# Developing Anti-infective Drugs for Patients with Unmet Need

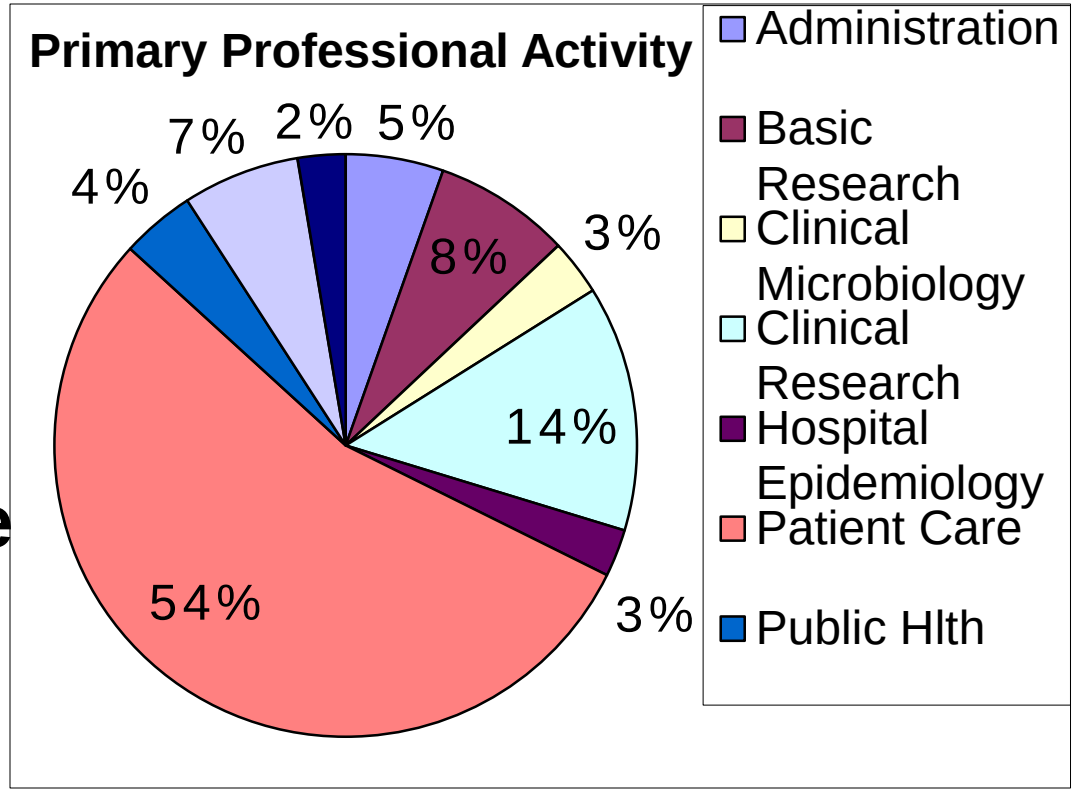
FDA Advisory Committee Meeting

April 13, 2017

# IDSA Membership

**11,000 strong**

**Majority physicians providing clinical care**

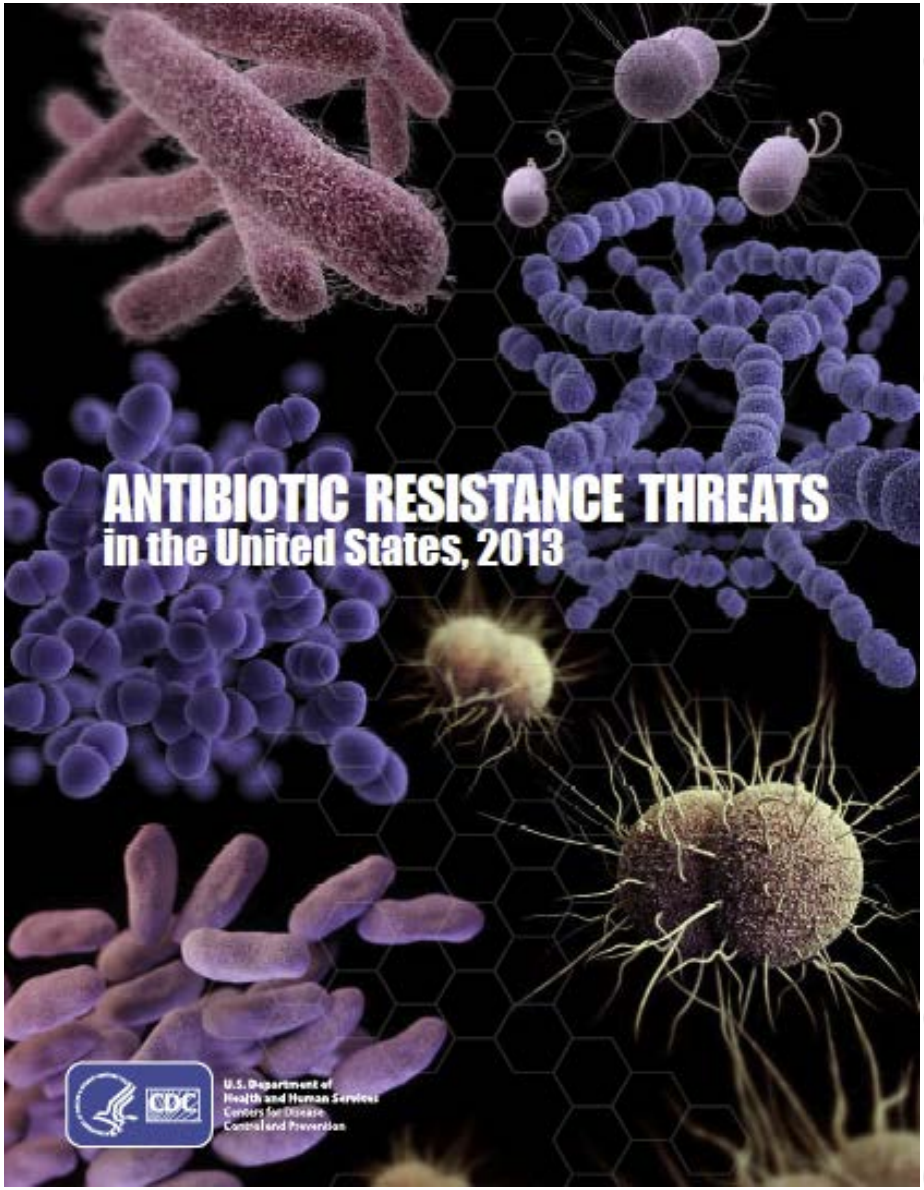


# Have we returned to the pre-antibiotic era?

**Maybe so…**

- **mcr-1/mcr-2**
  - **Transmissible (plasmid) colistin resistance**
  - **Already associated with KPC; true MDR/XDR possible**
- **We should be scared**
- **Forced to use drugs with extremely limited/negative data – e.g.,**
  - **Inhaled/parenteral colistin**
  - **Fosfomycin for ESBL infections**
  - **Tigecycline for MDR infections (despite warning re: death)**
- **Infection prevention, stewardship, surveillance of paramount importance**
  - **Progress is being made through CARB**

**McGann, et al. Antimicrob. Agents Chemother 2016; DiPlato et al. Antimicrob. Agents Chemother 2016**




## Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

## Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

## Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

# Clinical Impact of Antibiotic Resistant Infection Recent Case

**71 year old lady with laryngeal cancer post larengectomy, chemotherapy and radiation in 2012, COPD on home oxygen, and recent admission for tracheobronchitis now transferred from rehabilitation with fever, flank pain and respiratory failure**

- **Cured of cancer**

# Recent Case

**History:**

- **12/2015 Cough, sputum production with acute on chronic respiratory failure**
- **She had no fever, chills or other constitutional symptoms**
- **Evaluation for viruses, other infections negative**
- **Blood and sputum cultures grew GNR ultimately identified as MDR *K. pneumoniae,* + metallo-carbapenemase**
- **Did well, cleared blood cultures, did not need re-intubation**
- **Treated for 2 weeks with**
  - **IV tigecycline**
  - **IV colistin**
  - **inhaled colistin**
- **January, 2016 switched from colistin IV/inhaled to IV minocycline**

