Overview of Challenges in the Conduct of Interventional Trials to Address Antibacterial Resistance

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Symposium: New Frontiers in Antibacterial Resistance Research

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Slides happily shared. Just drop me a note: john.rex@astrazeneca.com

Point of View

- I am a board-certified internist & ID specialist
- This talk summarizes 28 years of experience
  - Academia, large pharma, and small pharma,
  - Antibacterial drugs & antifungal drugs,
  - Regulatory agencies around the world, and
  - Product success and product failure
- Core bias: Even when drugs are used correctly, development of resistance is inevitable
  - We need a sustained, vibrant pipeline of novel therapies
  - This talk is about ~90% focused on the issues around developing those novel therapies

Agenda

- Challenge: Nomenclature and its implications
- Scope: What questions will we study?
- Challenge: Core paradoxes
- Synthesis: Possible ways forward
- Summary

Nomenclature: “resistant bacteria”

- There’s a nomenclature problem that gets in the way of clear communication and thinking
- When we say “I want to know how Drug X works on resistant bacteria”, we actually mean
  - “How does Drug X work on bacteria that are
  - susceptible to Drug X *and*
  - resistant to other drugs?”
- But, *all* bacteria are resistant to some drugs and susceptible to others
  - How do we separate this idea from MDR and XDR?

Nomenclature: UDR vs. MDR/XDR

- What we really have are 3 categories, not 2
  - UDR: Usual Drug Resistance[1]
  - MDR: Multi-drug resistance
  - XDR: Extensive multi-drug resistance

We've considered
- EDR: Expected DR
- SDR: Standard DR
- TDR: Typical DR
- UDR: Usual DR

Let me know your favorite!

- This is a continuum and a mindset. If we think it's …
  - UDR: We have many safe choices. Empirical therapy is easy & reliable
  - MDR: It's harder: A second-line drug[2] may be required
  - XDR: It's really hard: A difficult or unusual drug[2] is needed
- Isolates may shift across categories from UDR to MDR…
  - … and a new drug or two might reverse things yet again
- Example of that continuum: MRSA
  - Once seen as MDR, it's now UDR (except in NW Europe!)

[1]This may or may not be the same thing as wild-type. See discussion of MRSA below. [2]Or combination of drugs

Nomenclature: Consequences

- We can now restate "I want to know how Drug X works on resistant bacteria" as
  - "How does Drug X work on bacteria that are
  - susceptible to Drug X *and*
  - UDR (or MDR or XDR) to other drugs?"
- This also exposes a second question:
  - If an isolate is susceptible to Drug X, does being UDR, MDR, or XDR to other drugs make a difference?
  - Stated differently, does the MIC to Drug X capture everything you need to know or not?

Is all the information in the MIC? (1)

Two possibilities exist. Here's the first:

- Might two isolates with
  - the same MIC to Drug X but
  - different MICs to Drug Y

  have different responses to Drug X?

- No. This has been convincingly proven untrue
  - Provided you deliver an adequate drug exposure to the site of infection, then the MIC is the key
  - Dr. Baquero also made this point yesterday. If you use a properly dosed and active drug, then outcomes are not worse for MDR/XDR infections

Is all the information in the MIC? (2)

- But, might two patients infected with isolates with
  - the same MIC to Drug X but
  - different MICs to Drug Y

  have different responses to Drug X?
- YES (1)
  - MDR/XDR carriage is a marker of exposure to health care
  - This links to higher frequencies of co-mordid conditions
  - And underlying disease of course influences outcome
- Yes (2)
  - PK of Drug X may be different in the critically ill
  - This is part of the background of different co-morbidities
- Key: The difference is not directly due to the drug!

With that in mind…

- So now when we ask
  - "How does Drug X work on bacteria that are
  - susceptible to Drug X and
  - UDR (or MDR or XDR) to other drugs?"
- We can see that useful data can be obtained from UDR, MDR, or XDR infections
  - If you ensure the PK is adequate at the site of infection,
  - *All the relevant data about the portion of the clinical outcome that can be influenced by antibiotic therapy are in the MIC to Drug X*

Why does this matter?

