I am going to cover a LOT of material today and taking notes will be hard. Slides gladly shared – just send me a note. I will also share via a newsletter and blog post on the website (above).
Agenda

• Funding and (sometimes) non-dilutive support
  • What’s available?

• Filing
  • Recent events & future meetings
  • Three key ideas

• Finance
  • Payor models
Major AMR development initiatives worldwide

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Funding &amp; Duration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>USD 1.2B (2010-19)</td>
<td></td>
<td>Phase 2 and 3 product development against 21st Century Health Threats, including drug-resistant bacteria, and CARB-X</td>
</tr>
<tr>
<td>USD 124M (2018-22)</td>
<td></td>
<td>Targets prevention of drug-resistant infections in low- and middle-income countries (LMICs). Disease surveillance, vaccine development, economic modeling, and CARB-X. Global</td>
</tr>
<tr>
<td>USD 550M (2016-21)</td>
<td></td>
<td>Hit-to-lead to Phase 1 product development of therapeutics, diagnostics, and preventatives against WHO and CDC priority drug-resistant bacteria. Non-dilutive. Global</td>
</tr>
<tr>
<td>Euro 270M (2017-23)</td>
<td></td>
<td>Product development from discovery to delivery including novel therapeutics, optimizing antibiotics, developing combinations. WHO priority pathogen list. Non-dilutive. Global</td>
</tr>
<tr>
<td>GBP 315M (2018-21)</td>
<td></td>
<td>Funded through Global AMR Innovation Fund (GAMRIF) and the Fleming Fund to help LMICs tackle AMR. Fleming Fund (surveillance capacity) &amp; GAMRIF (innovative R&amp;D) both have a ‘One Health’ focus</td>
</tr>
<tr>
<td>Euro 500M (2018-28)</td>
<td></td>
<td>Support of national research programs as well as contributions to international initiatives like CARB-X, GARDP and JPIAMR</td>
</tr>
<tr>
<td>Euro 700M (2014-20)</td>
<td></td>
<td>Basic science, novel therapeutics, diagnostics, economic models. Priority pathogens including pathogens on WHO priority list. Member states only</td>
</tr>
<tr>
<td>USD 1.4B (2016-18)*</td>
<td></td>
<td>Basic research, SBIRs, pre-clinical services and other R&amp;D against bacterial threats, for vaccines, therapeutics and diagnostics. Non-dilutive. Global. Mostly antibacterial, but also includes viral, fungal, and parasite resistance</td>
</tr>
<tr>
<td>USD 165M (2018-23)</td>
<td></td>
<td>Lead optimization to Phase I development of therapeutics &amp; diagnostics against priority drug-resistant bacteria defined by WHO and CDC. Dilutive. US and European companies</td>
</tr>
<tr>
<td>GBP 175M (2016-21)</td>
<td></td>
<td>Drug-resistant infections program focused on policy, strengthening evidence for action, clinical trial capabilities and innovative product development including CARB-X</td>
</tr>
</tbody>
</table>

Slide courtesy Kevin Outterson
Funding source details (1 of 3)

• NIH/NIAID: *many* opportunities here
  • Main NIAID funding page: [https://www.niaid.nih.gov/grants-contracts/opportunities](https://www.niaid.nih.gov/grants-contracts/opportunities)
  • DMID Research Services: [https://www.niaid.nih.gov/research/microbiology-and-infectious-diseases-resources](https://www.niaid.nih.gov/research/microbiology-and-infectious-diseases-resources)
  • ARLG ([https://www.arlg.org/](https://www.arlg.org/)): Clinical phase programs

• DTRA (US Defense Threat Reduction Agency)
  • [www.dtra.mil](http://www.dtra.mil): Multiple *open solicitations*¹ for biothreat-related ideas. Special interest in diagnostics (to my eye)

• BARDA: Clinical funding for Phase 2 and beyond
  • Recent example: $100m for ceftobiprole Phase 3

• CARB-X: Early discovery to Phase 1 🇬🇧 🇩🇪 🇺🇸
  • 2019 Funding round should be announced soon

Funding source details (2 of 3)

• EC: Horizon 2020¹ & IMI²
  • No currently open calls to my knowledge
  • https://ec.europa.eu/research/health/index.cfm?pg=area&areaname=amdr