# Recent Case

**Admitted with pneumonia again in late January and in May**

**She presented with respiratory failure and tracheobronchitis along with a urinary tract infection**

- **Discharged on a 5 day course of levofloxacin**
- **Sputum and urine cultures subsequently grew a carbapenemase-producing *Klebsiella pneumoniae***
- **4 days later, she was found to have an increased oxygen requirement**
- **ER: reports feeling very tired, still has urinary symptoms (dark, foul-smelling, with right flank pain), T 38.5C, increased oxygen requirements**
- **Urine culture >=100,000 CFU/mL *Klebsiella pneumoniae*, + Carbapenem resistance, MDR organism**

# Recent Case

**Culture Urine >=100,000 CFU/mL *Klebsiella pneumoniae*,**
**+ Carbapenem resistance, multidrug resistant (MDR) organism**

**Resistant to:**

- **Ampicillin**
- **Ampicillin/sulbactam**
- **Piperacillin/tazobactam**
- **Cefazolin**
- **Cefoxitin**
- **Ceftazidime**
- **Ceftriaxone**
- **Cefepime**
- **Meropenem**
- **Amikacin**
- **Gentamicin**
- **Tobramycin**
- **Ciprofloxacin**
- **Nitrofurantoin**
- **Trimethoprim/Sulfa**
- **Ceftolozane-tazobactam**
- **Ceftazidime-avibactam**

# Recent Case (continued)

**After discussion about limited options, predictable renal, neurological and other toxicity, patient and her family decided on hospice care**

**Summary:**

- **Cured of cancer**
- **Dying of resistant infection**

# Lessons from this case

- **Infections caused by resistant pathogens are serious**
  - **This could happen to you or your children**
- **Having drugs targeting single pathogens will be useful to clinicians and patients**
- **The data we have is often less than what we would want**
  - **Data on patients with infections at standard body sites (e.g., UTI) are the foundation from which we build**
  - **But, clinicians have to extrapolate everyday to treat infections … patients do not always present with textbook infections!**
  - **We work everyday with data from a variety of sources and variety of observations**

# Aim for today: Discuss approaches to creating a tractable pathway for registering narrow-spectrum agents

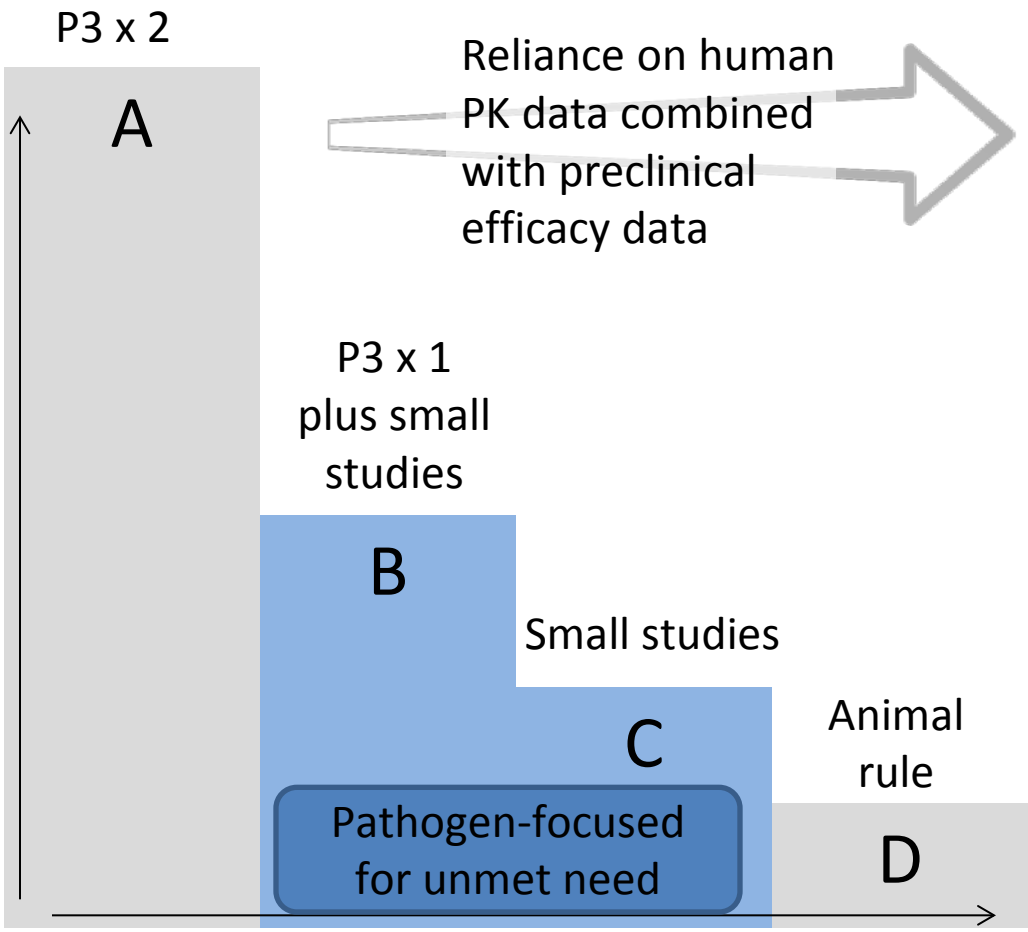
*Much progress has been made – we should not lose sight of that!*
*Here the remaining gaps as we see them*