- It's ***much*** harder to do prospective, randomized, registration-quality studies in patients with infections due to MDR/XDR isolates than due to UDR isolates
- AZ data: It's twice as slow and costs twice as much
  - Patients must present at a study site as referral is hard
    - Receiving a patient with an MDR/XDR infection is not popular
    - Infections move rapidly – therapy must start *now*
  - Sites work hard to make MDR and XDR rare!
    - No site wants to be a Center of MDR/XDR Excellence!
    - Chasing MDR/XDR is very frustrating: Lasagna's Law[1] in action
- And, we *want* MDR/XDR rates to stay low!!
  - If it's easy to recruit MDR/XDR, something is very wrong

[1]Louis Lasagna: "The incidence of patient availability sharply decreases when a clinical trial begins and returns to its original level as soon as the trial is completed." http://www.pmean.com/11/lasagna.html

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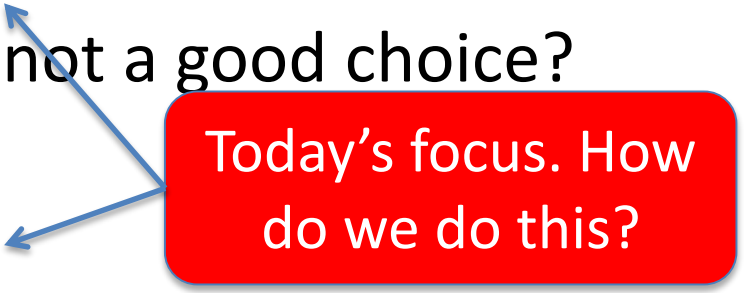
What should we study?

Reminder: For today, I am focusing on the type of prospective randomized trials needed for drug registration. Other trial design types (observational, non-randomized trials, etc.) do not generally suffice for this purpose.

- When antibiotics are needed, is Drug X effective?
  - Is Drug X better than no drug (placebo)?
  - Is Drug (the same as) (better than) Drug Y?
- Are there times when Drug X is not a good choice?
  - Infection-related:
    - Is Drug X effective at site Z?
    - How does Drug X work for UDR vs. MDR/XDR isolates?
  - Patient-related: How do we dose Drug X in the face organ dysfunction or drug-drug interactions?



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- Scope: What questions will we study?
- Challenge: Core paradoxes
  - Non-inferiority trials are the only long-term path
  - Pathogen-focused pathways are currently elusive
  - Endpoints must be clinical
  - Antibiotic alternatives face a mix of these issues
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Ethical study designs

- In animal models, we can study all variations of
  - UDR to MDR to XDR
  - Placebo, ranges of doses, combinations of drugs
- But, we can only do a limited amount of this in man
  - Placebo is only possible in very low acuity infection
    - Indeed, only when we agree that NO therapy is actually OK
    - This eliminates most important infections from study
  - It's hard to enroll MDR/XDR infections in man
    - See prior slides … and we want this to always be true
  - And, we must always provide a good therapy
    - Can't deliberately underdose or ignore MDR/XDR
    - Effectively, we design studies to make superiority rare

Consequences: Non-inferiority (NI) studies are (usually) key to progress

- Pivotal data on new antibiotics will almost always be from non-inferiority (NI) comparisons
  - (new) Drug X vs. (old) Drug Y at full doses of each
  - All isolates susceptible to X and Y
  - Expect to see X ≅ Y within some confidence limit
- Yes, superiority studies would be so much easier!
  - Superiority studies are self-validating
  - Superiority studies at times are *much* smaller
    - 80% vs. 20% can be shown with N = ~20/arm!
- But, that's not where we usually are (or want to be!)

I see no consistent way out of this

- Historical controls showing superiority to placebo?
  - Tricky outside very predictable diseases (e.g., meningitis?)
  - And, comparisons vs. current therapies will still be needed
- Wait for MDR/XDR to become sufficiently common that clinical trials vs. same are easy to do?
  - Obviously not! It takes 10+ years to create new therapies…
- Nested superiority from a subset of an NI trial?
  - You can always look for this (e.g., DOORS/RADAR idea)
  - But, this should be unlikely in registration trial as you can't deliberate undertreat a subset
- Beat a drug on toxicity?
  - Might do this once (e.g., beat colistin on toxicity)
  - Registration of the first new less-toxic drug ends this path

[1]Evans, S. R., D. Rubin, et al. (2015). "Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)." Clin Infect Dis 61(5): 800-806.

