Funding, Filing, and Finance

Superbugs & Superdrugs

19 Mar 2019, London

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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

BARDA	**USD 1.2B (2010-19)** Phase 2 and 3 product development against 21st Century Health Threats, including drug-resistant bacteria, and CARB-X
Bill & Melinda Gates foundation	**USD 124M (2018-22)** Targets prevention of drug-resistant infections in low- and middle-income countries (LMICs). Disease surveillance, vaccine development, economic modeling, and CARB-X. Global
CARB-X Combating Antibiotic Resistant Bacteria	**USD 550M (2016-21)** Hit-to-lead to Phase 1 product development of therapeutics, diagnostics, and preventatives against WHO and CDC priority drug-resistant bacteria. Non-dilutive. Global
GARDP Global Antibiotic Research & Development Partnership A joint DNDi / WHO initiative	**Euro 270M (2017-23)** Product development from discovery to delivery including novel therapeutics, optimizing antibiotics, developing combinations. WHO priority pathogen list. Non-dilutive. Global
UKaid from the British people	**GBP 315M (2018-21)** Funded through Global AMR Innovation Fund (GAMRIF) and the Fleming Fund to help LMICs tackle AMR. Fleming Fund (surveillance capacity) & GAMRIF (innovative R&D) both have a 'One Health' focus
Federal Ministry of Education and Research	**Euro 500M (2018-28)** Support of national research programs as well as contributions to international initiatives like CARB-X, GARDP and JPIAMR
imi ND4BB	**Euro 700M (2014-20)** Basic science, novel therapeutics, diagnostics, economic models. Priority pathogens including pathogens on WHO priority list. Member states only
jpiamr	**Euro 234M (2012-24)** Novel therapeutics, diagnostics, surveillance, prevention, stewardship. WHO priority pathogens. Non-dilutive. Member states only
NIH	**USD 1.4B (2016-18)*** Basic research, SBIRs, pre-clinical services and other R&D against bacterial threats, for vaccines, therapeutics and diagnostics. Non-dilutive. Global **Mostly antibacterial, but also includes viral, fungal, and parasite resistance*
repair impact fund novo holdings	**USD 165M (2018-23)** Lead optimization to Phase I development of therapeutics & diagnostics against priority drug-resistant bacteria defined by WHO and CDC. Dilutive. US and European companies
wellcome	**GBP 175M (2016-21)** Drug-resistant infections program focused on policy, strengthening evidence for action, clinical trial capabilities and innovative product development including CARB-X

Slide courtesy
Kevin Outterson

Funding source details (1 of 3)

- NIH/NIAID: *many* opportunities here
  - Open Partnership announcement (see AR under the therapeutics section): https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-17-026.html
  - Main NIAID funding page: https://www.niaid.nih.gov/grants-contracts/opportunities
  - DMID Research Services: https://www.niaid.nih.gov/research/microbiology-and-infectious-diseases-resources
  - ARLG (https://www.arlg.org/): Clinical phase programs
- DTRA (US Defense Threat Reduction Agency)
  - 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

1. http://www.dtra.mil/Contracts/Business-Opportunities/Current-Solicitations/

Funding source details (2 of 3)

- EC: Horizon 2020[1] & IMI[2]
  - 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 9[3] underway: focus on Diagnostics & Surveillance
- EIB Innovfin Infectious Diseases
  - Debt to equity, 7.5m to 75m EUR for EU-based work
  - http://www.eib.org/products/blending/innovfin/products/infectious-diseases.htm
- 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

1. https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/index.html
2. http://www.imi.europa.eu/
3. https://www.jpiamr.eu/activities/joint-calls/closed-calls/ninth-jpiamr-joint-call/

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…*

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See my blog for all of these
http://amr.solutions

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.
  - Talbot et al. J Infect Dis (11 Jan 2019) https://www.ncbi.nlm.nih.gov/pubmed/30649434)
- 2 Aug 2017 FDA Unmet Need Guidance (final)
  - You need to read this one!

