

Use of In Vivo and In Vitro Models to Guide Dose Selection for Neonatal Infections

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Disclosures

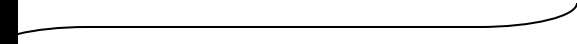
- William Hope has received research funding from Pfizer, Gilead, Astellas, AiCuris, Amplyx, Spero Therapeutics and F2G, and acted as a consultant and/or given talks for Pfizer, Basilea, Astellas, F2G, Nordic Pharma, Medicines Company, Amplyx, Mayne Pharma, Spero Therapeutics, Auspherix, Cardeas and Pulmocide.

First of all

DOSE

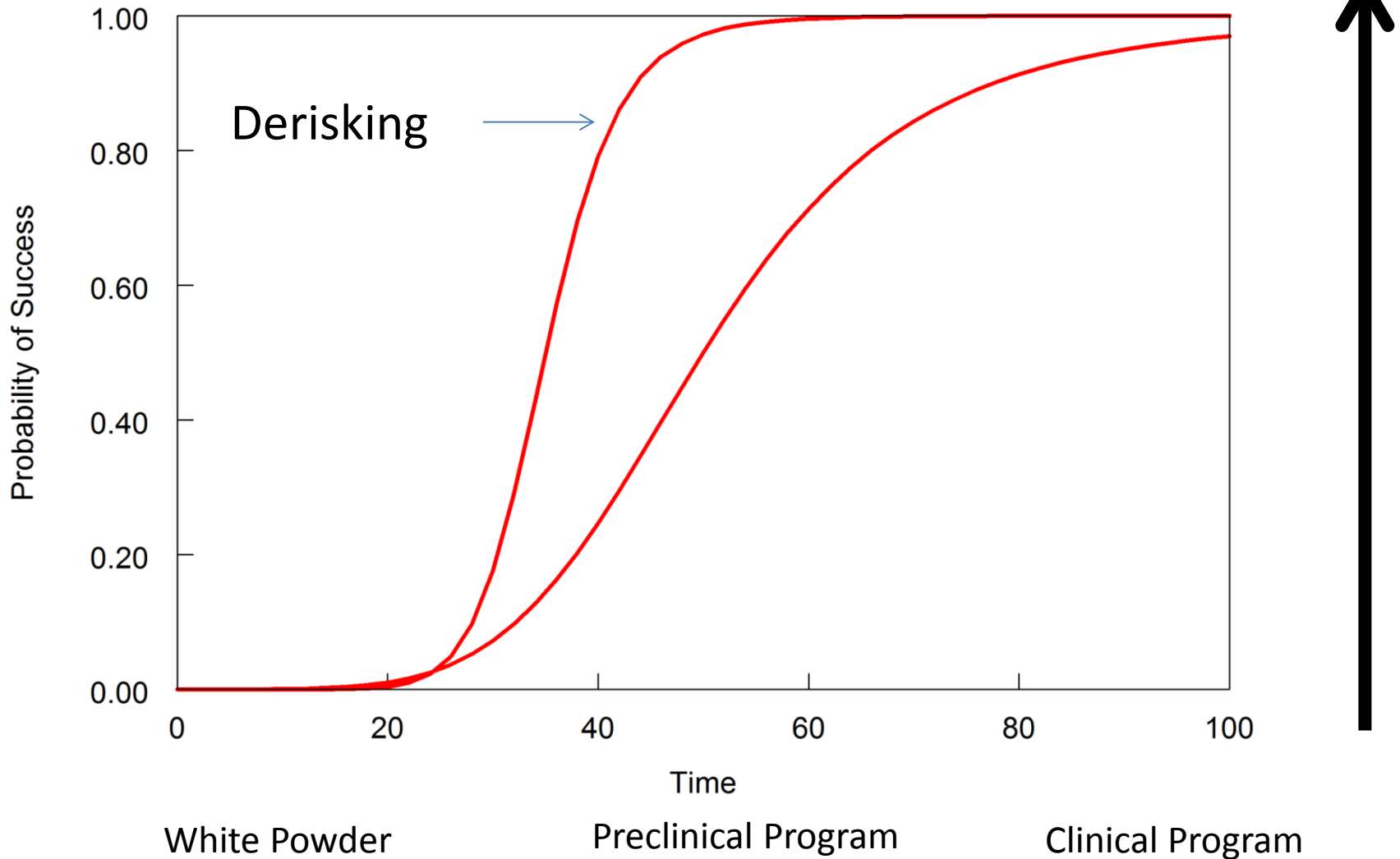
OUTCOME OF CLINICAL
INTEREST/IMPORTANCE

• Survival



Concept of Expensive Failure

COST



Concept from Trevor Mundell & Gates Foundation

And this...

Normal Therapeutics
Drug A, Dose A¹ versus Drug B, Dose B¹

Pharmacodynamics is the Bedrock of **ALL**
Therapeutics...it sits here without being seen

One of the reasons simple scaling
does not work is the fact
pharmacodynamics are different

Which means the conditions that
govern exposure response
relationships in neonates need to be
carefully considered