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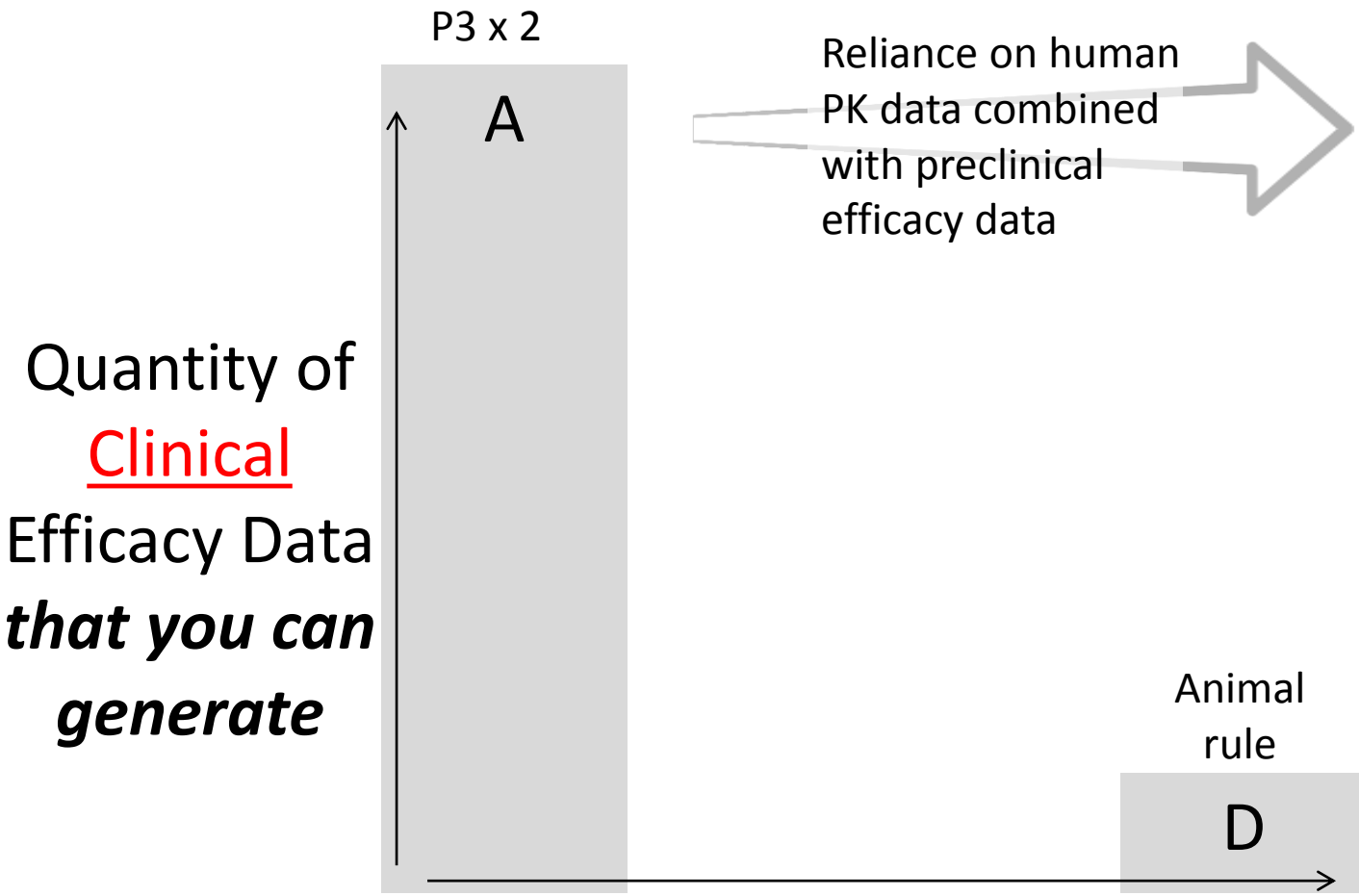
Pathogen-focused development

This mental schema was developed 2012-13



Rex et al. Lancet Infect Dis 13: 269-75, 2013.

Rex et al. Ann NY Acad Sci 2014, DOI 10.1111/nyas.12441.