• JPIAMR: Joint Programming Initiative for AMR
  • 2014-17: EUR 52m supporting 50 projects
  • Call 9³ underway: focus on Diagnostics & Surveillance

• EIB Innovfin Infectious Diseases
  • Debt to equity, 7.5m to 75m EUR for EU-based work

• Novo’s REPAIR fund: $165m over 5 years
  • Next EU round opens 1 April
  • https://www.repair-impact-fund.com/

• VALUE-DX: IMI DRIVE-AB-like project for diagnostics

Funding: Other notes

• The jockey matters more than horse
  • Investors know that programs hit roadblocks. The question is whether you then know what to do!
  • Be credible: show you know what it takes to succeed
  • Be clear: show that you know your own weaknesses

• Ways to learn
  • There are lots of events (e.g., ASM-ESCMID development meetings, Gordon Research Conference, etc.) where you can get in-depth exposure to latest ideas in a setting that promotes conversation with others
  • *We’ll discuss a list of future meetings in a moment*...
Agenda

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  • Payor models
Events to study (1 of 2)

• 13 Apr + 5 May 2017: FDA workshop + IDSA whitepaper on narrow-spectrum agents
  • Can we develop drug for P. aeruginosa or A. baumannii?
• 26 May 2017: Non-inferiority paper (Clin Infect Dis)
  • Survey of major designs, explains need for NI studies
• 14-15 Jun 2017: NIAID workshop: Robust PK-PD
  • Excellent talks, materials shared on request
• 16 Jun 2017: FNIH HABP-VABP docket submission
  • Supports mortality and mortality-plus as endpoints. Study of VABP + ventilated HABP as a group; non-ventilated HABP is different.
• 2 Aug 2017 FDA Unmet Need Guidance (final)
  • You need to read this one!
Events to study (2 of 2)

• 7 Nov 2017 FDA VRBPAC: Pfizer’s *S. aureus* vaccine

• Inhaled cipro FDA AMDAC (16 Nov 17, 11 Jan 18)
  • Two attempts, two failures

• 23 Apr 2018 ECCMID Expeditied Programs
  • EMA, FDA, PK-PD, & non-traditional agents

• 2 May 2018 Plazomicin FDA AMDAC
  • Yes on cUTI; no on CRE bacteremia (a complex story!)

• 21-22 Aug 2018: FDA workshop on alternatives to antibiotics
  • Excellent discussion (more on this later in this talk)

• 14 Jan 2019: EMA Draft guidance on antibacterials
  • Open for comment until 31 Jul 2019
  • My analysis: http://amr.solutions/blog/draft-ema-antibacterial-guidance-analysis
Future Meetings of Special Note

In addition to ECCMID, ASM Microbe, and IDWeek...

• 3-6 Sep 2019 ESCMID-ASM Conference (#4) on Drug Development for AMR (Boston)
  • Don’t miss this one! Includes two Bootcamp sessions on Tue 3 Sep and a CARB-X product developer meeting on Fri 6 Sep

• 19-27 Oct 2019 International Course on Antibiotics and Resistance (ICARe, Les Pensières, Annecy, France)
  • An excellent soup-to-nuts tour

• 1-6 Mar 2020 GRC on Antibacterial Discovery and Development (Il Ciocco, Tuscany, Italy)

• **Come to meetings like these!**
  • For more events, see footer of my newsletters
The paradox of antibiotics

• We want new drugs for bad bugs
  • The superiority of NEW is easily shown in the lab on the basis of MIC testing or in animal models of infection

• But, asking for clinical data leads to a problem
  • Trials must (usually) be designed to avoid superiority
  • Instead, we must use non-inferiority designs showing similar activity relative to another active agent

• Example: Limb-threatening infection due to MRSA*
  • It is not ethical to randomize to methicillin vs. NEW
  • Must instead do something like vancomycin vs. NEW
  • Must NOT enroll if known or likely resistant to NewDrug or comparator

*MRSA = Methicillin-resistant Staphylococcus aureus

Key Ideas: 1 of 3
This idea is very, very hard

• Non-life-threatening illness (e.g., migraine)
  • Delayed effective therapy is not dangerous

• Cancer: Placebo is (usually) not possible, but there is always room to improve on 5- or 10-year survival

• Infections: We routinely produce Cure of potentially fatal illness
  • And, it’s hard to improve on Cured

• But, the idea of non-inferiority is confusing
  • “We want a better drug.”
  • I get it, but insisting on clinical superiority before approving new agents means progress only when/if the pipeline (again) becomes inadequate

• Next 2 slides: Let’s discuss in two other ways
In Infection, superiority = something bad but preventable has happened: Example

• In 2012-13, colistin was the only alternative for CRE\(^1\). A study of plazomicin vs. colistin-based SOC\(^2\) for CRE was plausible

• Plazomicin wins, but efforts to control CRE made it very hard to find cases & enroll (note small N). Cost was $1m/case!