...Ignore these at your peril

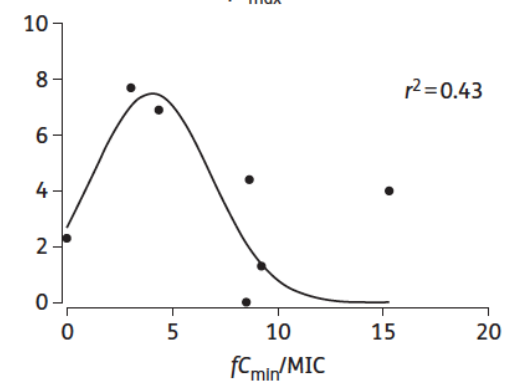
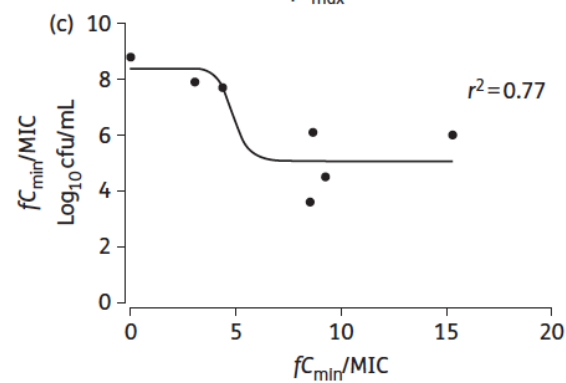
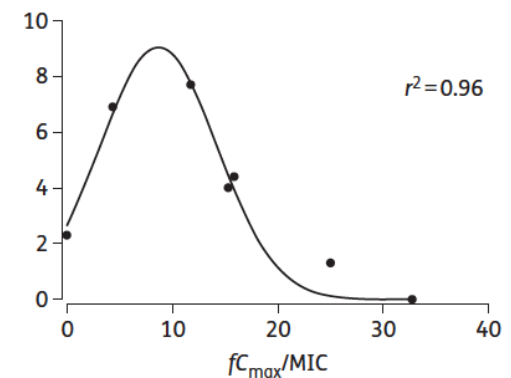
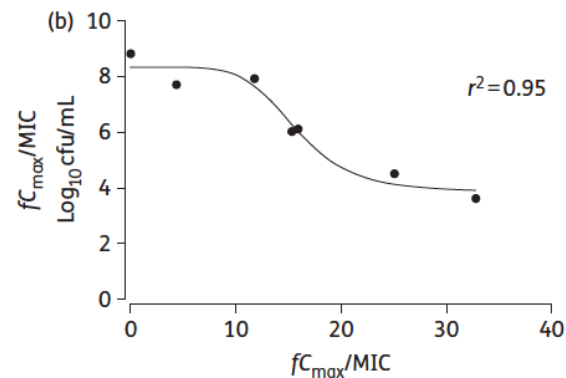
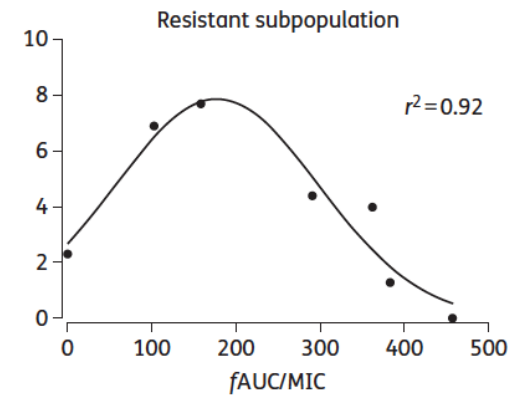
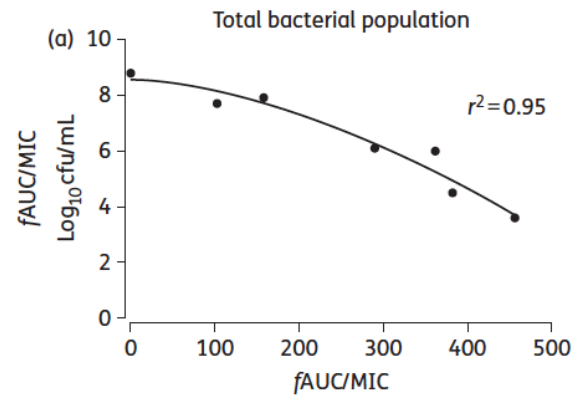
Summary of Preclinical Pharmacodynamic Studies for Neonates**

- Hope et al JID 2008
 - Micafungin for neonates
 - Primary question of HCME
 - Rabbit model with hematogenous dissemination
- Warn et al AAC 2010
 - Anidulafungin for neonates
 - Primary question of HCME
- Ramos-Martin et al (JAC 2016)
 - Vancomycin for neonates for CoNS
 - “NeoVanc”
 - New HFIM and new central line infection model
 - CRP as primary model readout in rabbits