Events to study (2 of 2)

See my blog for all of these http://amr.solutions

- 7 Nov 2017 FDA VRBPAC: Pfizer's *S. aureus* vaccine
  - Dec 2018: Terminated for futility: http://amr.solutions/blog/ouch-pfizer-terminates-s-aureus-vaccine-trial-due-futility
- Inhaled cipro FDA AMDAC (16 Nov 17, 11 Jan 18)
  - Two attempts, two failures
- 23 Apr 2018 ECCMID Expedited 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

Key Ideas: 1 of 3

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*

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

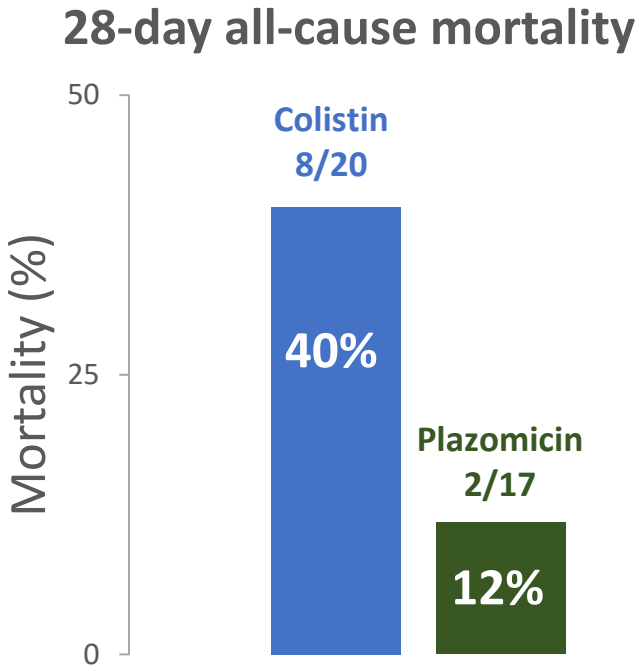


Figure adapted from slide 24 the Jan 2017 Achaogen corporate presentation. Downloaded 24 Feb 2017 from http://files.shareholder.com/downloads/AMDA-2JY46Z/3956962155x0x922829/80C50E00-4B27-4F84-B13F-55DE31AABA28/AKAO-Corporate-Deck-January-2017.pdf

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?*

	Migraine	Cancer	Human Infection	Animal Health
1. Durable cure is routine	No	No	*Yes*	*Yes*
2. Placebo is routinely acceptable	Yes	*No*	*No*	Yes
3. Existing agents lose utility over time → new agents always needed	No	No	*Yes*	*Maybe*
4. New agents are really for use…	Today	Today	*Tomorrow*[1]	Today

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!

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/).
2. See this cite for more on Animal Health issues: Page SW, Gautier P. Use of antimicrobial agents in livestock. Rev Sci Tech 31:145-88, 2012.

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)

Safety + (some) efficacy

The efficacy the world wants to see

*NI RCT: Non-Inferiority design Randomized Controlled Trial. See extended discussion of these trials in 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 65: 141-146, 2017.

Key Ideas: 2 of 3

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
  - Boucher H et al. "Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs." J Infect Dis 216: 228-36, 2017.
  - My blog notes on the 13 Apr 2017 + 5 May 2017 FDA workshops
  - EMA draft (2019) antibacterial guidance
  - Fleming TR, Ellenberg SS. "Evaluating interventions for Ebola: The need for randomized trials." Clin Trials 13(1): 6-9, 2016.
  - Cox E et al. "Needed: Antimicrobial development." NEJM 380: 783-5, 2019.

[1]Rex JH, Eisenstein BI, Alder J, Goldberger M, Meyer R, Dane A, et al. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. Lancet Infect Dis. 2013;13(3):269-75.

