Why is the antibacterial pipeline drying up?

Brad Spellberg, MD
Associate Professor of Medicine
Gffen School of Medicine at UCLA
Division of General Internal Medicine
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center

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“For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care. Then came the explosive news of sulfanilamide, and the start of the real revolution in medicine.”

Lewis Thomas, MD
• Albert Lasker Award winner
• Member of the National Academies of Science
• National Book Award

Lewis Thomas. Notes of a Medicine Watcher. ‘83. Viking Press
“I remember the astonishment when the first cases of pneumococcal and streptococcal septicemia were treated in Boston in 1937. The phenomenon was almost beyond belief. Here were moribund patients, who would surely have died without treatment, improving...within a matter of hours...and feeling entirely well within the next day...we became convinced, overnight, that nothing lay beyond reach for the future. Medicine was off and running.”
Fast forward 67 years...antibiotic development is dying

Trends in Antimicrobial Drug Development: Implications for the Future

Published '04 CID
Fast forward 71 years...antibiotic development is dying

The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America

Published '08 CID
Fast forward 73 years...antibiotic development is dying.
Why No Antibiotic R&D?

2 Major Categories of Causes

1. Economic/Return on Investment
2. Regulatory
Why No Antibiotic R&D?

1. Economic/Return on Investment (ROI)
   • Antibiotics taken for short durations & cure disease—victims of their own success
   • In contrast, treatments for chronic diseases taken forever & sell much better

   **Sales (return on investment) of antibiotics not competitive with most other drug classes**
Why No Antibiotic R&D?

Courtesy Tom Parr, based on:

How Stimulate Antibiotic R&D?

**Must Improve Antibiotic Return on Investment**

1. Decrease cost of development (e.g. tax credits, grants, contracts, liability protection)

2. Increase income linked to antibiotics (e.g. market exclusivity, patent extensions, prizes)

3. Need a variety of types of incentives—there is no single, rate-limiting step to overcome
Developmental Incentives

Drug Development Pathway

- **Pre-Discovery**: 5,000–10,000 compounds over 3–6 years.
- **Preclinical**: 250
- **Clinical Trials**: 5 phases, with increasing number of volunteers: PHASE 1 (20–100), PHASE 2 (100–500), PHASE 3 (1,000–5,000) over 6–7 years.
- **FDA Review** and **Large-Scale Mfg** over 1/2–2 years.

Science Bench → TRANSLATE → Technology Bedside
A Chinese menu of incentives is needed to overcome the blocks to development

### Drug Development Pathway

<table>
<thead>
<tr>
<th>Stage</th>
<th>Challenges</th>
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<tbody>
<tr>
<td>Dearth of pre-clinical</td>
<td>No resources to support translation of rare, promising pre-clinical molecules from academic labs or biotech start-ups into Phase I trials; Phase II “valley of death”; Phase III only afforded by Big Pharma (~$100 million)</td>
</tr>
<tr>
<td>research in antibiotic</td>
<td>FDA under terrible political and public pressure not to approve drugs; antibiotics routinely not approved; regulatory standards are murky and ever-shifting</td>
</tr>
<tr>
<td>discovery and resistance</td>
<td>due to inadequate federal funding, and cancellation of industry discovery programs</td>
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</table>
Bench Bedside

TRANSLATE

Science Technology

Developmental Incentives

Basic science & small business grants
Contracts, tax credits, & BARDA
Patent extension, guaranteed markets, liability protection

New FDA approach to antibiotics

No resources to support translation of rare, promising pre-clinical molecules from academic labs or biotech start-ups into Phase I trials;
Phase II “valley of death”;
Phase III only afforded by Big Pharma (~$100 million);
FDA under terrible political and public pressure not to approve drugs;
antibiotics routinely not approved;
regulatory standards are murky and ever-shifting.
Need Incentives

Bottom Line

- We can’t make companies develop new antibiotics
- We have to make them want to develop new antibiotics
Why No Incentives Yet?

