Trial Design for Narrow-Spectrum Agents: Overview & Drug X-1

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Focus for today:

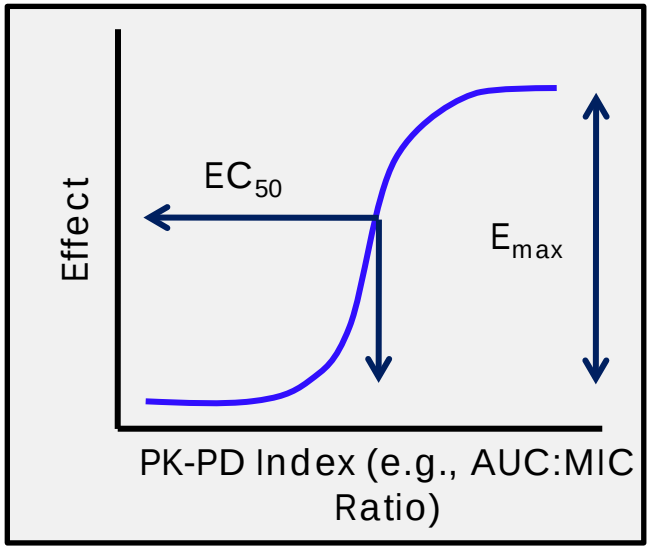
Tools for developing narrow-spectrum drugs

- The examples we'll discuss
  - Drug X-1: Hypothetical, *Pseudomonas*-only
  - POL7080: Real, *Pseudomonas*-only
  - Sulbactam/ETX2514: Real, *Acinetobacter*-focused
- Points of departure for our discussion
  - The urgent Unmet Need requires action
  - Clinical trials can only get us so far for these drugs
  - There are ideas that can help…

Three key ideas

#1 PK-PD

- Unlike most other drugs…
  - Drug levels, the minimum inhibitory concentration (MIC) of the drug for the bug, and response have an unusually predictable relationship