Key Ideas: 3 of 3

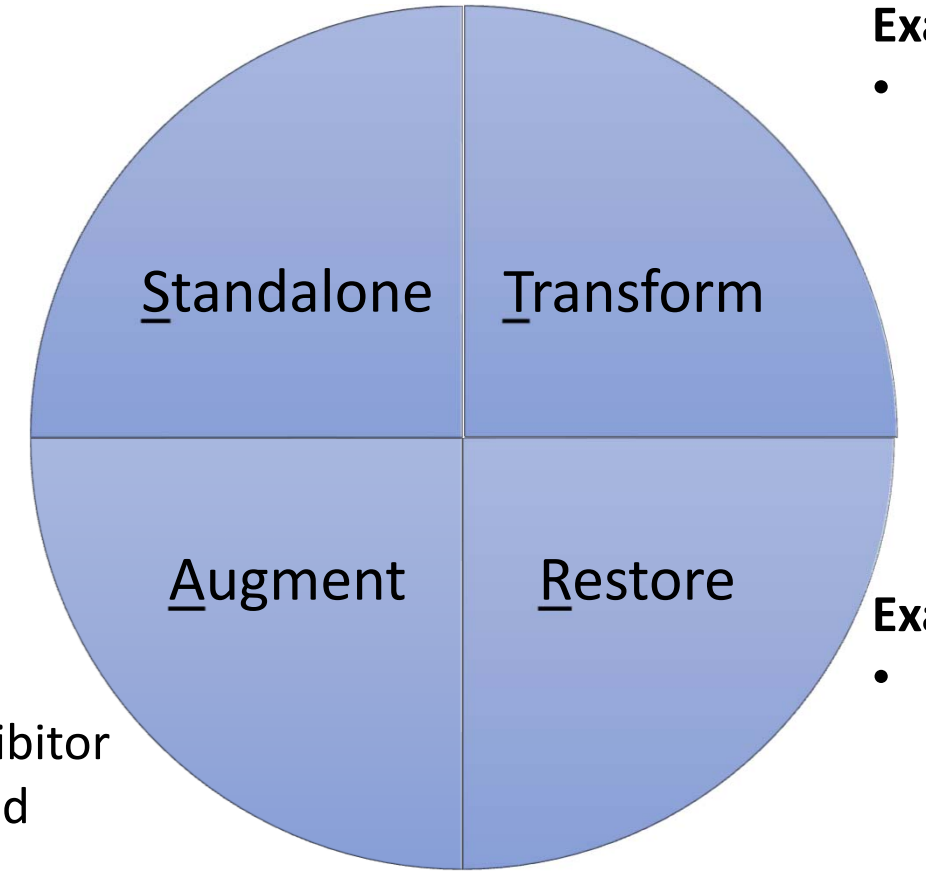
Non-traditional products

- 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[1]

Examples
- Penicillin
- Phage
- Lysins
- Antisense



Example[2]
- Gram-negative activity from colistin + approved Gram-positive antibiotic

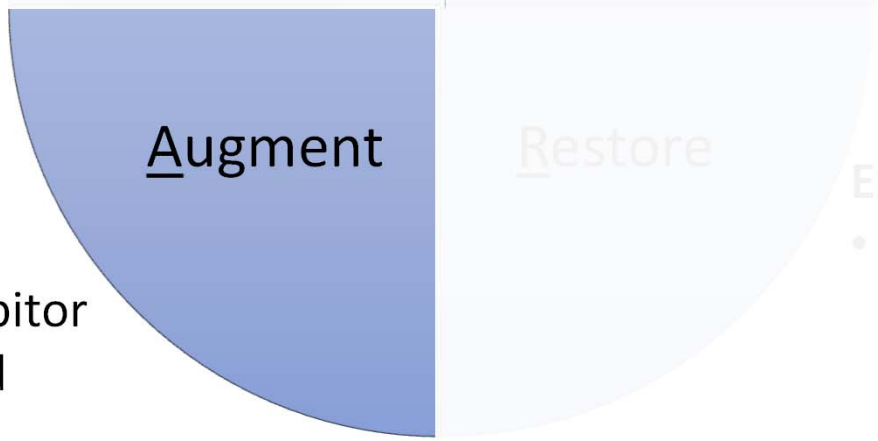
Example[2]
- Virulence factor inhibitor + approved antibiotic

Example[2]
- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

1. Rex, Fernandez-Lynch, Cohen, Darrow, Outterson, Designing development programs for non-traditional antibacterial agents. Nature Communications (invited paper, in review), 2019
2. The terms “Potentiator” or “Enhancer” have been used for products in all 3 of these categories