• “Toxic pharmaceutical politics”

• Politicians are reactive...respond to constituent concerns and beliefs

• IOM can help educate politicians and the public regarding need for incentives
2. Regulatory Uncertainty for Abx Trials

• Currently, regulatory barriers are far greater problem than economics for preventing new antibiotic development

• FDA has been re-evaluating acceptability of “non-inferiority” clinical trials

• Concerns have disproportionately crushed antibiotics
If the experimental drug is similarly effective to the comparator drug in a non-inferiority trial, there are 2 possible statistical interpretations of this outcome:

1. BOTH drugs are better than placebo

2. NEITHER drug is better than placebo
To distinguish these possibilities, FDA wants comparator drugs in non-inferiority studies to have been previously shown to be superior to placebo.

If comparator drug > placebo;
AND
experimental drug = comparator drug;
THEN
experimental drug > placebo
The Non-Inferiority Problem

• BUT, antibiotics arrived in US in late ‘36, 20 years before placebo-controlled trials

• By the time placebo-controlled trials came around, it was unethical to do them for serious/life threatening infections

• They were never and will never be done
Antibiotic Superiority Paradox

• “the patients in whom a new antibiotic is most likely to be superior to a comparator (i.e. those with bacteria resistant to the comparator) are excluded from enrollment in the study”—John Rex

• Superiority studies are not feasible for most infections—we must have non-inferiority studies for antibiotics
In 2007, the Infectious Diseases Society of America learned that FDA was going to begin requiring placebo-controlled trials for community acquired pneumonia due to lack of previous placebo-controlled data on antibiotic efficacy for this disease (!)
“In the mortality bills, pneumonia ... has become, to use the phrase of Bunyan, ‘the Captain of the Men of Death’”

**Do Antibiotics Work for Pneumonia?**

Mortality from Pneumonia With & Without Antibiotics (Abx) by Patient Age/Clinical Status*

<table>
<thead>
<tr>
<th>Pneumonia Mortality</th>
<th>&lt;30 year old or “good” status</th>
<th>30-59 year old or “fair” status</th>
<th>≥60 year old or “poor” status</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Abx</td>
<td>12%</td>
<td>32%</td>
<td>62%</td>
</tr>
<tr>
<td>With Abx</td>
<td>1%</td>
<td>5%</td>
<td>17%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decrease in Mortality from Abx</th>
</tr>
</thead>
<tbody>
<tr>
<td>11%</td>
</tr>
<tr>
<td>27%</td>
</tr>
<tr>
<td>45%</td>
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</tbody>
</table>

*Table reproduced from IDSA position paper ’08 Clin Infect Dis 47(S3):S249-65; references are Tilghman ‘37, Bullowa ‘37, Heinzelman ‘37, Evans ‘38, Dowling ‘51.
Do antibiotics work for skin infections?

Historical Studies of Cellulitis Mortality

Cook County

Norway National Registry

Hoyne et al '39 JAMA

Madsen '73 Infection
Antimicrobial Agents for Complicated Skin and Skin-Structure Infections: Justification of Noninferiority Margins in the Absence of Placebo-Controlled Trials

Brad Spellberg,1,2 George H. Talbot,2 Helen W. Boucher,4 John S. Bradley,2,4 David Gilbert,7 W. Michael Scheld,8 John Edwards Jr.,1,2 and John G. Bartlett,9 for the Antimicrobial Availability Task Force of the Infectious Diseases Society of America

2009 Clinical Infectious Diseases

Antibiotics for Cellulitis Save Far More Lives Than Aspirin or Streptokinase for MI!

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mortality No Treatment</th>
<th>Mortality With Treatment</th>
<th>Reduction in Mortality</th>
<th>NNT to Save a Life*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>10.7%</td>
<td>0.3%</td>
<td>10.4%</td>
<td>9</td>
</tr>
<tr>
<td>Acute MI†</td>
<td>12%</td>
<td>9%</td>
<td>3%</td>
<td>33</td>
</tr>
</tbody>
</table>

*Number Needed to Treat to save a life
†From ISIS-2 Study published in 1988 in Lancet 2:349-60
The “Dark Ages”

• 4 yo girl in excellent health suddenly developed facial cellulitis

• Spread relentlessly, fever to 104°F

• Could not sleep because her face and neck so swollen she could not swallow her own secretions

• Began gasping for breath

Herrell ’43 Proc Staff Meetings Mayo Clinic 18:65-76
The “Dark Ages”