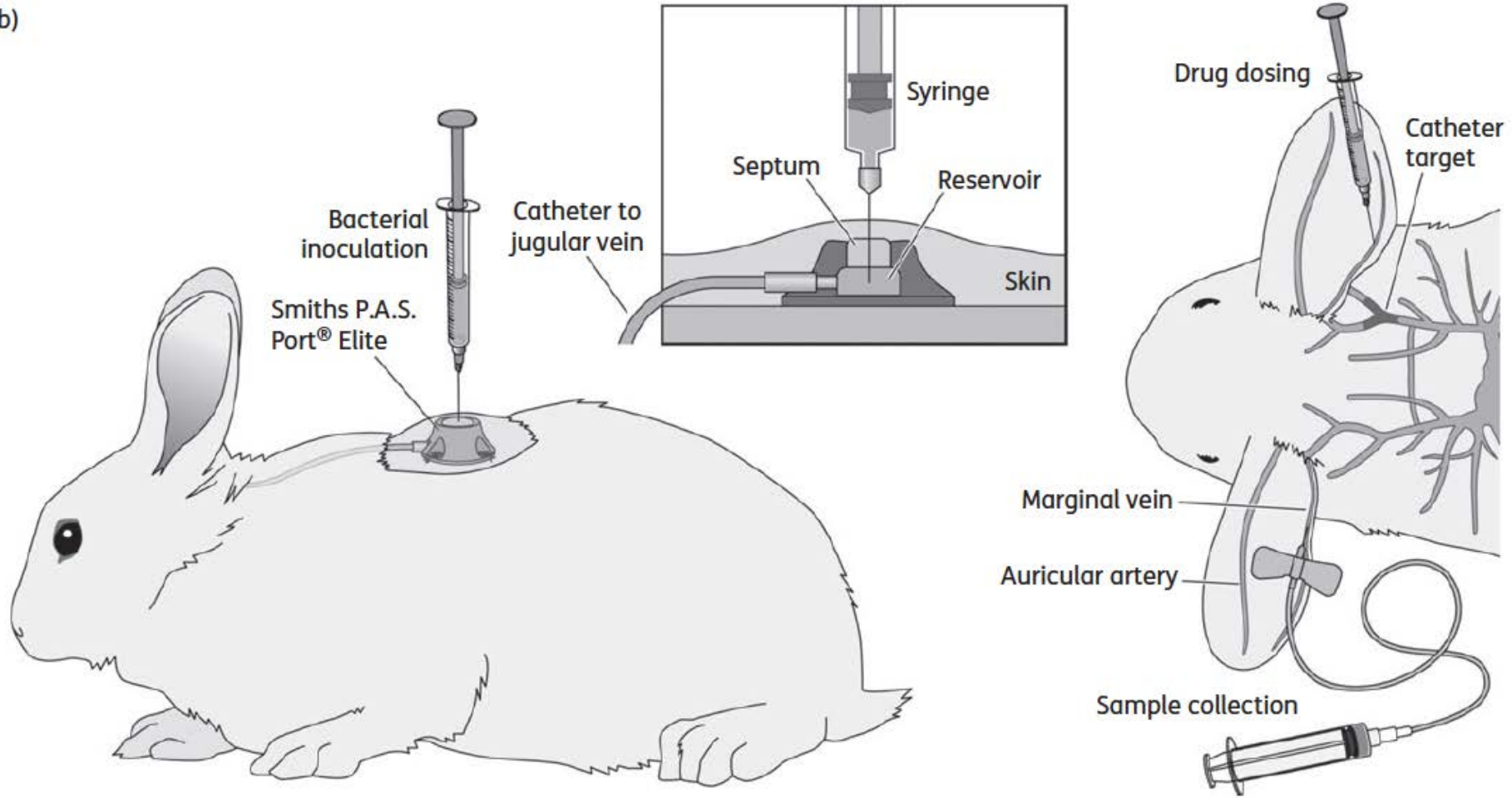
** Produced in collaboration with many in this room