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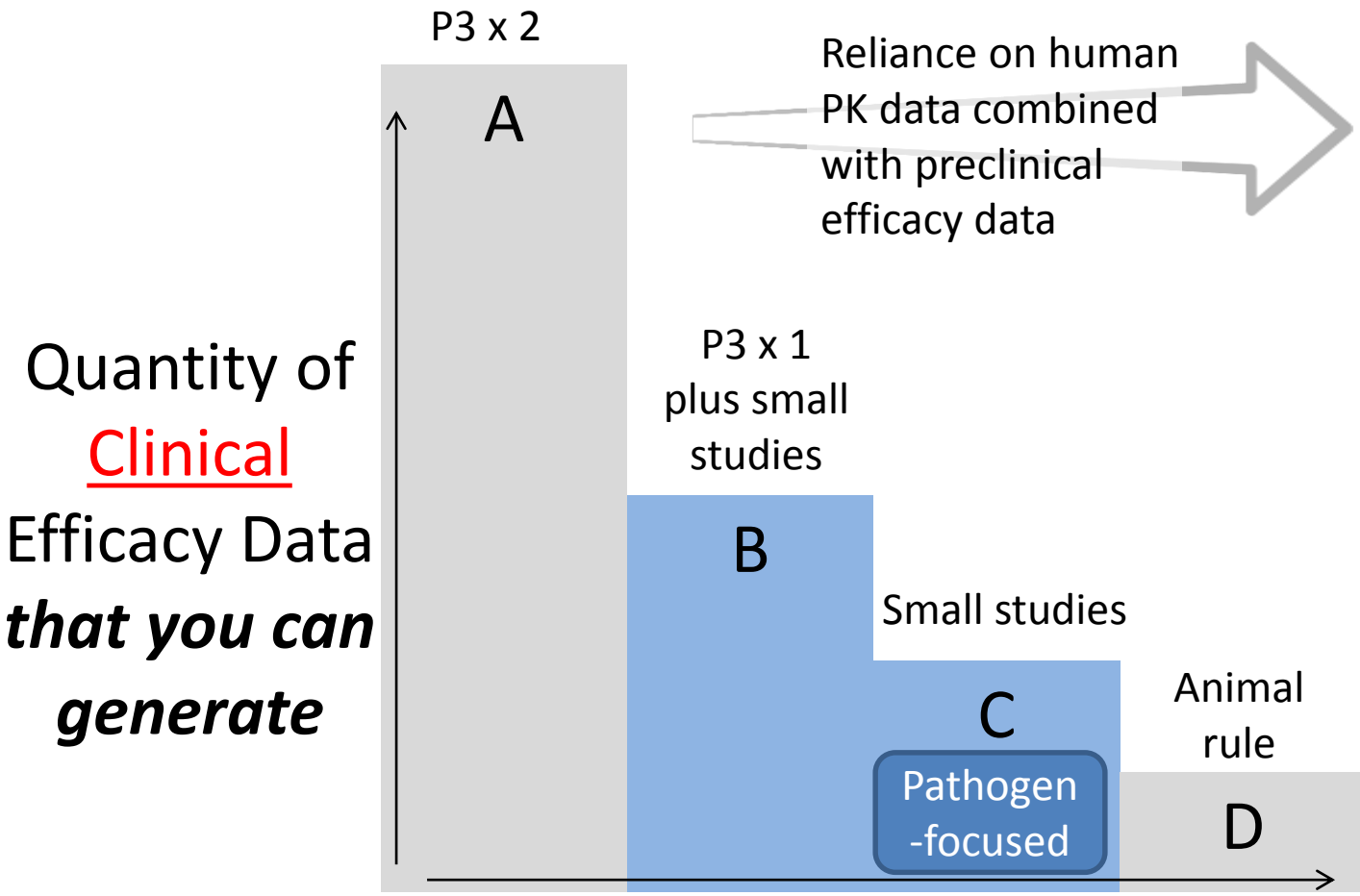

Acceptance of smaller clinical datasets in response to unmet medical need

Rex et al. Lancet Infect Dis 13: 269-75, 2013.

Rex et al. Ann NY Acad Sci 2014, DOI 10.1111/nyas.12441.