• And, 40% mortality is not good!

• Future studies will need to use plazomicin (or one of the other new agents with comparable data) as the comparator

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1. CRE = Carbapenem-resistant Enterobacteriaceae
2. SOC = Standard of Care
But, superiority trials are used in other areas! Tell me again: **Why not in Infection?**

<table>
<thead>
<tr>
<th></th>
<th>Migraine</th>
<th>Cancer</th>
<th>Human Infection</th>
<th>Animal Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Durable cure is routine</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Placebo is routinely acceptable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Existing agents lose utility over time → new agents always needed</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Maybe</td>
</tr>
<tr>
<td>4. New agents are really for use...</td>
<td>Today</td>
<td>Today</td>
<td>Tomorrow(^1)</td>
<td>Today</td>
</tr>
</tbody>
</table>

**Points 1 & 2:** Superiority is routinely used in some areas not but others  
- **Migraine (non-life-threatening example):** Placebo with rescue is possible  
- **Cancer:** Durable cure without complications is not routine and hence continual improvement (e.g., improve 5- or 10-year survival) is always possible  
- **Animal Health:** Placebo is acceptable  
- **Human Infection:** Placebo not usually acceptable & it’s hard to improve on Cured!

**Points 3 & 4:** We need to develop new anti-infectives despite this limitation  
- There are negative Public Health issues if superiority is (or becomes) possible!

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1. This points to part of the reason why new antibiotics suffer from several forms of market failure. For more on this, see the DRIVE-AB report, various blogs on my website, and any of the writings of Kevin Outterson (his 11 Apr 2018 op-ed in STAT News is a great place to start: [https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/](https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/)).

Solution: The (emerging) 2-study path for new traditional antibiotics

• 1x NI RCT* vs. a good comparator
  • UDR (Usual Drug Resistance) setting: both agents are predicted to be active
  • Done in one of the major indications (cUTI, cIAI, etc.)

• 1x study for difficult (MDR-XDR) pathogens
  • Randomized vs. Best-Alternative Therapy (BAT) if possible, Open-label if N small or no BAT

• Example: Plazomicin initial registration program
  • NI RCT: 1x complicated UTI NI RCT vs. meropenem
  • Difficult: 1x study in CRE vs. colistin (prior slide)

Rare pathogens & infections

- Small ("Tier C"\(^1\)) trial programs: just barely (or not) powered
- Possible? Maybe, but remains difficult ... more work needed
  - Not (just) regulatory: Payor evidence is important!
  - Unless treatment effect is unquestionably large, randomized data are likely required. But not clear how to handle very small datasets.

- Multiple relevant papers
  - My blog notes on the 13 Apr 2017 + 5 May 2017 FDA workshops
  - EMA draft (2019) antibacterial guidance

Non-traditional products

• Products with interesting potential to augment
  • Virulence factor inhibitors, etc.
  • I would love to see success, but this is hard because...
• Must often show NEW + SOC\(^1\) beats SOC alone

• Prevention also has a superiority challenge
  • Reducing carriage does NOT work
  • Must show an effect on a subsequent infection
  • Must show this with best available prevention methods
  • **Frustratingly hard,** can require very large studies
  • See Pfizer’s failed *S. aureus* vaccine trial

• *Let’s talk more about superiority in general...*

\(^1\)SOC = Standard of Care
STAR: Four treatment archetypes

Examples
- Penicillin
- Phage
- Lysins
- Antisense

Example
- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

Example
- Gram-negative activity from colistin + approved Gram-positive antibiotic

Example
- Virulence factor inhibitor + approved antibiotic

2. The terms “Potentiator” or “Enhancer” have been used for products in all 3 of these categories
STAR: Four treatment archetypes

- Products in the Augment category always require a demonstration of *clinical* superiority
- **AUGMENT + EXISTING** must beat **EXISTING** alone
- **EXISTING** must be fully & properly dosed

Example²
- Virulence factor inhibitor + approved antibiotic

2. The terms “Potentiator” or “Enhancer” have been used for products in all 3 of these categories
STAR: Four treatment archetypes

- Products in the Augment category always require a demonstration of *clinical* superiority
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- **EXISTING** must be fully & properly dosed

**Augment**
- Virulence factor inhibitor + approved antibiotic

- As modern therapies are pretty good, this is a steep hill!
- **Translation:** Probability of success is very low unless the add-on has a dramatic effect relative to **SOC**
- Please think long and hard before pursuing this path!