- Narrow-spectrum, e.g., single-pathogen, drugs
  - Focus of recent workshop and today's discussion
  - Pooling of data from multiple body sites is included here
- Other important issues for separate, parallel discussion
  - Bloodstream infection (with infective endocarditis); osteomyelitis
    - Rarity of syndrome creates challenges similar to those of narrow-spectrum agents – solutions may overlap
  - Development of Antimicrobial Susceptibility Test Devices
    - FDA Workshop 29 September 16
  - A pathogen-specific indication (and/or site-specific PK data in label)
  - An approach to uncomplicated UTI and hence oral Gram-negative drugs

# Narrow-spectrum agents

# Details

# Context: Mental schema




Acceptance of smaller clinical datasets in response to unmet medical need

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

# Disambiguation: Pathogen-focused

- The phrases “Tier C” & “pathogen-focused pathways” can confuse and might be taken to be any of:
  1. Truly narrow: *Acinetobacter* only
  2. Broad-spectrum, including a rare pathogen (*Acinetobacter*)
  3. Any spectrum, developed to focus on MDR/XDR variants in that spectrum (e.g, active vs. Enterobacteriaceae) and seek to develop for carbapenem-resistant strains (CRE)
- “Pathogen-focused pathways” really only means #1
  - For #2, do Tier B plus a small study for the rare pathogen
  - For #3, see #2. Chasing MDR/XDR is high-risk. Develop for UDR while collecting a few MDR/XDR on the side

# Good news, Bad news

- Good news: Tier B is well and truly launched
  - FDA & EMA guidance support it
  - Development programs are proceeding
- Bad news #1: Tier B has been criticized
  - Ideology-driven critiques abound. Get a helmet.
- Bad news #2: Design options for rare pathogens and narrow-spectrum drugs are not obvious
  - Efforts to directly pursue MDR pathogens and show superiority have consistently failed (Achaogen)
  - Tier C designs are very difficult in practice (next slide)

# 19 July Workshop

- Hypothetical narrow-spectrum drug (X-1)
  - Detailed & credible case study was prepared
  - Activity limited to *Pseudomonas aeruginosa*
- Core challenges:
  - Organism is rare at any given body site
  - Initial therapy must often include a second agent so that empiric spectrum is adequate

| | Lit. | Recent drug #1 | Recent #2 | Recent #3 | Kollef 2014 | Consensus |
|---|---|---|---|---|---|---|
| NP | 20% | 13% | 10% | 23% | 26% | 15% |
| cIAI | 10% | 7% | | | | 10% |
| cUTI | 3% | 4.3% | 2.0% | 2.4% | | 3% |
| ABSSSI | Rare | | Rare | | | Rare |

NP = Nosocomial pneumonia (Hospital- and Ventilator-Acquired Bacterial Pneumonia), cIAI = complicated Intra-Abdominal Infection, cUTI = complicated Urinary Tract Infection, ABSSSI = Acute Bacterial Skin and Skin Structure Infection