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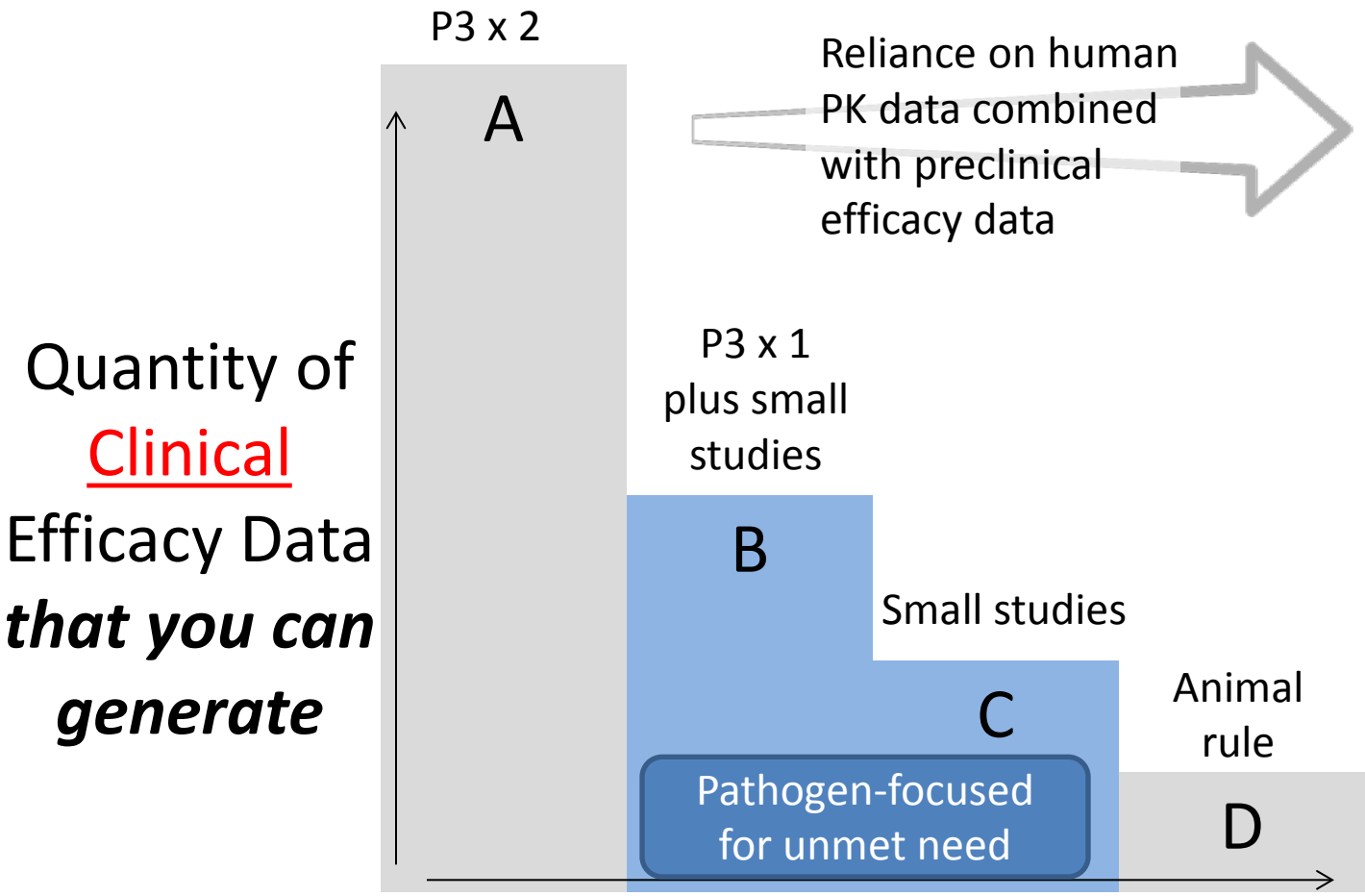
- Blood & tissue levels that work in a mouse are likely to do so in man
  - PK-PD gives an independent proof of causality that reduces the need for empirical causality validation[3] via clinical trials
  - That said, there have been (and will again be) exceptions[2]
  - Hence, we should always seek as much clinical data as possible while being willing to lean more on PK-PD if required

[1]PK-PD = Pharmacokinetic-Pharmacodynamic relationship. See the work of Craig, Drusano, Mouton, Ambrose, Hope, MacGowan, Nicolau, and many others. [2]A classic example is the lack of efficacy of daptomycin in pneumonia that was ultimately found due to the effects of surfactant on daptomycin (Pertel 2008 CID). [3]Peck CC, Rubin DB, Sheiner LB. Hypothesis: a single clinical trial plus causal evidence of effectiveness is sufficient for drug approval. Clin Pharmacol Ther 2003;73:481-90.