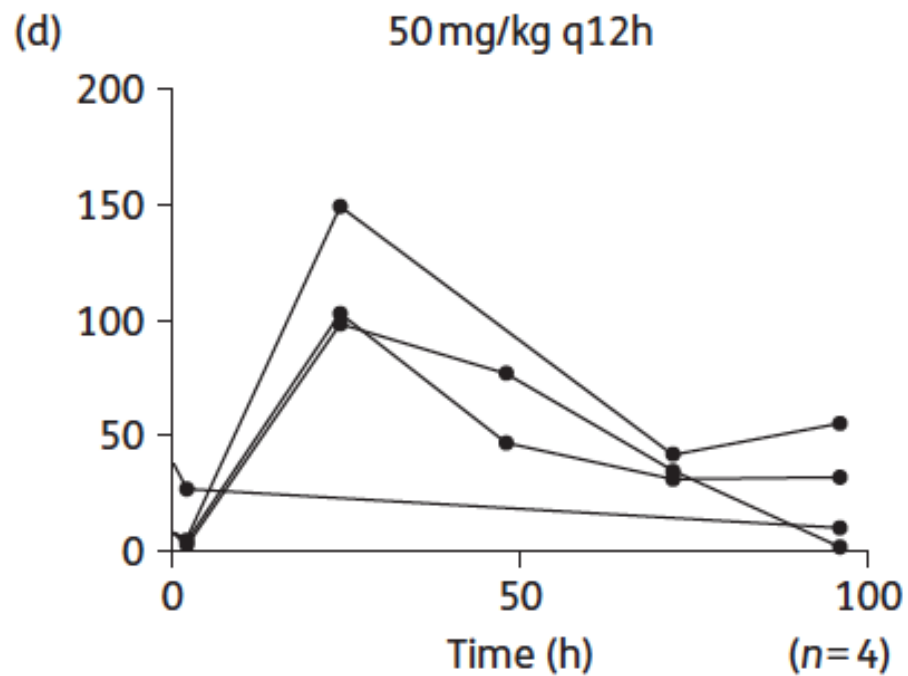
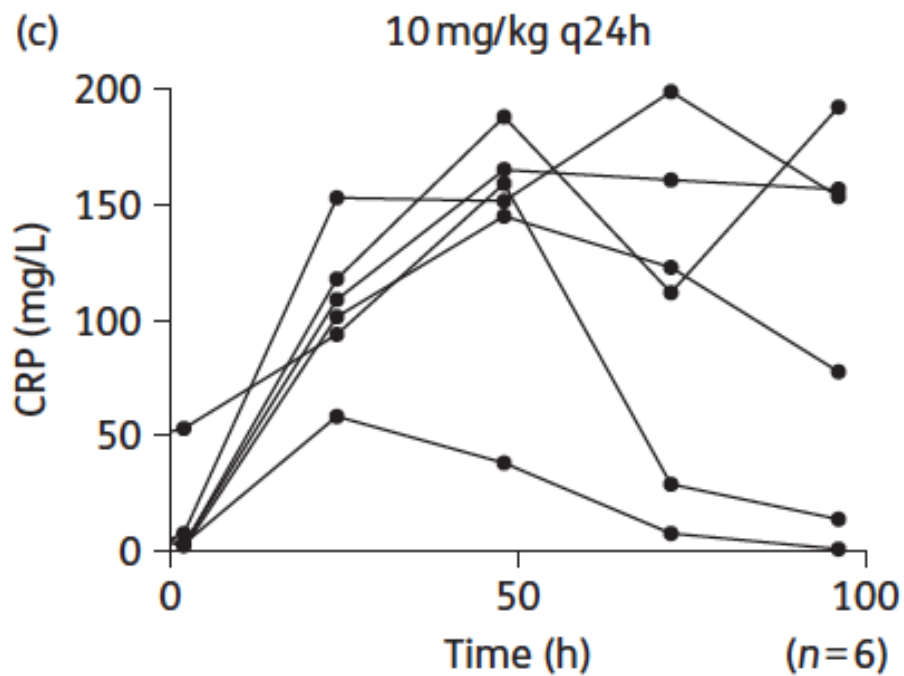
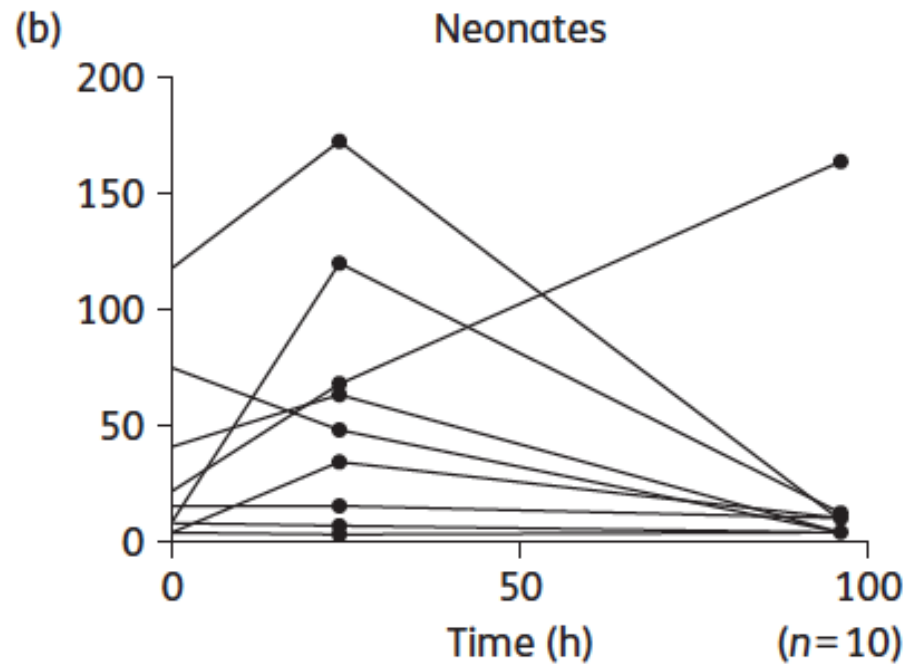
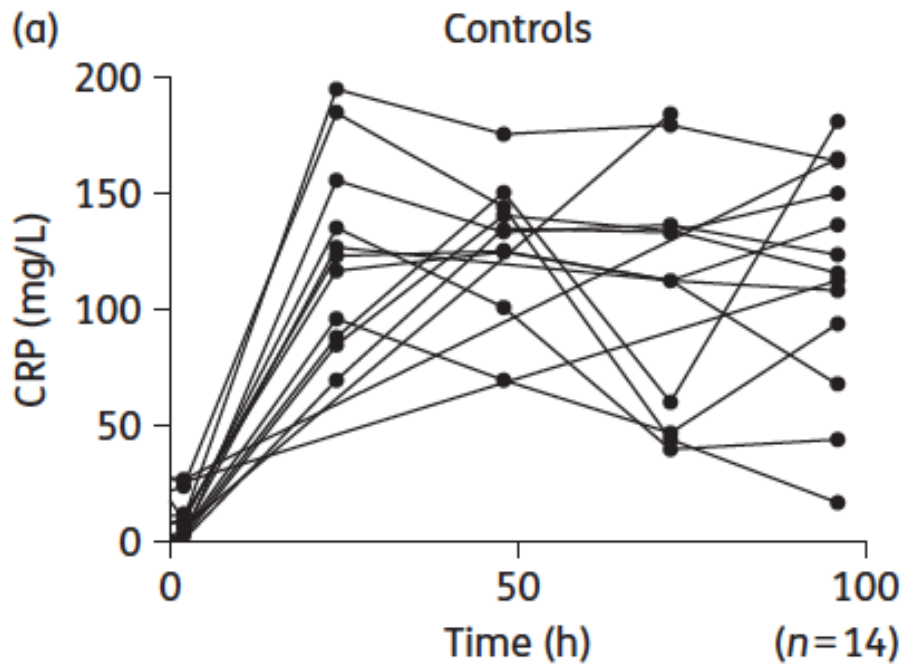
Question is the appropriate regimen of vancomycin in neonates