STAR: Four treatment archetypes[1]

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



Example[2]

- Virulence factor inhibitor + approved antibiotic

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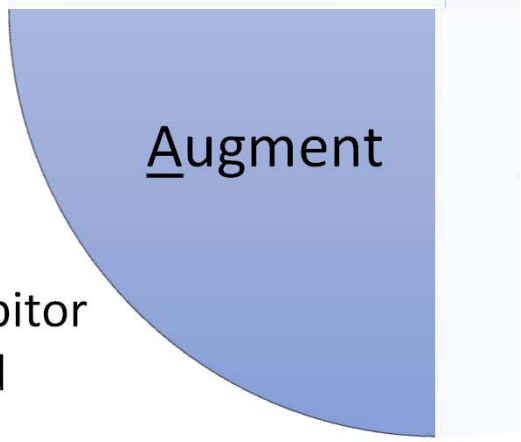

Example[2]

- 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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Antibiotic benefits go beyond simple use

Antibiotics are the fire extinguishers of medicine![1]

- **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.

DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

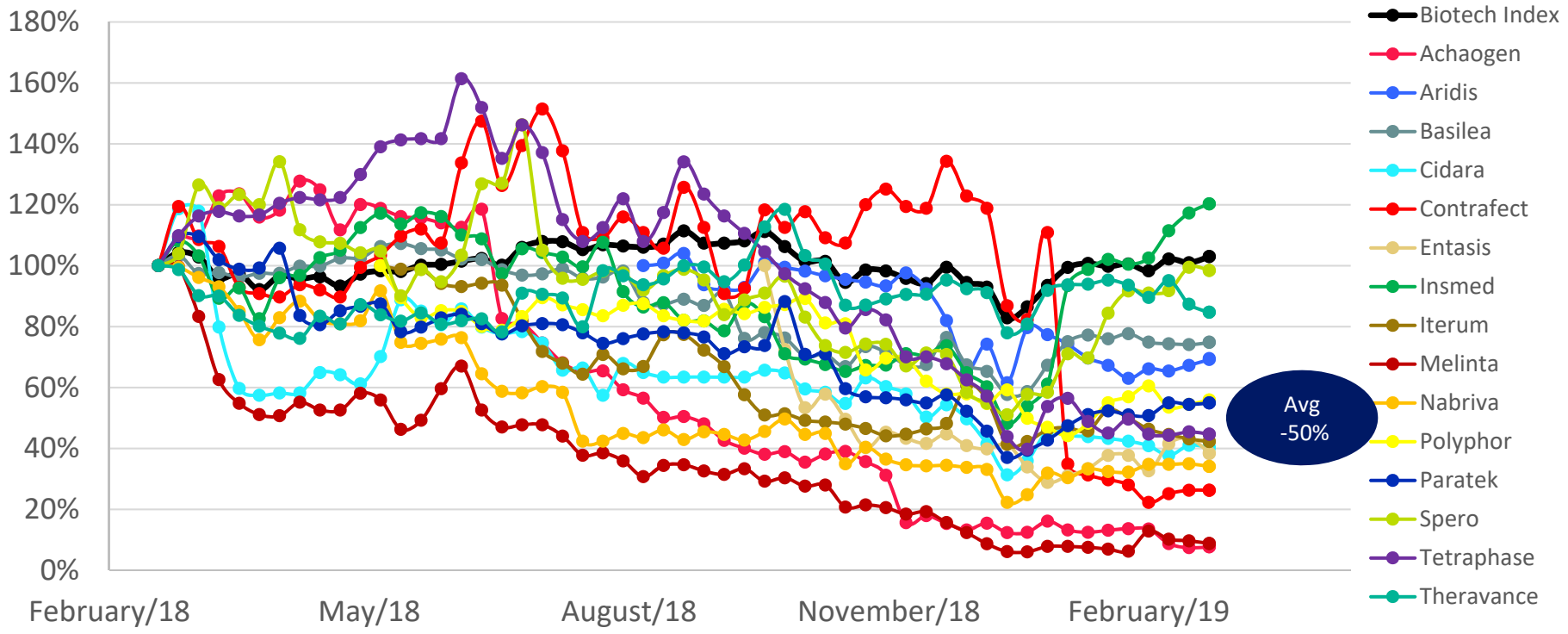
[1]Rex JH, Outterson K. Antibiotic Reimbursement in a Sales-Delinked Model: Context and a Benchmark-Based Global Approach. The Lancet Infectious Disease. 2016;16:500-5.