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2. The terms “Potentiator” or “Enhancer” have been used for products in all 3 of these categories
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Antibiotic benefits go beyond simple use

- **Enabling value:** Many surgical and medical procedures rely on prophylaxis with effective antibiotics.
- **Option or insurance value:** We may want to have an antibiotic in reserve before we really need it, so it’s ready if resistance arises or worsens.
- **Diversity value:** Having multiple antibiotics may reduce selection pressure and delay resistance.

“Antibiotics are the fire extinguishers of medicine!”

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But, current economic model is broken

- Current approach
  - Everyone is delighted to have a new drug
  - But, use is delayed in effort to preserve new antibiotic
- Stewardship perspective: Entirely rational
- Economic perspective: A financial loss
  - Many analyses show same thing: Not financially rational to do antibiotic R&D
- Problem: Current pay-per-use model reimburses for only a piece of the value
AVERAGE PUBLIC ANTI-INFECTIVE COMPANY SHARE PRICE HAS DROPPED BY 50% OVER THE LAST 12 MONTHS
ENTERPRISE VALUE OF SEVERAL COMPANIES IS NEGATIVE
(USD millions)

As of Feb 26, 2019
Many efforts to analyse and fix this

- DRIVE-AB (IMI / ND4BB)
  - Recommended push & pull incentives
- Duke-Margolitis project (US)
- UK AMR Review (“O’Neill report”)
- It’s slow, but we are now seeing progress
  - UK: Committed project
  - US: Legislative progress
Key Idea:

• Market entry reward
• Payment for registration of an interesting new agent
• Delinks use from income
Work underway on these ideas

• US: Two pieces of legislation under discussion
  • DRG carveout (DISARM): eliminates financial penalty for using novel inpatient antibiotics in a bundled care system. Is not really a MER but it is a start
  • Transferrable exclusivity (REVAMP): Registration of an interesting new agent provides extended market exclusivity that can be used for another product

• UK: Recently announced 5-year national action plan
  • “We will test a new model that will de-link the payments made to companies from the volumes of antibiotics sold, basing the payment on a NICE-led assessment of the value of the medicines and supporting good stewardship.”
You can help!

• There is an immediate opportunity to support PR campaign for DISARM (de-coupling of payment from DRG) and need for longer-term pull incentives (e.g., subscription model)

• $10,000+/company support requested

• Contact me for details
Not all will earn an award: Novelty!

- Fire extinguishers come in different categories
  - You only need one of each!
- Incremental extensions
  - Some of this is OK
  - But, it will only go so far
- Scientific value + Unmet Need is best path to economic value
  - Novel mechanisms
  - Novel molecular basis of resistance
  - Addressing *strong* Unmet Need
How much financing is needed?

DRIVE-AB recommended a global plan:

• to start at **USD 800 million per year in 2018**, 
• increasing to **USD 1 billion per year in about 2020**, and 
• to **USD 1.2 billion in about 2021**, including the USD 550 million/year spent as of 2017.
Must continue other funding...

Adapted from Hoffman S, Outterson K et al JLME 2015
Can this be done?
Example – International Space Station

- No pooled budget
- Bilateral agreements between participating countries
- $150b cost (2010 estimate)
  - $7.5m/person-day for the 20k person-days of 2010 to 2015
Example - CERN

- USD 1.2 billion per year (operating budget)
- Agreed 50+ years ago
Summary

• Change is coming
  – Must stop paying for antibiotics as if we were paying firemen per fire
  – This requires a change to the entire ecosystem

• Developers also need to think differently
  – Push funding is pretty easy to find
  – Accessing future Pull rewards will require careful selection of projects
  – Not all products will have equal value
  – Program design must also be carefully considered
Thank you!

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Slides happily shared – just drop me a note or see the newsletter’s website.