# Size of required NI study

*Assuming NI test done on subset with a positive culture*

| Response rates | Placebo | Active | | DPE | M1 | M2 |
|---|---|---|---|---|---|---|
| NP | 38% | 80% | | 42% | 20% | 10% |
| cIAI | 61% | 82% | | 21% | 14% | 10% |
| cUTI | 33% | 70% | | 37% | 30% | 10% |

DPE = Difference in Point Estimates; M1 and M2 from FDA guidances

| Sample sizes: 10% margin and 85% power @ 80% response rate | | | | | | |
|---|---|---|---|---|---|---|
| % culture-positive | N/arm | Total N | | % culture-positive | N/arm | Total N |
| 100% | 287 | 574 | | 25% | 1149 | 2298 |
| 75% | 383 | 766 | | 20% | 1437 | 2874 |
| 50% | 575 | 1150 | | 15% | 1915 | 3830 ← NP |
| 40% | 718 | 1436 | | 10% | 2873 | 5746 ← cIAI |
| 30% | 958 | 1916 | | 6% | 9577 | 19154 ← cUTI |

# A diagnostic test will not solve this

- The diagnostic does not create the patients
  - The rate of infection due the organism is what it is
  - The diagnostic only helps select the patients who are more likely to have a positive culture
- The sponsor still has to screen at least the indicated number of patients
  - If the diagnostic has a false-negative rate of > 0%, the number to be screen becomes even larger

# Superiority is not a reliable path

- Approach A: Superiority vs. XDR *P. aeruginosa*
  - Requires emergence of XDR strains (no BAT*)
  - Not predictable
  - Very bad for public health if this is an easy path
- Approach B: New + SOC vs. SOC
  - SOC will be designed to be reliably active
  - Very low chance that New + SOC can beat SOC
  - Tamma 2012: "…meta-analyses that have been conducted exclusively evaluating RCTs demonstrate no difference … but there are well-documented increases in toxicities with combination therapy."

*BAT = best available therapy; Tamma, P. D., S. E. Cosgrove, et al. (2012). "Combination therapy for treatment of infections with gram-negative bacteria." Clin Microbiol Rev 25(3): 450-470.

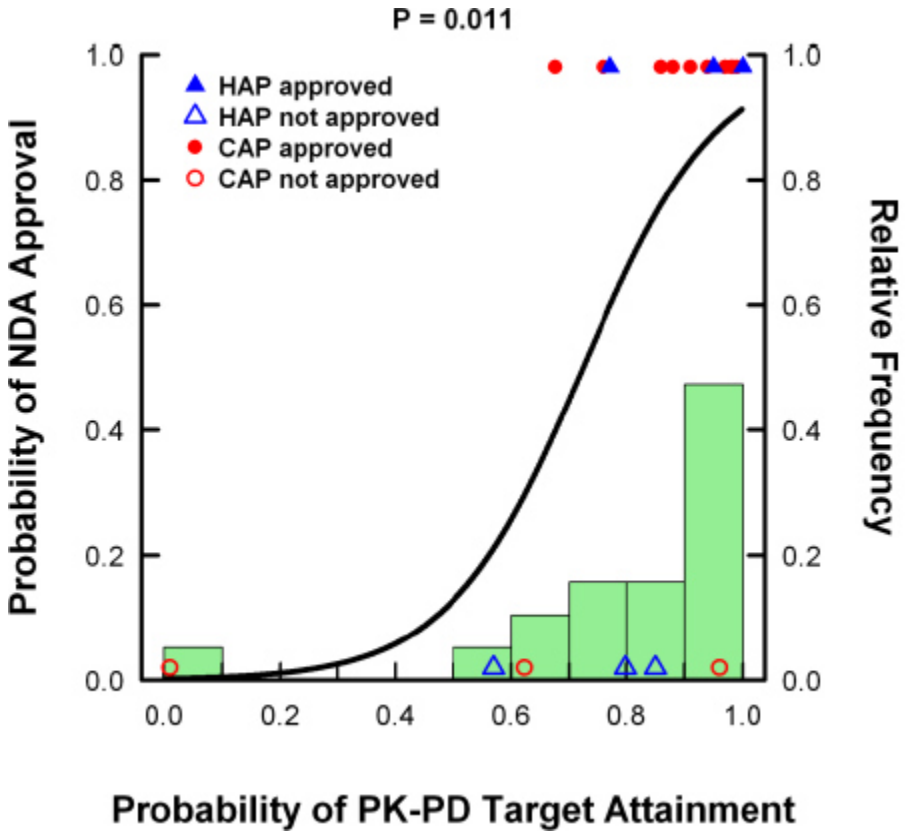
# So, what do we do?
# *Ideas that have emerged*