Typical Tier B & Tier C Programs[1]

Good candidate drug for Tier B vs. Tier C

- Tier B: Sufficiently broad spectrum that monotherapy for a syndrome such as intra-abdominal infection is possible
- Tier C: A narrow-spectrum agent that covers but one of many possible pathogens in a syndrome

The Phase 3 development program for these drugs is then

- *(Tier B):* Drug X vs. a standard comparator at one body site[2]
  - Non-inferiority design study that enrolls only UDR pathogens
  - PK-PD provides link to activity vs. MDR & XDR pathogens
- *(Tiers B and C):* **Resistant pathogen study:** Drug X vs. Best Available Therapy (BAT) for MDR or XDR pathogens
  - Prospective, randomized, open-label, and (mostly) descriptive
  - N ≅ a few hundred. Multiple body sites.

[1]The example presumes that a clear exposure target is known from preclinical PK-PD and that there is a clear ability to produce a corresponding drug exposure in patients. See literature (Rex et al. Lancet Infect Dis 13: 269-75, 2013) for detailed examples. [2]E.g., pneumonia or UTI

Tier B is universal. Tier C is not.

- EMA Antibacterial guidance (2013)
  - Explicit description of options that match Tiers B & C
- FDA Antibacterial guidance (2013)
  - Explicit description of options that match the Tier B ideas
  - Unless the data permit inferential testing, Tier C is not possible for FDA
  - This position was re-affirmed as recently as ICAAC 2015
- Translation to action
  - For a narrow-spectrum (Tier C) drug for (say) *Pseudomonas*…
  - You'd seek the largest possible dataset on infections with it at a single body site. You'd then argue for a wide margin on the NI comparison
    - Personal experience: VERY hard, even with rapid diagnostics
  - Superiority on pooled data across body sites could be accepted, but this requires optimistic assumptions that I don't like
  - We need to work on better ways to do this

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Endpoints must be clinical

- For drug development, we expect the primary endpoint to be based on something related to how you (the patient) "feel, function, or survive"
- Cultures and lab tests do not (usually) qualify
  - No one ever says, "Doc, my cytokine levels are too high!"
  - They say instead, "Doc, I don't feel well."
- A developer is free to use non-clinical measures for dose-selection or other early proof of concept
  - Example: Speed of sputum culture conversion in TB
- But, you ultimately must show clinical benefit
  - This is a common point of confusion

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Developing Alternative Therapies[1]

- If it has the efficacy of a standalone antibiotic:
  - Then see above: Develop as such
- If an add-on (e.g., many anti-virulence approaches)
  - Then you are forced into Antibiotic vs. Antibiotic + Add-On
  - Need to show superiority in the +Add On arm
  - A high hurdle: We're going to maximize the Antibiotic (full dose!) and provide as much secondary support as we can
- This should not be thought of as a regulatory hurdle!
  - None of us will use Add On if we can't see what it offers
- Also, many Alternatives are narrow-spectrum
  - See discussions above … the same problems apply

[1]Prevention (e.g., vaccines) is also good but is a separate topic!

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Implications for new drugs

- If at all possible, generate a standard dataset on new Drug X vs. excellent comparator Y in UDR infections
  - Do this in a standard serious infection (e.g., cIAI)
  - The focus on UDR is not as limiting as it might sound: If Y is a penem, can study anything but penem-R
  - Data like this underpin every drug we currently use
- The data you can generate in MDR/XDR are limited and often anecdotal in nature
  - I understand the (emotive) wish for these data
  - But, the science of PK-PD is real and predictable
- Diagnostics will help a bit but aren't a complete fix
  - See above: We want MDR/XDR to be rare!

FDA at ICAAC 2015[1]
Top 5 mistakes made by sponsors

- "Development Program
  - Sponsor preference for a more difficult program targeting a relatively infrequently occurring resistance phenotype vs. a more feasible pathway such as a study in an all-comer population at a single body site of infection."*

**My commentary: I think this is largely self-explanatory. In brief, FDA is telling us that they're seeing programs struggle to study MDR/XDR and that UDR-focused development makes sense to them.*

[1]Excerpted from a presentation by Sumati Nambiar

MHRA (EMA) at ICAAC 2015[1]
Top 5 mistakes made by sponsors

In a discussion of a hypothetical agent with activity vs. carbapenem-resistant Enterobacteriaceae (CRE):

- "The indication will not be for treatment of CRE.*
- There is no need to acquire large amounts of nonclinical or clinical data on activity vs. CRE for an agent whose activity is clearly unaffected by resistance to other classes."

