Antibiotics – The Next Big Thing, Again?

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Today’s Panel

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The Heightened Concern Over Antibiotic Resistance is Not a New Phenomenon

Factors impacting on the problem of antibiotic resistance


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

CID 208:46 (15 January)

*PubMed*
The Most Important Areas of Focus Have Been Well-Established

- Top resistance threats have been categorized by level of concern
- Among “urgent” and “serious” categories, majority are Gram negative and are estimated to lead to >25M infections in the US annually

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>CDC Threat Level</th>
<th>Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Urgent</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Carbapenem-resistant <em>Enterobacteriaceae</em> (CRE)</td>
<td>Urgent</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Drug-resistant <em>Neisseria gonorrhoeae</em></td>
<td>Urgent</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Multi-drug resistant <em>Acinetobacter</em></td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Drug-resistant <em>Campylobacter</em></td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Extended-spectrum β-lactamase producing <em>Enterobacteriaceae</em></td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus</em> (VRE)</td>
<td>Serious</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Multi-drug resistant <em>Pseudomonas aeruginosa</em></td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Drug-resistant non-typhoidal <em>Salmonella</em></td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Drug-resistant <em>Salmonella Serotype Typhi</em></td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Drug-resistant <em>Shigella</em></td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td>Serious</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Drug-resistant <em>Streptococcus pneumoniae</em></td>
<td>Serious</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Drug-resistant tuberculosis</td>
<td>Serious</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Staphylococcus aureus</em></td>
<td>Concerning</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Erythromycin-resistant Group A <em>Streptococcus</em></td>
<td>Concerning</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Clindamycin-resistant Group B <em>Streptococcus</em></td>
<td>Concerning</td>
<td>Gram positive</td>
</tr>
</tbody>
</table>

- Require **urgent and aggressive** action
- Require **prompt and sustained** action to ensure infection does not spread
- Require **careful monitoring** and require **preventive** action

CDC; SunTrust Robinson Humphrey Sector Update 11/3/2015
If Left Unaddressed, Morbidity, Mortality, and Cost from AMR Will Skyrocket

- Globally, about **700,000 people die** every year from antimicrobial resistance (AMR).
- In the US, more than **2M infections annually** are caused by bacteria that are resistant to at least first-line antibiotic treatments
  - 23,000 deaths
  - $20B in excess direct healthcare costs
  - $35B in lost productivity costs
- If left unaddressed, AMR could result in **10M deaths** and cost **$100 trillion** annually

“Even when recorded, tens of thousands of deaths from drug-resistant infections – as well as many more infections that sicken but don’t kill people – go uncounted because federal and state agencies are doing a poor job of tracking them….. Not even the CDC has a good handle on the extent of the problem. The numbers are regularly cited in news reports and scholarly papers, but they are mostly guesswork. Reuters analyzed the agency’s math and found that the estimates are based on few actual reported deaths from a drug-resistant infection.”
AMR Addressed at UN General Assembly Meeting

Only the 4th time that the general assembly has held a high-level meeting for a health issue

Primary Objectives:

☑ Summon and maintain strong national, regional, and international political commitment in addressing antimicrobial resistance

☑ Increase and improve awareness of antimicrobial resistance

☑ All 193 member states signed a declaration to combat the proliferation of antibiotic resistance
Crisis Strengthened By a Dearth of New Antibiotic Drug Classes

➢ More than a **30-year void** in the discovery of new classes of antibiotics
There Has Also Been an Overall Decline in the Number of New Antibiotic Approvals

- Decline in the number of new antibiotic approvals over the last 30+ years
- Much of the innovation from new generations of existing classes or modifications of approved drugs

### New Antibiotic Approvals Over Time

<table>
<thead>
<tr>
<th>Period</th>
<th>Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983-1987</td>
<td>16</td>
</tr>
<tr>
<td>1988-1992</td>
<td>14</td>
</tr>
<tr>
<td>1993-1997</td>
<td>10</td>
</tr>
<tr>
<td>1998-2002</td>
<td>7</td>
</tr>
<tr>
<td>2003-2007</td>
<td>5</td>
</tr>
<tr>
<td>2008-2012</td>
<td>3</td>
</tr>
<tr>
<td>2013-YTD</td>
<td>6</td>
</tr>
</tbody>
</table>