1. **PK-PD-based dose selection and validation**
   - **Optimize PKPD to understand and predict efficacy at a variety of body sites, e.g.,**
     - **Lungs**
     - **Bloodstream**
     - **Intra-abdominal infection**
2. **Validated animal models**
   - **Validation after the fashion of the Animal Rule**

**February 26th FDA Workshop**

# 1. PK-PD

*Doesn't tell you about toxicity, but drugs with well-validated dosing regimens very consistently succeed in their P3 studies*




| Quartile | Target Attainment Median (Range) | % NDA Approval (n/N) |
|---|---|---|
| 1 | 0.62 (0.01-0.76) | 40% (2/5) |
| 2 | 0.85 (0.77-0.88) | 60% (3/5) |
| 3 | 0.94 (0.88-0.96) | 80% (4/5) |
| 4 | 0.985 (0.97-0.99) | 100 % (5/5) |

20 pneumonia programs; 17 antibiotics in total, with 14 regulatory approvals and 6 failures

*Paul Ambrose

# Validated Animal Models

- 21 CFR 314 (Subpart I): Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible
- *Applies to certain new drug products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances... definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic …substance; and field trials…have not been feasible.*

Biologics 21 CFR 601.90 (Subpart H)

# Animal Rule (Additional Requirements)

- Postmarketing studies (e.g., field studies) to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical
- Restrictions to ensure safe use, if needed (e.g., restricting distribution to facilities or health care practitioners with special training, requiring specified types of follow up, or imposing record keeping requirements)
- Information in labeling to patients that explains that for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone

**A small clinical trial could be conducted**

21 CFR 314.610(b)(1) through (3) for drugs and 21 CFR 601.91(b)(1) through (3) for biological products

# So, what do we do?
# *Ideas that have emerged*

1. PK-PD-based dose selection and validation
2. Validated animal models
   - Validation after the fashion of the Animal Rule
3. Validated external controls
   - Paired with open-label data with the test agent
4. Very small clinical datasets
   - Perhaps also pooling data from multiple body sites

# 3. Validated External Controls

- Assemble a well-defined set of control cases
  - Have enough control cases to permit reasonable (over) matching to patients tested with Test agent
  - Have enough data on controls to be able to say these patients could have meet study entry criteria
- Pros
  - Feasible to implement, does offer a form of control
  - Permits clinical study to put all patients on Test and hence maximize experience with Test
- Cons
  - Very easy to criticize as a weak approach

# 4. Very small clinical datasets

- "Squeeze Play"
  - Meropenem resistant rates are ~20% for *P. aeruginosa*
  - For a new drug for *P. aeruginosa*, could study as
    - Test + meropenem vs. Aminoglycoside vs. meropenem
  - So, about 20% of cases would reduce to Test vs. aminoglycoside
  - Focus analyses here, but do not expect NI testing unless you will increase sample size 5x again
- "Kitchen Sink"
  - Pool data from multiple body sites
  - Permit up to 48h prior therapy so that can enroll only with a positive culture
  - There might be a role for a Bayesian analysis here – but making this convincing is hard unless at least 3 sites are studiable
- Both routes: Patient quality (validation) is key
  - And there will still be complaints…

# So, what do we do?
# *Ideas that have emerged*

1. **PK-PD-based dose selection and validation**
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**Possible plans:**

- **Fully validated Animal Rule animal models +**
  **ZERO clinical efficacy data (Tier D)**
- **Good animal models (? Multiple, explored options 26 February 17) +**
  **SOME clinical efficacy data**