**My commentary:* This point merits unpacking. As there is no guarantee that *every* CRE isolate is susceptible to the new drug, the indication will be for treatment of infections due to New Drug-susceptible strains of Enterobacteriaceae. Resistance to other drugs is usually not mentioned in product labeling.

[1]Excerpted from a presentation by Mair Powell

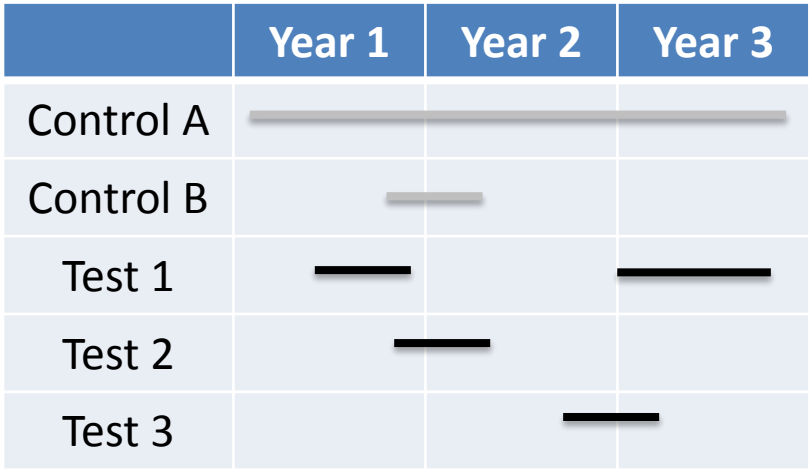
Translation to action

- We need to support a diverse pipeline
  - Delighted to see the discussions at this meeting!
  - In parallel, I'm working hard on reimbursement
    - Big press release[1] today: Call for ways to delink reimbursement from usage as current model is akin to paying firemen per fire
- In terms of the science…
  - New agents are most reliably developed in comparative NI studies vs. a standard comparator for UDR infections
    - International collaboration is needed on these studies (next slide)
  - Anecdotal data on MDR/XDR can be generated in parallel
    - Not a cornerstone for registration but still interesting
    - International collaboration is hugely important here
    - If it's ever easy to study MDR/XDR, we've done something wrong!

[1] Full text can be found on the UK AMR Review website: http://amr-review.org/industry-declaration

UDR trial networks as a tool[1]

- Focus on well-characterized standard infections with well-understood study designs (see next slide)
  - Protocol is drug-independent
- Network is always running
  - Sites are stable & well-trained
  - Recruiting UDR infections is predictable and efficient
  - Study drugs added at will
- *Significant benefits possible*
- Time benefit could exceed that of priority review



- *No site initiation delays*
- *No time lost to learning the protocol and ramping up*
- *Sharing of controls should be possible would shrink N required, thus saving time & cost*
- *Bio-creep risk eliminated*

[1]McDonnell, Rex, Goosens, Bonten, & Fowler: Manuscript in preparation

Well-characterized infections

- I would focus a UDR network on any of the 5 serious infections for which we have clear trial designs
  - cUTI, cIAI, HABP/VABP, CABP, and ABSSI[1]
- These serious infections are all
  - well-characterized,
  - occur regularly,
  - have predictable rates of morbidity and mortality,
  - and have well-understood study designs
- Studies of important but less common infections (e.g., endocarditis) are slow to enroll & hard to blind

[1]cUTI: complicated urinary tract infection, cIAI: complicated intra-abdominal infection, HABP/VABP: hospital-associated or ventilator associated bacterial pneumonia (aka NP, or Nosocomial Pneumonia), CABP: community-acquired bacterial pneumonia, ABSSSI: acute bacterial skin or skin-structure infection

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Summary

- For new agents, MIC and PK at the site are the keys
  - Do not fall into the "MDR/XDR fallacy"[1]
  - Provide you ensure similar PK, data on UDR infections predict response to MDR/XDR
  - Yes, the patients with MDR/XDR and comorbidities may well do worse – but this would be true for any drug
- NI studies on UDR pathogens are often the best tool
  - They can reliably generate clear, clean data
  - Trial networks could powerfully support new agents
- Frustratingly, pathogen-focused registration is elusive
  - I'm looking hard for a "Supreme Court case" to resolve this