### Generations of Approved Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic Classes</th>
<th>Examples (generic name)</th>
<th>Total Approved Generations</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams: cephalosporins</td>
<td>ceftaroline</td>
<td>5</td>
</tr>
<tr>
<td>Quinolones</td>
<td>ciprofloxacin</td>
<td>4</td>
</tr>
<tr>
<td>β-lactams: penicillins</td>
<td>oxacillin</td>
<td>4</td>
</tr>
<tr>
<td>Macrolides</td>
<td>telithromycin</td>
<td>3</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>telavancin</td>
<td>2</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>tobramycin</td>
<td>1</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>ofloxacin</td>
<td>1</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>daptomycin</td>
<td>1</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>linezolid</td>
<td>1</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>minocycline</td>
<td>1</td>
</tr>
<tr>
<td>β-lactams: carbapenems</td>
<td>imipenem</td>
<td>1</td>
</tr>
</tbody>
</table>

FDA; SunTrust Robinson Humphrey Sector Update 11/3/2015
Antibiotic R&D Has Been Plagued with Development and Commercial Challenges

**Development Challenges**

- Attraction of capital
- Patient enrollment in clinical trials and high associated costs
- Regulatory path improved but still not harmonized between the US and EU
- High safety bar
- Difficult to predict future resistance
- Effective approaches for Gram-negative bacteria

**Commercial Challenges**

- Low ROI due to stewardship and acute nature of treatments
- Skewed value perception and pricing models for antibiotics
- Lack of rapid point-of-care diagnostics
Performance of Recently Launched Antibiotics Has Been Modest

![Graph showing the performance of recently launched antibiotics over time. The graph compares the sales of various antibiotics, including Avycaz, Dalvance, Orbactiv, Sivextro, Zerbaxa, Zevtera, and others. The y-axis represents USD million, and the x-axis represents the years from 2014 to 2022.]
Few Big Pharma Players Remain in the Space

M&A and Pharma R&D Departure for the Antibiotic Space

M&A Deal Count

Year Pharmaceutical Companies Exited Antibiotic R&D


- Roche 1999
- Lilly 2002
- Sanofi 2004
- Pfizer 2011
- J&J 2011
- AstraZeneca 2015

SunTrust Robinson Humphrey Sector Update 11/3/2015
However, a Number of Key Initiatives in the Past Few Years Have Driven Increased Interest in the Space

- **GAIN ACT**
  - US
  - 2012
- **BARDA**
  - US
  - 2010
- **10 x ‘20**
  - EU
  - 2010
- **COMBACTE**
  - EU
  - 2013
- **ENABLE**
  - EU
  - 2014
- **New Drugs 4 Bad Bugs**
  - 2013

SunTrust Robinson Humphrey Sector Update 11/3/2015; International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development
These Initiatives Are Complementary and Additive, Addressing Different Parts of the Value Chain

**GAIN ACT**
- Provides the following benefits:
  - An additional five years of market exclusivity
  - Priority Review
  - Fast-Track Designation
  - FDA guidance for antibiotic development
- Value chain targeted:
  - Market approval
  - Commercialization

**BARDA**
- Provides direct funding for the development of antibiotics in the areas of the greatest unmet need
  - FY15: US$79M; FY16: US$182M
- Value chain targeted:
  - Preclinical development
  - Clinical development

**10 x ‘20**
- Public-private partnership for legislative, regulatory, and funding solutions to antibiotic R&D
- Aims to produce 10 new systemic antibiotics by 2020
- Value chain targeted:
  - Basic research
  - Preclinical development
  - Clinical development
  - Market approval
  - Commercialization

SunTrust Robinson Humphrey Sector Update 11/3/2015; International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development
These Initiatives Are Complementary and Additive, Addressing Different Parts of the Value Chain

**COMBACTE**
Involves the setting up of a sustainable high-quality pan-European clinical research network of investigators/clinical sites (CLIN-Net) and laboratory surveillance network (LAB-Net). Sub-programs focus on carbapenem resistance and Gram-negative infections.

Value chain targeted:
- Basic research
- Preclinical development
- Clinical development

**ENABLE**
Supports preclinical and early clinical research into antibiotics that target gram-negative bacteria; designed to fund only most promising programs at any given time. 32 public and private partners across 13 countries.

Value chain targeted:
- Basic research
- Preclinical development
- Clinical development

**New Drugs 4 Bad Bugs**
Program under the Innovative Medicines Initiative; Facilitates collaboration of big pharma, biotech, academic, governmental & non-governmental organizations.

