in patients who all get Drug A to propose a margin
- Hard to know if Drug A has a causal effect on success without a randomized evaluation.
  - Margin may be questionable

Randomizing to Dose allows a causal conclusion about drug effect

Causal effect of Drug



A New Path for Licensure

- Decide on a clinically acceptable **margin** e.g. **10%.**
- Licensure supported if
  - NI margin of **10%** met
  - Superiority of B over A shown in patients for whom it is *a priori* most likely
    - Large MIC to drug A, Small AUC to drug A