Three key ideas

#2: Mental shorthand: Tiers A-D



Acceptance of smaller clinical datasets in response to unmet medical need

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

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Three key ideas

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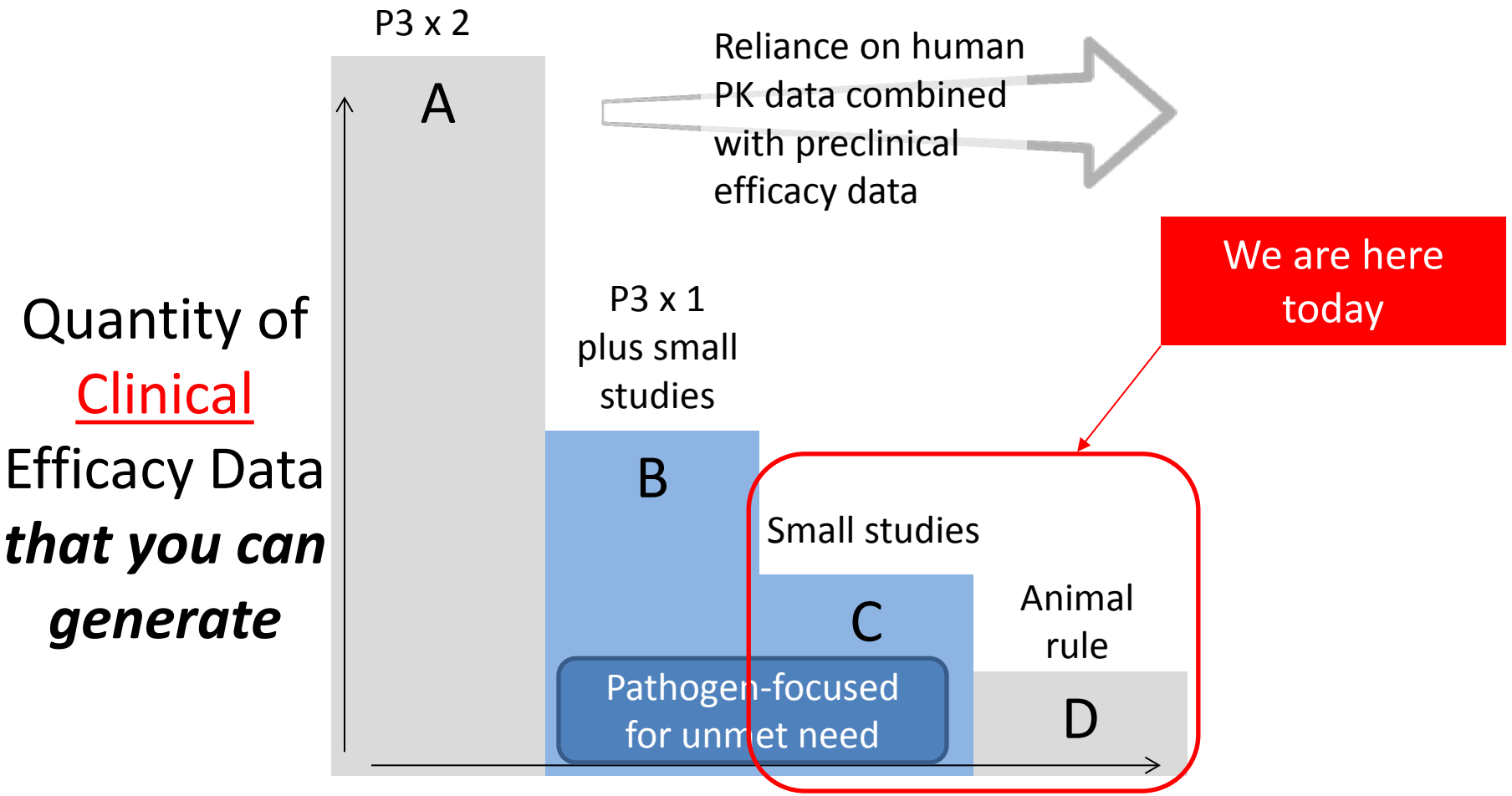

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Three key ideas

#2: Mental shorthand: Tiers A-D

- Animal Models + Clinical Data (Tier C)
  - Animal models are used to validate the PK-PD relationship
  - Clinical data possible but not at usual statistical strength
  - These two are taken together as independent supports
- Animal Rule (Tier D): No clinical efficacy data possible
  - Human safety data can be generated but …
  - The animal model data *are* the controlled clinical trial
  - These models need to be strong mimics of human disease
- Tier A-D are a continuum – you do the best you can
  - As needed, drug labeling would be cautious (e.g., LPAD language[1]) to reflect the pragmatic balance achieved

[1]FDA (LPAD language, 21st Century Cures Act): "This drug is indicated for use in a limited and specific population of patients." EMA (2013-10-23 Addendum): "It is recommended that {agent name} should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases."

