Antibiotic R&D 3.0: Taking full advantage of the promising idea of LPAD

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Slides happily shared

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We've come a long way…

- Antibiotic R&D v1.0: 1950 to ~2005-6
  - Generally easy to see the value of new drugs
  - But, weaknesses in pivotal designs gradually become obvious, especially for upper respiratory infection
- Antibiotic R&D v2.0: 2007-2019
  - Rapid refinement of non-inferiority designs for major indications → clear roadmaps for skin, UTI, etc.
  - Agreement that single pivotal trials were acceptable for approval
  - Substantial harmonization between EMA and FDA

It's time for Antibiotic R&D v3.0

1. LPAD as a springboard
2. From that springboard, R&D v3.0 needs to build on v2.0 to address several really hard problems
3. The idea of superiority designs as a consistently viable path is a mirage that must be swept away
4. This is not (just) a regulatory problem – the entire community must collaborate to move us forward
5. Suggestions for next steps
6. Closing thoughts

1. LPAD as a springboard

LPAD's two key gifts to us…

1. The idea of LPAD itself
   - The very name is a clear reminder that patients & physicians make different risk-benefit decisions when options are limited
   - And, LPAD defines settings in which this is true
2. A way to mark LPAD-approved drugs as different
   - LIMITED POPULATION: "This drug is indicated for use in a limited and specific population of patients."

Combined with robust stewardship programs and CDC's ongoing surveillance, we can be comfortable that LPAD agents would be used wisely

2. The hard problems that remain

- Antibiotic R&D 3.0 needs to address these issues
  - Developing for very rare pathogens
  - Developing (just) for resistant pathogens
  - Developing for less common infections
- The issues reduce to study size and how we think about “substantial evidence of efficacy based on adequate and well-controlled trials.”
- Importantly, alpha = 0.05, 10% margins, specific endpoints, and concurrent randomized controls are not legal requirements
- We are permitted to consider risk-benefit

3. Superiority is not the answer

- Antibiotics *cure* … and it's hard to improve on cured
- If it's easy to run a superiority trial, something terrible has happened in public health
  - Resistance must be so common good choices do not exist
  - Except for the very mildest of infections, a superiority result means someone has gotten hurt (or possibly died)
- We want antibiotic superiority trials to be impossible
  - And if superiority is possible due to a gap, successful use closes the path to repeated superiority studies
- Instead, non-inferiority must be our main tool
  - Modern NI designs are proven sensitive to drug effects
  - These designs enable drugs to be developed now
  - We must be very clear about this in our public documents

4. Not (just) a regulatory problem

- We are all part of this problem
- It's easy to be critical and ask for more: We all do it
- The agency is just the first group to do this…
  - Physicians: *I'll wait for the guidelines to change*
  - Payors: *I expected superiority data!*
  - Patients: *Non-inferiority sounds so dodgy*
- This is a communication and education problem
  - Confusion and debate on the scientific principles[1,2]
  - We need to clarify this in public
- Non-traditional agents face the same issues[3]

1. Rex JH et al. Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. Clinical Infectious Diseases. 2017;65:141-6.
2. Powers JH et al. Studying new antibiotics for multidrug resistant infections: are today's patients paying for unproved future benefits? BMJ. 2018;360:k587.
3. Rex JH et al. Designing development programs for non-traditional antibacterial agents. Nature Communications (in press), 2019.

5. Suggestions (1 of 2)

We are preparing here for the future! When the real crisis emerges, it will be too late!

- Agency: Convene working groups (FNIH?) to develop credible pathways for the rare(r) infections
  - Engage with the trade-offs to create feasible pathways
  - We must use LPAD to expand what is now approvable
- Agency & professional societies: Spread the word
  - Non-inferiority is a not a synonym for "worthless drug"
  - In infection, superiority comes at a huge societal cost
- Professional societies: Updating guidelines every 10 years is completely inappropriate!
  - Example: use of colistin must come to a screeching halt

5. Suggestions (2 of 2)

- Industry: The focus must be on novel agents that clearly move the needle
  - There is a need for a different reimbursement mechanism (Push & Pull incentives) for new antibiotics
  - This is not a discussion for today: pull incentives are needed but are not within the purview of the FDA
  - Rather, today is about FDA's regulatory powers. My comments address a necessary (but not sufficient!) condition for a healthy antibiotic ecosystem
  - In any future Pull mechanism, novelty will be the key to selecting products that receive meaningful incentives
  - In addition, the LPAD mechanism really must be used only for products that can’t otherwise be developed

6. Closing thoughts

- At heart, I'm a doc who moved into Industry in 2003 because of the problem of AMR
  - As a university-based Infectious Diseases physician, I had begun to see truly untreatable infections
- Since then, I've had the opportunity to walk all sides of the challenge of antibiotic R&D
  - Fund raising within large & small companies. Lyophilizer failures shutting down supply chains. Corporate decision-making. The pressure of time.
- Tradeoff-free solutions to AMR don't exist
  - If they did, we'd all be using them
  - Since they don't, we as a community need to find pragmatic solutions to real-world problems
  - We need to do this NOW