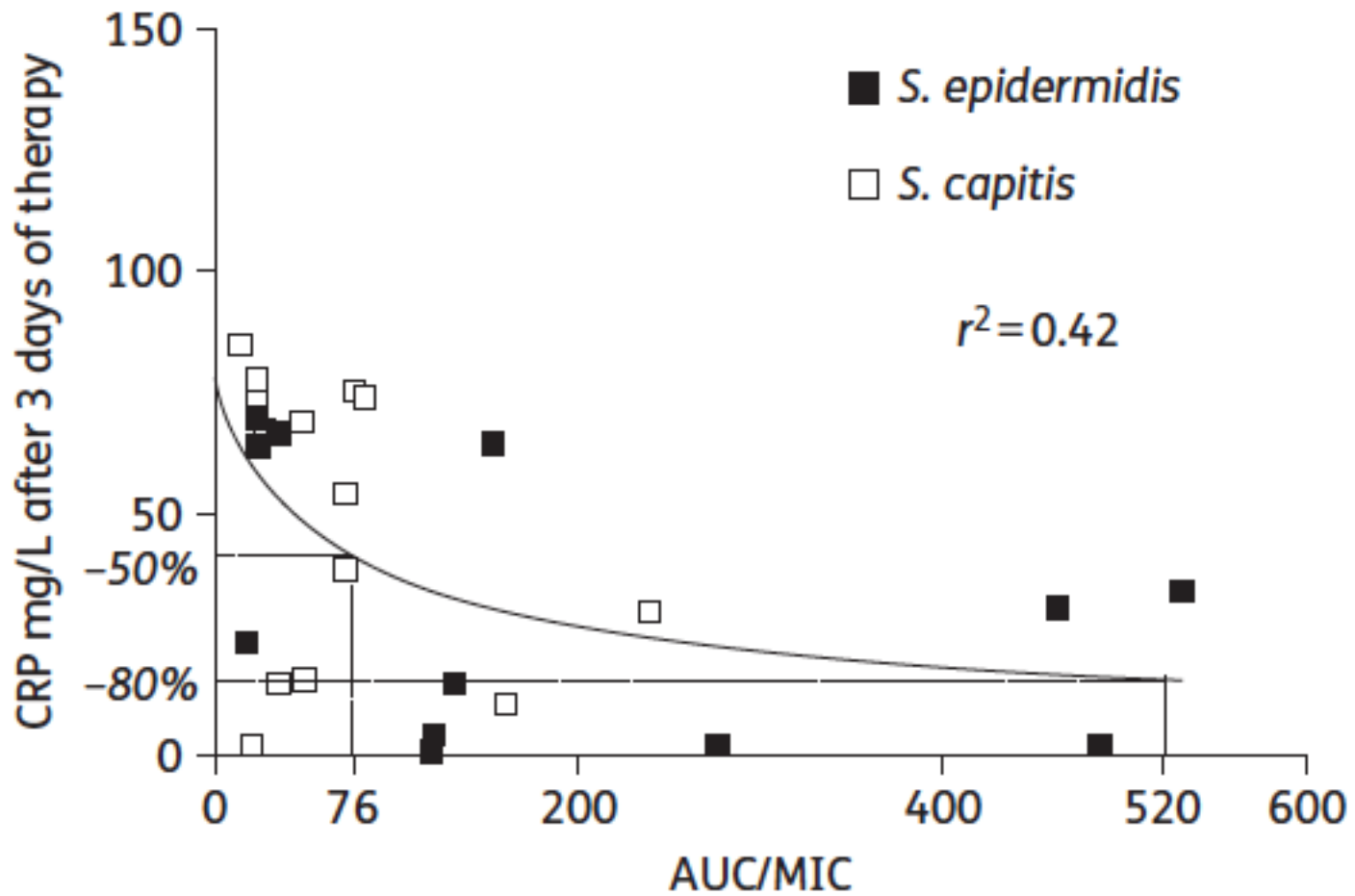
Hollow Fibre Infection Model with CoNS

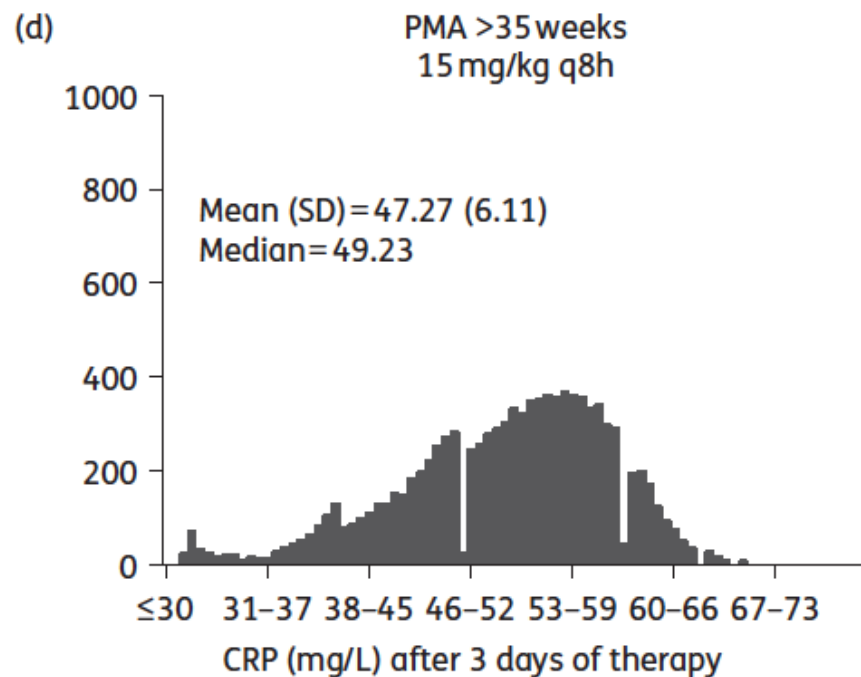