Three key ideas

#3: Superiority is not an escape

- A wish to resolve the problem by showing New Drug is clinically superior to Old Drug is understandable
- Paradoxically, superiority is a painful path for antibiotics
- We are not treating migraines: inadequate therapy of serious infections leads to death
- We must never knowingly randomize to ineffective therapy
- Hence, routinely showing superiority requires that
  - We allow AMR to progress such that (a) highly resistant strains are sufficiently common to be captured in trial and (b) the best available standard of care (SOC) therapy is (in truth) not very effective
  - We show superiority based on excess deaths (or morbidity) due to the (ineffective) SOC therapy in the comparator arm
- This is not hypothetical…

Example: Plazomicin and CRE

CRE = Carbapenem-resistant Enterobacteriaceae

- Plazomicin vs. colistin-based SOC for CRE

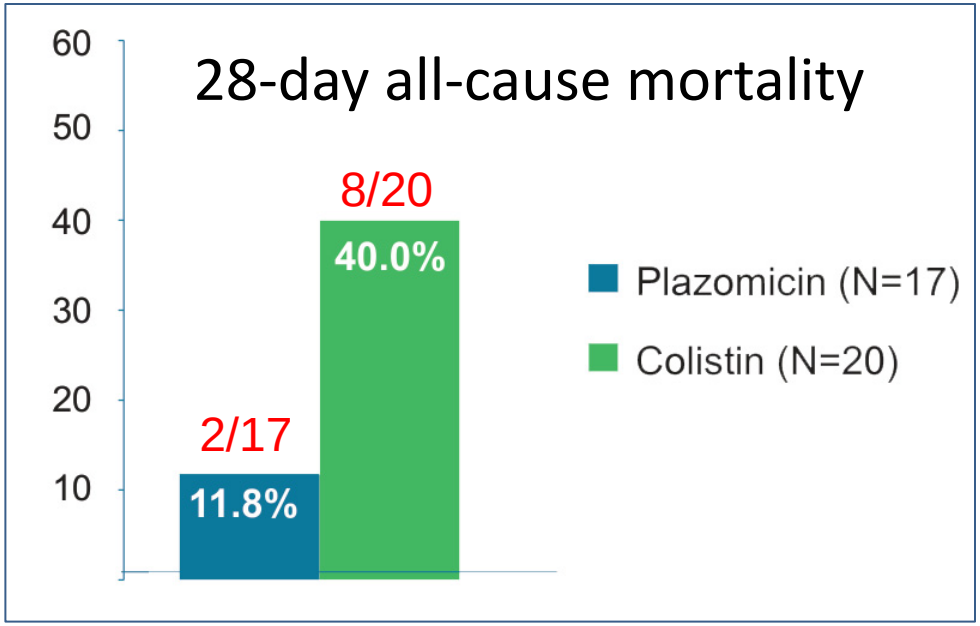

Figure adapted from slide 24 the Jan 2017 Achaogen corporate presentation. Downloaded 24 Feb 2017 from http://files.shareholder.com/downloads/AMDA-2JY46Z/3956962155x0x922829/80C50E00-4B27-4F84-B13F-55DE31AABA28/AKAO-Corporate-Deck-January-2017.pdf

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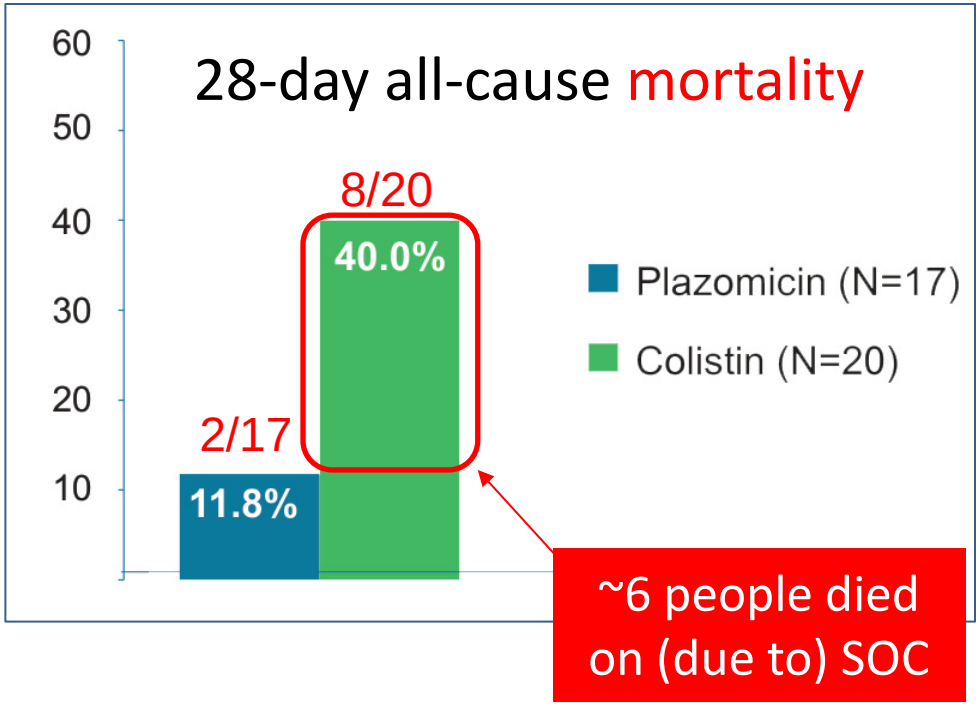
- Plazomicin vs. colistin-based SOC for CRE
- Superiority is shown because …