- Pus from I&D grows S. aureus
- Pneumonia and bacteremia present
- Infection “almost universally fatal”
- PCN administered: 20,000-30,000 units per day
• After losing the placebo debate, critics changed tact and now demand mortality endpoint for community acquired pneumonia

• They say the clinical response curves of patients treated with and without antibiotics eventually converge for both pneumonia and skin infections
Must Have Clinical Endpoints

Practical Flaw
• Mortality endpoint will require 5000 patient studies—impossible to do

Theoretical Flaw
• By definition, clinical response effect size of antibiotics vs. no therapy must be at least as great as their mortality effect size
• By definition, clinical response curves with and without antibiotics cannot converge—more are dead without antibiotics
Must Have Clinical Endpoints

• Clinical response more sensitive than mortality to detect less effective drugs

• We know that non-inferiority trials using clinical (but not mortality) endpoints have detected inferior antibiotics:
  1) daptomycin for pneumonia,
  2) iclaprim for skin infection,
  3) tigecycline for nosocomial pneumonia
“The determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment”
Why Clinical Judgment Matters!

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Hazardous journeys

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials.

What is already known about this topic
- Parachutes are widely used to prevent death and major injury after gravitational challenge
- Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury
- Studies of free fall do not show 100% mortality

What this study adds
- No randomised controlled trials of parachute use have been undertaken
- The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect
- Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

BMJ '03 327:1459-61
Solution

• FDA must move past radical skeptics and use available data to enable antibiotic non-inferiority trials with clinical endpoints.

• This may require statutory change to acknowledge that antibiotics are unique—they are the only drugs that lose efficacy over time and hence must be continually replaced.
Solution

• Physicians and their patients should not be held hostage—we need new antibacterial drugs

“The perfect is the enemy of the good.”

--Voltaire
Another Puzzle

Why is it that:

• Antiretrovirals are approved for the treatment of HIV; and

• Antifungals are approved for the treatment of “invasive candidiasis” and “invasive aspergillosis”; but

• Antibacterials are approved for “pneumonia” or “skin infections”, rather than “invasive Acinetobacter”, etc?
Organism-Specific Studies

• The current system of approving antibiotics creates perverse incentives

• Companies are forced to study drugs for diseases with many available options—skin infections, pneumonia, etc.

• Companies CAN’T study drugs for diseases we do need new drugs for—those specifically caused by highly resistant bacteria
Organism-Specific Studies

Example of perverseness & impact

• Tigecycline is approved and marketed for skin infections and community pneumonia
• Its use is encouraged where it is not needed (dropping atom bomb on an ant), driving resistance to the drug
• Conversely, it is not approved for, and cannot be marketed for, extreme resistant gram negative bacilli infections, where it actually saves lives!
In Summary, We Need 4 Things

1. Far more basic, translational, and clinical research into bacteria, resistance, infections, and antibiotics

2. Economic incentives for antibiotic R&D

3. FDA to enable non-inferiority antibiotic clinical trials using clinical endpoints

4. Organism-specific studies
“...with today’s [antibiotics] it is possible to place in the hands of a barefoot, nonliterate villager more real power to affect the outcome of a...critically ill [patient]...than could have been exerted by the most highly trained urban physician of 25 years ago.”

(Dr. Walsh McDermott 1960 Science 131:197-205)
“It is not too much to state that the introduction of [antibiotics] has represented a force for change in the 20th century of the same general kind as James Watt’s modification of the steam engine did in the 18th. The crossing of the historic watershed could be felt at the time. One day we could not save lives, or hardly any lives; on the very next day we could do so across a wide spectrum of diseases. This was an awesome acquisition of power.”

(Dr. Walsh McDermott in McDermott & Rodgers. ‘82 Johns Hopkins Med J 151:302-12)
• IDSA spearheaded initiative
• JFK-like call to action
• Need all levels of constituents to buy in
• Calls for 10 new antibiotics by 2020
The Stakes Are High

Rebecca Lohsen (17 yr)--Dead

Mariana Bridi da Costa (22 yr)--Dead

Bryce Smith (14 mo)—survived, $1 million hospital bill

Tom Dukes—8” of colon resected, colostomy

Carlos Don (12 yr)--Dead

Ricky Lannetti (21 yr)--Dead
Thank You!