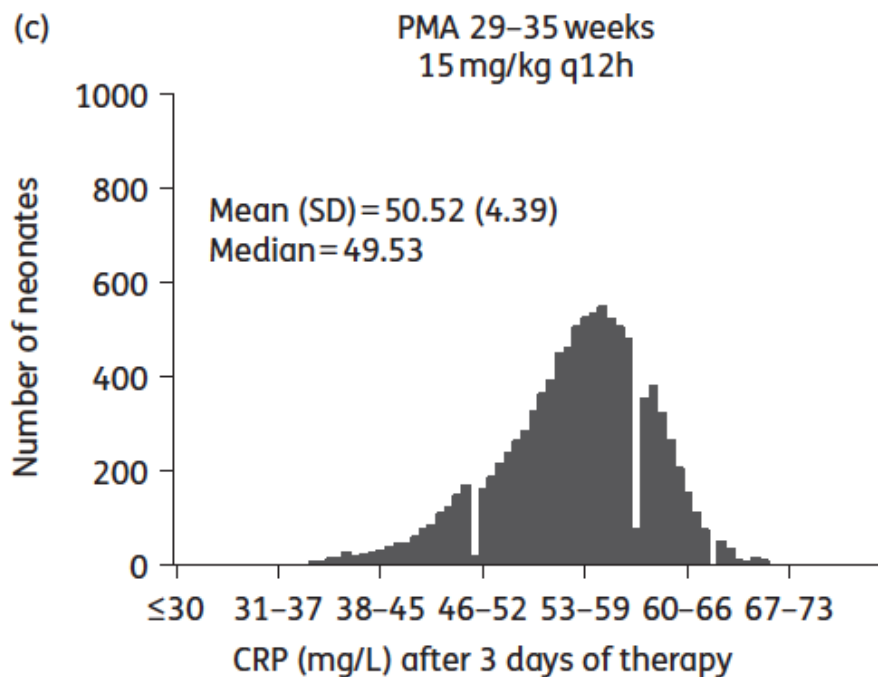
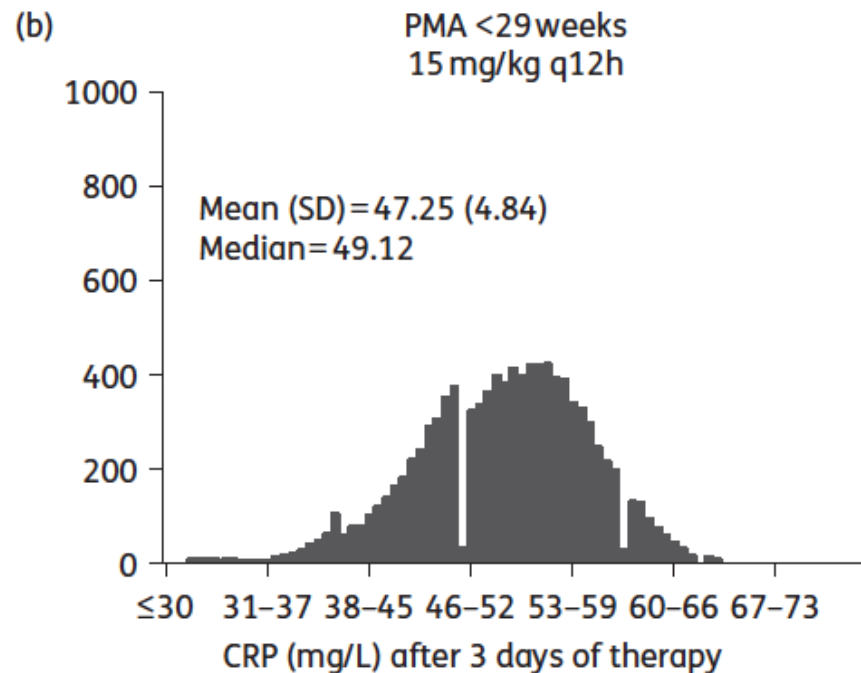
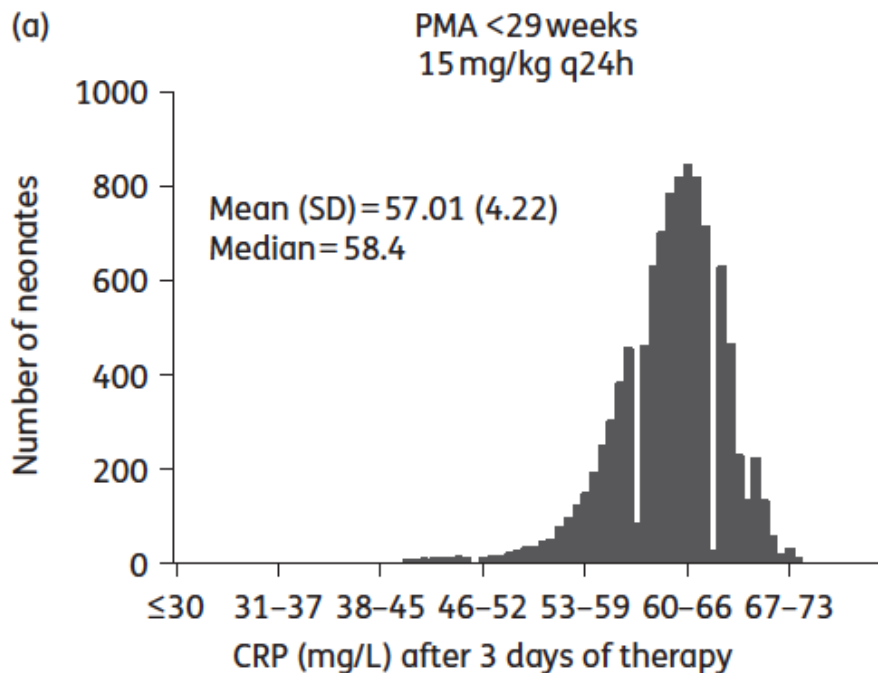