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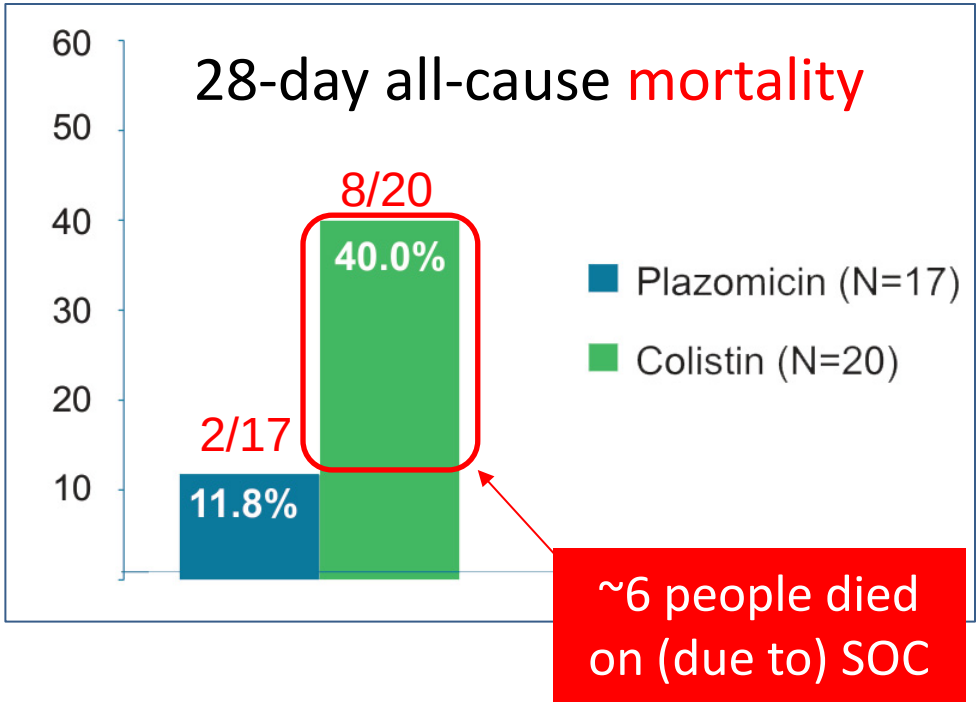
Example: Plazomicin and CRE

CRE = Carbapenem-resistant Enterobacteriaceae

- Plazomicin vs. colistin-based SOC for CRE
- Superiority is shown because …
- We are glad to have clarity on colistin's relative inefficacy but this is a steep price!
  - As colistin is displaced as SOC, future drugs should not be able to plan on similar data



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Drug X-1

18-19 July 2016 Workshop[1]

- Approximately 100 attendees
- We examined a hypothetical drug: X-1
  - Novel mechanism
  - Activity limited entire to *P. aeruginosa*
  - Simple pharmacology, well-defined PK-PD
  - Phase 1 dose finding (including ELF studies) showed adequate plasma & tissue exposures

Clear & simple story

  - Phase 2 study in non-CF bronchiectasis demonstrated reduced bacterial burden with proposed dose
    - Alert: Data like this are not always possible
- X-1 looked useful! But, how to study it?