Value chain targeted:
- Basic research
- Preclinical development
- Clinical development
- Market approval
- Commercialization

SunTrust Robinson Humphrey Sector Update 11/3/2015; International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development
Other New Initiatives Are Expected to Also Drive Increased Interest

**IMI2**
Extension of New Drugs 4 Bad Bugs

*Value chain targeted:*
- Preclinical development
- Clinical development
- Market approval
- Commercialization

**CARB-X**
$350M trans-Atlantic public-private partnership

*Value chain targeted:*
- Basic research
- Preclinical development

**ADAPT ACT**
Seeks to create path for prompt approval for life-threatening diseases via LPAD pathway

*Value chain targeted:*
- Market approval
- Commercialization

**DISARM ACT**
Seeks to create a new regulatory designation status to increase federal reimbursement for certain antibiotics

*Value chain targeted:*
- Commercialization

SunTrust Robinson Humphrey Sector Update 11/3/2015; International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development; IMI2 Strategic Research Agenda; phe.gov
Growing Wave of Activity in Antibiotics

-Absolute number of deals and VC funding in the antibiotic space has increased over the last 3 years
-Third most active area, behind oncology and CNS

Activity Mostly Led by Biotechs

- Big pharma is responsible for only a small portion of the antibiotic pipeline
- Since passage of GAIN ACT in 2012, more than two dozen biotechs focused on antibiotics have been established

Biotechs focusing on:
- New antibiotic classes
- New MOAs
- New delivery methods
VCs are Regaining Enthusiasm and Responding

Antibiotics Upstart Allegra Nabs $24.7 Million Series B Financing

6/15/2016

Another startup jumps into antibiotics R&D as Iterum grabs a $40M round

Mar 24, 2016 11:06am

Atlas startup Spero gets $30M to give new life to old antibiotics

Feb 2, 2016

MicuRx raises $55M to wrap up Phase III antibiotic trials, file NDA in China

Sep 26, 2016 8:29am

Anti-Infectives Startup Entasis Therapeutics Raises $50M Series B

Updated April 4, 2016

Appili Raises $3.2M in Seed Round To Develop Novel Antibiotics

May 25, 2016

Zavante raises $45 million for antibiotic

APRIL 13, 2010, 5:11 PM

Chinese startup nabs $25M to combat GI antibiotic resistance in Phase III

Sep 19, 2016 8:25am
Interest From Big Pharma Appears to be Picking Up, Even From Companies which Previously Exited

**Long-Standing Players**

*MERCK*

“We are proud to reaffirm our long-standing commitment to develop new therapeutics to fight infectious diseases, and to continue to collaborate with others to support antimicrobial stewardship to help slow the rate of emerging resistance.”

“Antibiotic resistance is one of the biggest threats to human health we face today, but at GSK, we see this as a challenge, rather than a deterrent. Through a combination of our own expertise and smart, collaborative and innovative methods of working, we’re convinced we can develop innovative new ways of tackling bacteria, to protect human health for generations to come.”

**GSK partners with startup to develop antibiotic alternative**

Oct 25, 2016

**Re-Entered the Space**

*Roche*

*Roche inks a $750M antibiotics deal as it re-embraces the field*

Jan 13, 2015

*Pfizer*

*It didn’t get the whole package, but Pfizer will pay $1.5B for AZ’s antibiotics biz*

Aug 24, 2016
Today’s Panel

Dov Goldstein, MD, MBA
Managing Partner, Aisling Capital LLC

Dennis J. Purcell, MBA
Founder and Senior Advisor, Aisling Capital LLC

Daniel S. Shapiro, MD
Professor of Internal Medicine, University of Nevada School of Medicine, Department of Internal Medicine
Key Questions to be Addressed

• What are the primary drivers of this investment activity?
• What are the likely headwinds to sustained investment?
• Do you expect that pipeline products are going to face the same commercial challenges as recently launched antibiotics?
• Outside of the normal factors that you routinely consider when evaluating companies, are there any issues or concerns that are unique to investing in antibiotic companies?
• What advice can you give to drug developers in this space to sustain or drive continued interest and investment?
• How big of an issue is pricing with regard to program valuation?
• What technologies and approaches in development excite you the most and why?
• What do you see as the key value inflection points for both preclinical and early stage clinical programs?
• Where would you like to see future investment focused?
Performance of Recently Launched Antibiotics Has Been Modest

![Graph showing the performance of recently launched antibiotics](image-url)
Defined Health is pleased to present:

**CANCER PROGRESS**

28th Annual Cancer Progress Conference  
March 7-8, 2017 | Westin Times Square  
www.cancerprogressbyDH.com

**THERAPEUTIC INSIGHT**

BioEurope Spring | March 20-22, 2017  
Barcelona, Spain  
www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:

**ASH Annual Meeting** | December 3 - 6, 2016 | San Diego, CA | [http://www.hematology.org/Annual-Meeting/](http://www.hematology.org/Annual-Meeting/)


**JP Morgan Healthcare Conference** | January 9 - 13, 2017 | San Francisco, CA