(b)





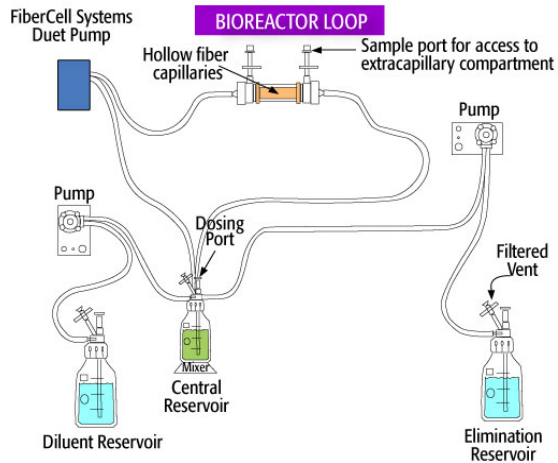




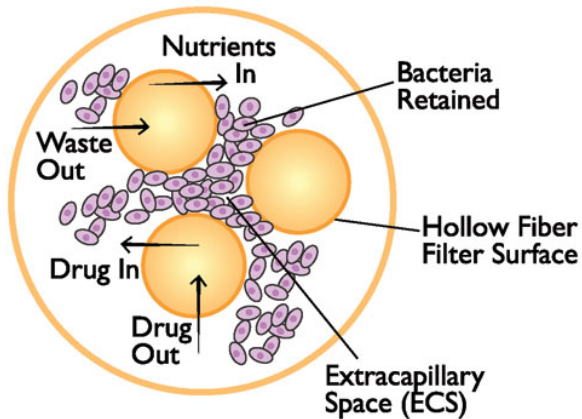
Now...on reflection

Key Steps & Issues for a Preclinical
PK-PD Program for Neonates

Experimental Models for Neonates: Understand Strengths and Limitations



AND/OR



Hollow Fibre Infection Models

- Strengths
 - Enable significant perturbations in dosing to define relevant biology and pharmacology
 - Good for resistance studies
 - Data rich with PK and PD from each model system
 - Increasingly accepted for other drug-pathogen combinations
- Limitations
 - No protein
 - Very expensive!
 - No immune effectors
 - Need to understand which compartment is being simulated (e.g. CNS, plasma etc.)
 - Need human PK (or a pretty good guess about human PK) (chicken & egg problem)
 - Unvalidated in many contexts
 - Don't look like a baby
 - Binding of drug to circuit

Laboratory animal models

- Strengths
 - (Can and should) provide a faithful mimic of human disease
 - Have anatomical barriers that are human-like
 - Enable site specific idiosyncrasies to be captured
 - e.g. daptomycin in lung
 - Have protein to enable binding
 - Have immune effectors
- Limitations
 - PK can be significantly different from neonates
 - Expensive, resource intensive
 - May not enable emergence of resistance to be modelled (inoculum too low, duration too short)

My own view...

- You should consider both
 - [I am generally of this view for all PK-PD studies]
 - At APT, we tend to do as much work as possible in one model, with confirmation of key ideas in a second model system
- Information often complementary
 - e.g. learn about resistance from HFIM, but more about the regimen from lab animals
- Of course having both may bring its own problems
 - Have to manage discordant results
 - More expensive and takes longer
- I think replicating human pathogenesis and disease can be extraordinarily valuable
 - Especially for neonates
 - A thigh model is not acceptable if the CNS is the primary site of infection

My view on other commonly raised (but difficult) things

- Protein binding
 - I truly don't know what to do about this
 - Its helpful when binding is similar in lab animals & humans
 - It's also pretty easy with drugs that are not highly bound
 - I don't know what to do about alterations in binding in early neonatal life
- Juvenile animals
 - This really doesn't bother me (but I think it bothers others)
 - But, I do think it is important to replicate the conditions under which drug may engage its microbiological target
 - And to convince yourself about the relevance of the model
- Tissue penetration
 - I agree CSF (and ELF) are useful and should be measured if possible
 - But, brain infections involve multiple sub-compartments some of which are not well represented by CSF
 - I'm broadly of the view that the dynamics should tell you almost everything about the tissue compartment in question