[1]Materials available at https://www.fda.gov/Drugs/NewsEvents/ucm497650.htm

Thinking it through…

- Suitable study arms are possible
  - Drug X-1 + ertapenem vs. standard carbapenem
- Ertapenem is…
  - A carbapenem, stable to ESBLs, inactive vs. *P. aeruginosa*[1]
  - Indicated in cIAI, ABSSSI, CABP, cUTI
  - PK (including ELF data) looks acceptable for VABP[2]
- Hence, ertapenem + X-1 is a valid empiric regimen
  - Drug X's effect on *P. aeruginosa* can then be seen clearly
  - There is still a unresolved complexity around managing the frequent desire for dual initial coverage[3]

1. Only about 10% of *P. aeruginosa* isolates have an ertapenem MIC below the generally accepted susceptible breakpoint of 1 mg/L.
2. The PK-PD of ertapenem at 1g q24h supports its use in VABP (Lakota et al., Accepted abstract, ASM Microbe, New Orleans, 1-5 June 2017).
3. As guidelines often encourage dual coverage for this pathogen, a day or two of second agent (e.g., an aminoglycoside) may have to be used at study initiation. This will, however, further complicate data analysis and final labeling may need to capture this limitation

But, there's a problem!

- The rate of cases of *Pseudomonas* is low
  - Must usually enroll before culture result becomes available
  - Typical rates: HAP-VAP: 22%[1, 2], cIAI: 11%[3], cUTI: 3%[4]
- A diagnostic test won't fix this entirely
  - The diagnostic does not create cases … it only find them
  - You still have to screen a large enough population
- This creates a significant trial problem…

1. Chastre J et al. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: A multicenter, randomized study. Crit Care Med 36:1089–1096, 2008.
2. Brun-Buisson C et al. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin vs. ceftazidime/amikacin: A multicenter, randomized controlled trial. Clin Infect Dis 26;346-54, 1998
3. Lucasti C et al. Efficacy and Tolerability of IV Doripenem Versus Meropenem in Adults with Complicated Intra-Abdominal Infection: A Phase III, Prospective, Multicenter, Randomized, Double-Blind, Noninferiority Study. Clin Ther 30:868-83, 2008.
4. Naber KG et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother. 53:3782-92, 2009

The painful math

- Assume some typical general parameters
  - An endpoint with about a 20% failure rate
  - A non-inferiority margin of 10%, power of 90%
  - You need ~672 evaluable cases (336/arm)
- Evaluable = culture-proven → so now we need…
  - If 22% *P. aeruginosa*, need 3,064 (1,532/arm)
  - If 11% *P. aeruginosa*, need 6,128 (3,064/arm)
  - If 3% *P. aeruginosa*, need 22,466 (11,233/arm)
- Certainly big enough for the safety database!
  - But, not feasible for actual development
  - One recent HAP-VAP trial took 5 years to enroll ~1,200 pts[1]
  - Another took just under 3 years to enroll ~900 pts[2]

1. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Randomized, Controlled Study. Clin Infect Dis 2012;54:621-9.
2. https://www.astrazeneca.com/media-centre/press-releases/2016/AstraZenecas-antibiotic-Zavicefta-met-primary-endpoints-in-Phase-III-trial-for-treatment-of-hospital-acquired-pneumonia-21072016.html