# Criticism should be expected

- Both action and inaction have risks…
  - …and will lead to criticism
- Some key stakeholders show unrealistic thinking
  - Recent approval of Isavuconazole for mucormycosis
  - Editorial in which three senior academics said first
    - FDA needs to facilitate simpler & less challenging pathways
  - and then
    - The approval of ISA was wrong – not enough data
- These stakeholders usually do not understand the core issues

# Development Options
# FDA Briefing Document

1. Non-inferiority trial, perhaps using a margin equal to the full estimated treatment effect
   - *A fine idea, when it is feasible. Often not feasible*
2. Superiority trial, but not routinely feasible
   - *Absolutely agreed – and registration can depend on rare and accidental events such as window in time when standard therapies are inadequate*
3. Approval based on the Animal Rule
   - Available animal models for key bacteria (*P. aeruginosa*, *A. baumannii*) have not been developed to meet the Animal Rule requirements
     - Indeed, it may not be possible to develop such models
   - *Approving based on clinical trials in animals just doesn't make sense when it is possible to produce at least <u>some</u> clinical data*
4. Use of surrogate endpoints and accelerated approval
   - Microbiologic endpoints are not thought suitable
   - Potential use of PK as a surrogate
   - *Basing approval heavily on PK-PD makes good sense but, and as with the animal rule, there should be at least <u>some</u> clinical data. PK-PD evidence of efficacy provides a strong (Bayesian) prior that makes it more likely that clinical responses seen in a small dataset are offering reliable information*

5. FDA has done an exhaustive job of surveying the options!
   - *There simply aren't other ideas. There's no trick to pull out of a hat!*

# In Summary…

# Summary

**Current status 2017 - forced to use drugs with extremely limited/negative data**

- **Inhaled/parenteral colistin**
- **Fosfomycin for ESBL infections**
- **Tigecycline for MDR infections despite warning re: death**

**Looking ahead:**

- **Traditional clinical development plans, NI or superiority studies may not be feasible**

**Outside of a few areas, there is no easy path for narrow-spectrum antimicrobials**

- **Non-action not a possibility**

**A reliable path seems possible by combining 4 ideas**

- **PK-PD**
- **Validated Animal Models**
- **Validated External Controls (esp. if treatment effect is really large)**
- **Very small clinical datasets**
  - **Adequate, well controlled data - small RCTs with wide NI margins & uneven randomization or really small (Tier C) studies with external controls**
    - **Strong case definitions and (if possible) include severe infections**
    - **Data quality key**
    - **Trial networks may facilitate**
  - **Including multiple body sites/infection types provides useful clinical data**

**HW Boucher, PG Ambrose, HF Chambers, RH Ebright, A Jezek, BE Murray, JG Newland, B Ostrowsky, JH Rex.**
**White Paper: Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs. JID 2017; in press.**

# Summary

- **Animal studies, perhaps with use of the Animal Rule, in addition to robust PKPD studies can provide foundation for development**
  - **Fully validated Animal Rule studies + ZERO clinical efficacy data**
  - **Good animal models + SOME clinical efficacy data**
- **LPAD mechanism ensures use in limited population with needed safeguards**
- **ID physician led stewardship (JC requirement) ensures expert management of all patients in whom these medicines are used**