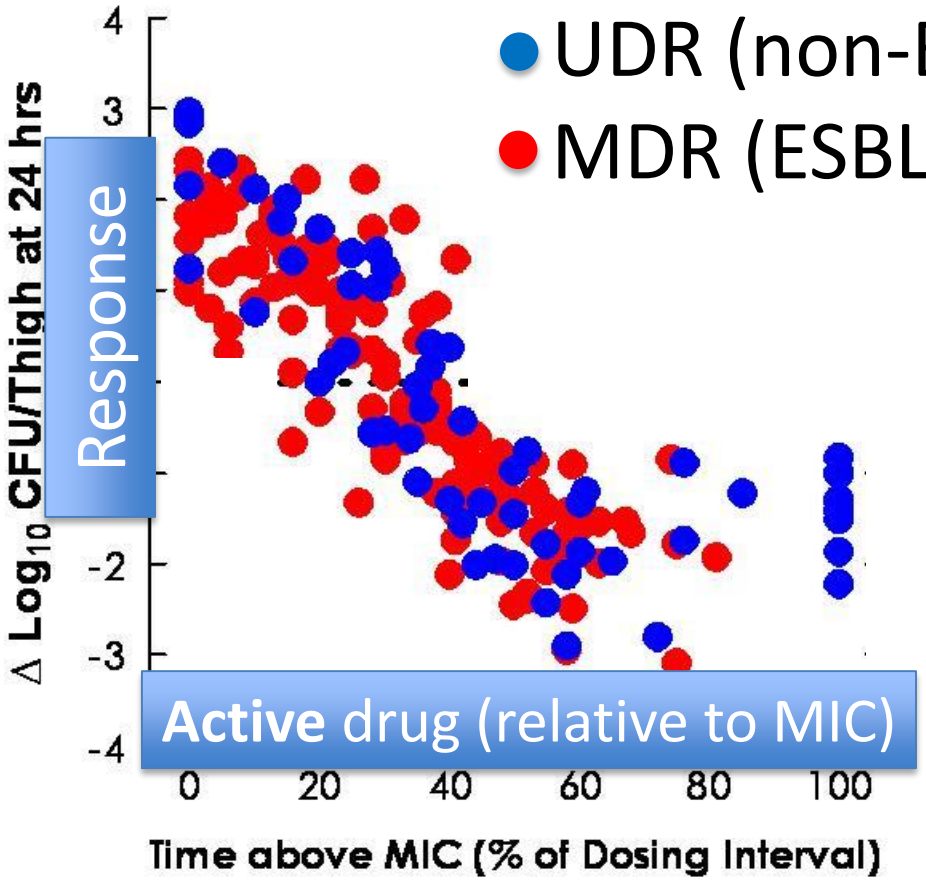
[1]Paul Ambrose

Thank you!

Backups

Slide borrowed & adapted from Paul Ambrose

EXPOSURE & RESPONSE IN MICE *ESBL Versus Non-ESBL Producing Strains*



The UDR and MDR dots overlap <u>when a drug active vs. both</u> is studied.

This has been shown in many settings, in vivo and in man.

Dr. Baquero's showed this on Wednesday: MDR infections have the same outcome **if you use an active drug.**

Craig WA and Andes DR. Treatment of infections with ESBL-produ
pharmacodynamic considerations. Clin Microbiol Infect. 2005;11

No placebo, no dose-ranging

This is worth another slide

- In a comparative study in man, we can't enroll if we think the comparator might be inadequate
  - We expect curative therapy for infections
- Further, we must always use a strong comparator
  - Using a weak comparator leaves bio-creep[1] concerns
- In short, we design our trials to make superiority unlikely
  - If superiority is plausible because current choices are inferior or toxic (or both, such as colistin), then
  - The window for superiority closes when a new therapy is introduced
- We should be pleased when we have this problem!
  - If it's easy (or plausible) to show superiority, then we're in a situation similar to that with the Ebola virus

[1]TOdem-Davis K, Fleming TR. A simulation study evaluating bio-creep risk in serial non-inferiority clinical trials for preservation of effect. Statistics in Biopharmaceutical Research 2015;7:12-24.