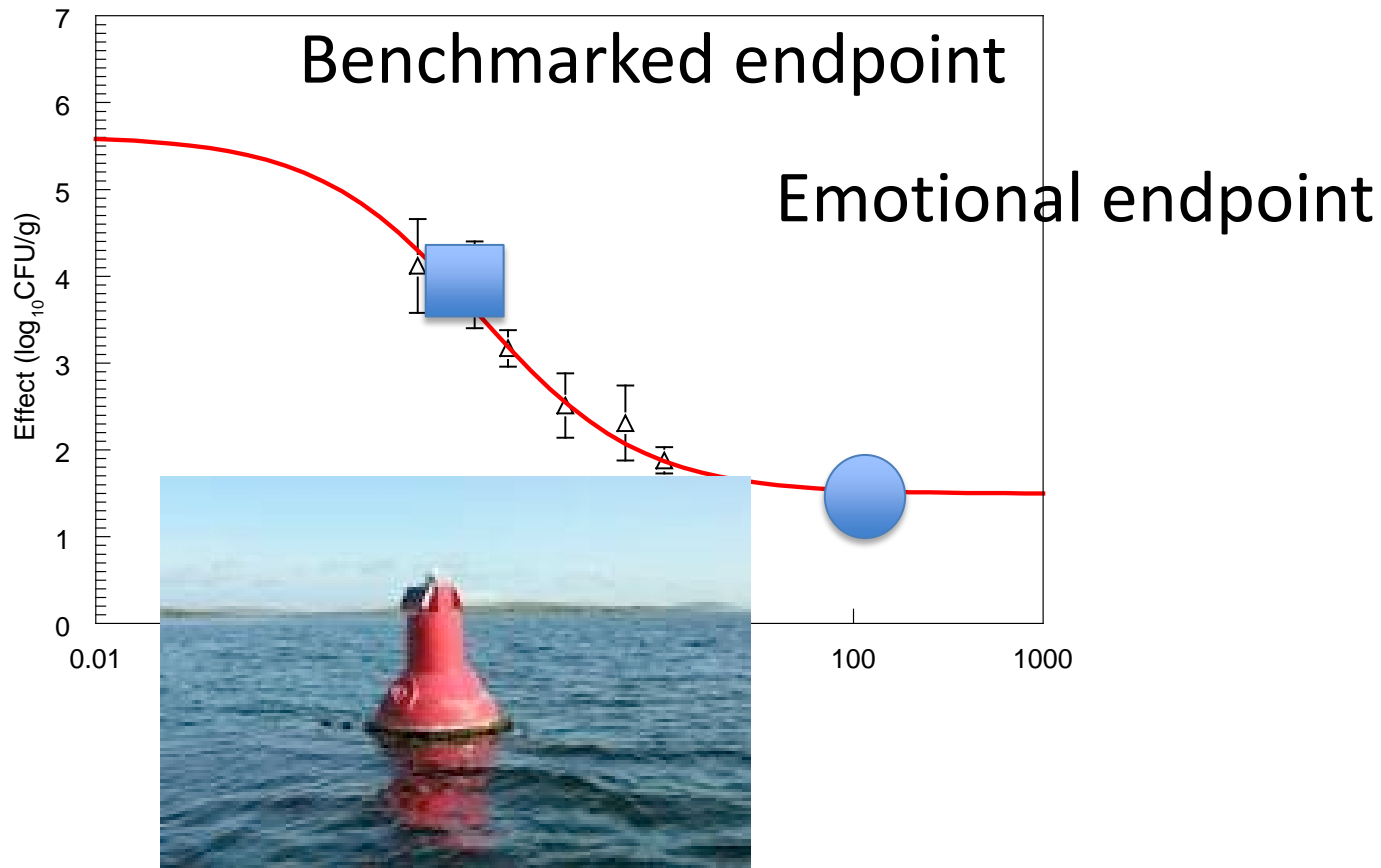
Other advances in (my) thinking in this area

(Here, I must also acknowledge John
Rex and George Drusano)

1. A requirement to study more than one strain

- How many is not known
 - Clearly not possible to study too many...just way too expensive, time consuming and ethically dubious
 - But one strain is risky
 - Perhaps do the majority of work with one strain and confirm key ideas with additional strains
- Ideally, need to have more than one study endpoint
 - Avoid “true and true and unrelated”
- May need more than one lab

2. The endpoint problem: I really hate cutting continuous data



2 (cont.) Endpoints & Benchmarking

- Means using positive controls
- A useful positive control would have broad agreement about
 - The clinical indication
 - A regimen that is effective
 - Enough information to enable an experimental-clinical PK-PD bridge
 - i.e. preclinical PK-PD, neonatal population PK
- Would be good to build a collection of these “positive controls” for future drug development in neonates
 - The performance of a new agent could then be geared to compete with the positive control

3. Setting up experimental models to produce “on scale” readouts

- Behavior of all experimental models is governed by the (arbitrarily) chosen experimental conditions
 - Strain
 - Inoculum
 - Background immunosuppression
 - Delay in initiation of treatment
 - Duration of experiment
- The key idea is that clinically relevant exposures of a positive control induces a response in the middle of exposure response relationship
 - Not too little
 - Not too much

What does a PK-PD data package for a new agent for neonates contain?

- Generic information
 - MOA, chemistry, solubility, formulation etc. etc.
 - Relevant PD index (AUC:MIC etc. etc.) that best links efficacy and emergence of resistance
 - Spectrum of activity (MICs of wild type and drug resistant strains)
- Neonate-specific PK-PD studies
 - Using neonatal PK (real or best guess with the ability to recheck)
 - Using appropriate experimental model(s)
 - With due consideration to protein binding, site-specific PK and explicit demonstration of activity at that site
- Early Phase Neonatal PK
 - Define PK in relevant compartments (plasma, CSF)
 - To back inform experimental models
 - Enable a PK-PD bridge for later phase clinical studies for dosage selection

Summary

- Thank you!
- This is an exciting and rapidly moving field
- There are many people to thank and acknowledge
 - Virginia Ramos-Martin, Danny Benjamin, Brian Smith, Micky Cohen Wolkowicz, Laura Kovanda, Tom Walsh, Mike Sharland, Mark Turner, John Rex, George Drusano...to name a few