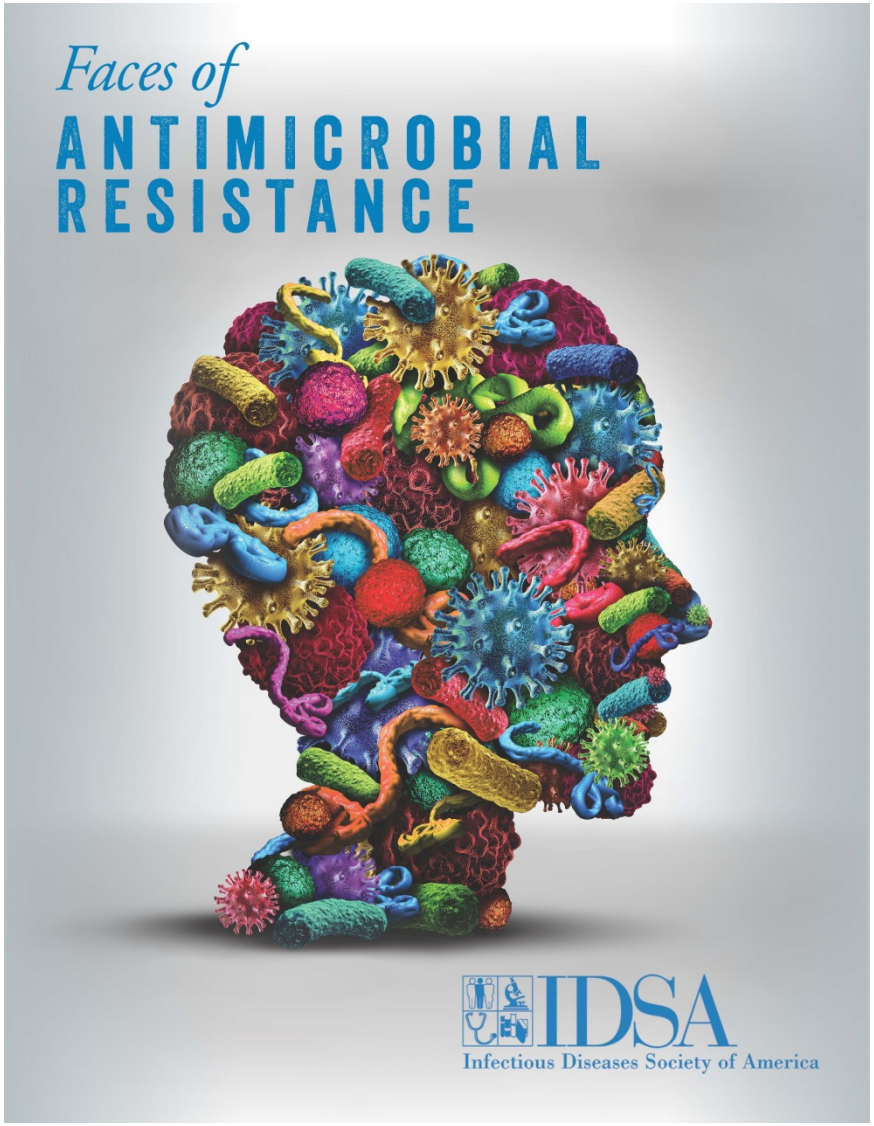
**2017 WHO Critical priority pathogens:**

- ***Acinetobacter baumannii*, carbapenem-resistant**
- ***Pseudomonas aeruginosa*, carbapenem-resistant**
- ***Enterobacteriaceae*, carbapenem-resistant, ESBL-producing**
  - ***P. aeruginosa* and *A. baumannii* have moved from serious to critical in last 3 years**

# What Else Can IDSA Do?

- Public education
  - Need for robust and sustainable pipeline of anti-infective drugs to provide for our patients now and in future generations
- Clinician education
  - Treatment guidelines
  - Guideline development
    - Stewardship
  - IDWeek
  - Online education tools
- Federal advocacy
  - Robust funding for CARB implementation
  - Economic Incentives for Antibiotic R&D (READI Act—tax credits)
  - CMS COP for Stewardship in acute and long-term care hospitals
- Technical expertise
  - FNIH, CTTI efforts, FDA Workshops
  - Guidance Development

# We need to act NOW



# Faces of Antimicrobial Resistance

**Meredith Littlejohn, St. Louis, MO.** Successfully battled leukemia, died at age 19 from a multidrug resistant infection.

**Catherine Duff, Carmel, IN.** Years of recurrent antibiotic resistant *C. diff* infections caused severe illnesses, multiple hospitalizations, missed work.

**Simon Sparrow, Chicago, IL.** Toddler dies of MRSA lung infection within 24 hours of diagnosis.

**Mary Millard, Bennett, NC.** On highest dose of antibiotic for 2+ years. Pain, digestive, cognitive side effects, many hospitalizations. Still uncured.

# Thank You!

- **P. Ambrose**
- **H Boucher**
- **H. Chambers**
- **R. Ebright**
- **A. Jezek**
- **B. Murray**
- **J. Newland**
- **B. Ostrowsky**
- **J. Rex**
- **M. Cavaleri**
- **E. Cox**
- **S. Nambiar**