Common-sense constraints on options

- Proposals had to be credible, non-BFMI solutions
  - BFMI (Brute Force, Massive Ignorance): e.g., enroll 20k cases
- Perfect diagnostics not assumed: e.g., we can't have
  - Instant susceptibility of all pathogens in sputum
  - Instant knowledge that only *P. aeruginosa* is present
- Superiority via study of just MDR *P. aeruginosa* not possible
  - Much too rare: Would require a well-timed outbreak
- Funding is (only) enough for ~1000 enrolled in P3
  - And it's not just funding … if we needed to enroll 20,000, then other drugs may struggle to proceed in parallel
- Add-on therapy approach is too risky
  - Hard to envision SOC* + X-1 showing superiority to SOC + placebo
- In short, # of required miracles was kept at < 1
  - Luck would have been welcomed but was not expected

**SOC: Standard of Care*

Imaginary sponsor analysis (1 of 2)

- (Imaginary) screening device is available
  - Lateral-flow immunochromatographic device
  - Low tech, simple training, 20-minutes to develop
  - Gets to 25% culture-positive in NP, 16.5% in cIAI
    - Plausible, modest improvement over 22% and 11%
  - NOT cleared, not definitive: still must be culture-positive for microITT popultion

Imaginary sponsor analysis (2 of 2)

- Putting it all together: Two trials, 3 indications
  - RCT with separate sub-arms for NP and cIAI
    - Can (just barely) eek out non-inferiority designs
    - NI margins:[a] 30% for NP and 25% for cIAI at 85% power
      - MicroITT (Culture-positive) is primary analysis population
      - Wide margins, but consistent with available data
    - Randomize 2:1 & enroll 288 (NP) + 627 (cIAI) = 915[b]
  - Open-Label in Limited Treatment Options (OL LTO)
    - All-comers, NP, cIAI, cUTI
- Feasible? Maybe – hitting these numbers will be hard
- Credible? Maybe – really pushes NI design limits

[a]These margins are wider than usual but were supported by a supplemental literature-based argument for this setting; [b]Assumed 25% and 16.5% culture-positive in NP & cIAI

Discussion at the workshop

- Two main ideas discussed
  1. Following from the imaginary sponsor's analysis, debate focused on designing a program based on trials (just) large enough for non-inferiority-based hypothesis testing
  2. Vs. can't get to sufficient N for realistic hypothesis testing
     - Rare organisms are rare … diagnostics don't make them appear
     - Yet such organisms (e.g., *Acinetobacter*) can devastate
     - What about the Animal Rule? What about External Controls?
- Core conclusions
  - No easy path forward – there is no overlooked trick
    - In some cases, clinical data will be ***very*** limited
  - To have new options, trade-offs must be accepted
  - *Summary white paper under revision at J Infect Dis*[1]

[1]Boucher et al. White Paper: Developing Antimicrobial Drugs for Resistant Pathogens and Unmet Needs. J Infect Dis 2017.

Back to the big picture:

Tools for developing narrow-spectrum drugs

- The examples we'll discuss
  - Drug X-1: Hypothetical, *Pseudomonas*-only
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  - Sulbactam/ETX2514: Real, *Acinetobacter*-focused
- Points of departure for our discussion
  - The urgent Unmet Need requires action
  - Clinical trials can only get us so far for these drugs
  - There are tools that can help
  - And lack of action is an action with consequences!

Backup

2016 IDSA Guidelines

Mono or combo for P. aeruginosa?

- **EMPIRIC:** We suggest prescribing one antibiotic active against *P. aeruginosa* for the empiric treatment of suspected VAP in patients without risk factors for antimicrobial resistance who are being treated in ICUs where ≤10% of gram-negative isolates are resistant to the agent being considered for monotherapy *(weak recommendation, low-quality evidence).*
- **KNOWN (A):** For patients with HAP/VAP due to P. aeruginosa who are not in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, we recommend monotherapy using an antibiotic to which the isolate is susceptible rather than combination therapy *(strong recommendation, low-quality evidence)*.
- **KNOWN (B):** For patients with HAP/VAP due to P. aeruginosa who remain in septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known, we suggest combination therapy using 2 antibiotics to which the isolate is susceptible rather than monotherapy *(weak recommendation, very low-quality evidence)*.

Kalil, A. C., M. L. Metersky, et al. (2016). "Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society." Clin Infect Dis.