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

Slide courtesy Aleks Engel, Novo

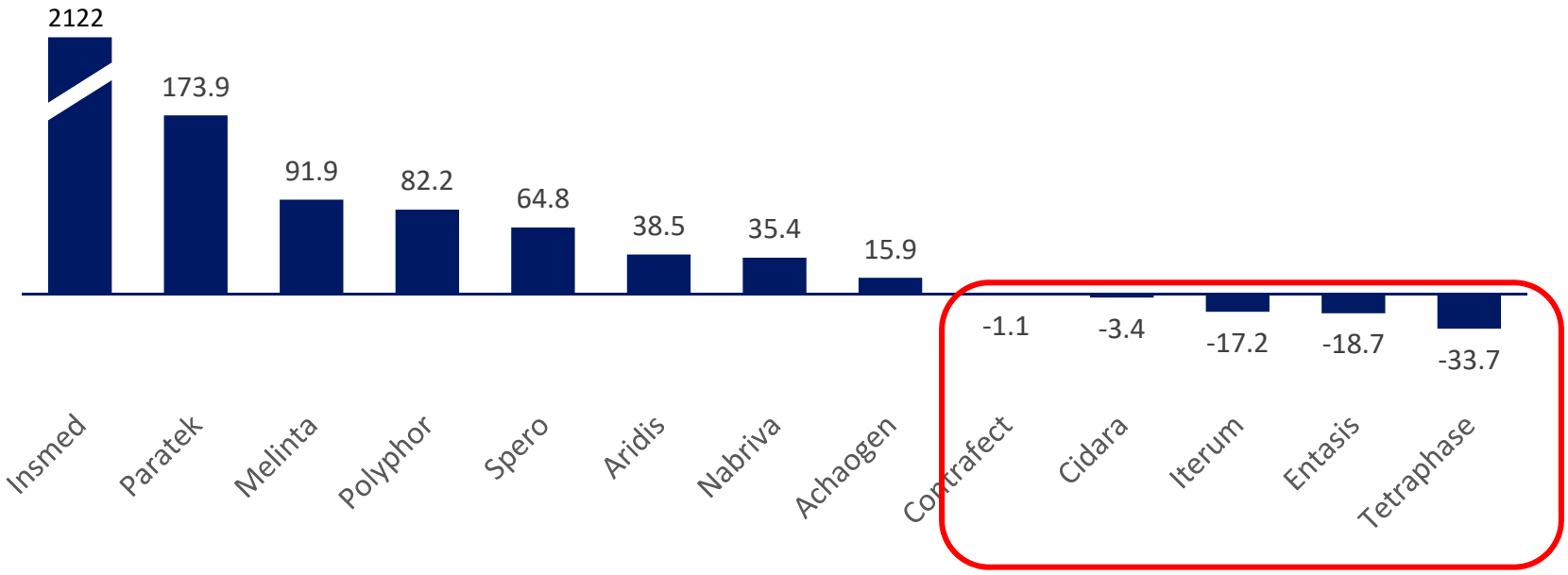
AVERAGE PUBLIC ANTI-INFECTIVE COMPANY SHARE PRICE HAS DROPPED BY 50% OVER THE LAST 12 MONTHS



Slide courtesy Aleks Engel, Novo

ENTERPRISE VALUE OF SEVERAL COMPANIES IS NEGATIVE

(USD millions)



Programs

Marketed	1	2	4					1					1
Ph 3				1	1	1	2			1	1		
Ph 2	2		1	1		2			1			2	
Ph 1	1			1	3	1	1	1				1	1

As of Feb 26, 2019

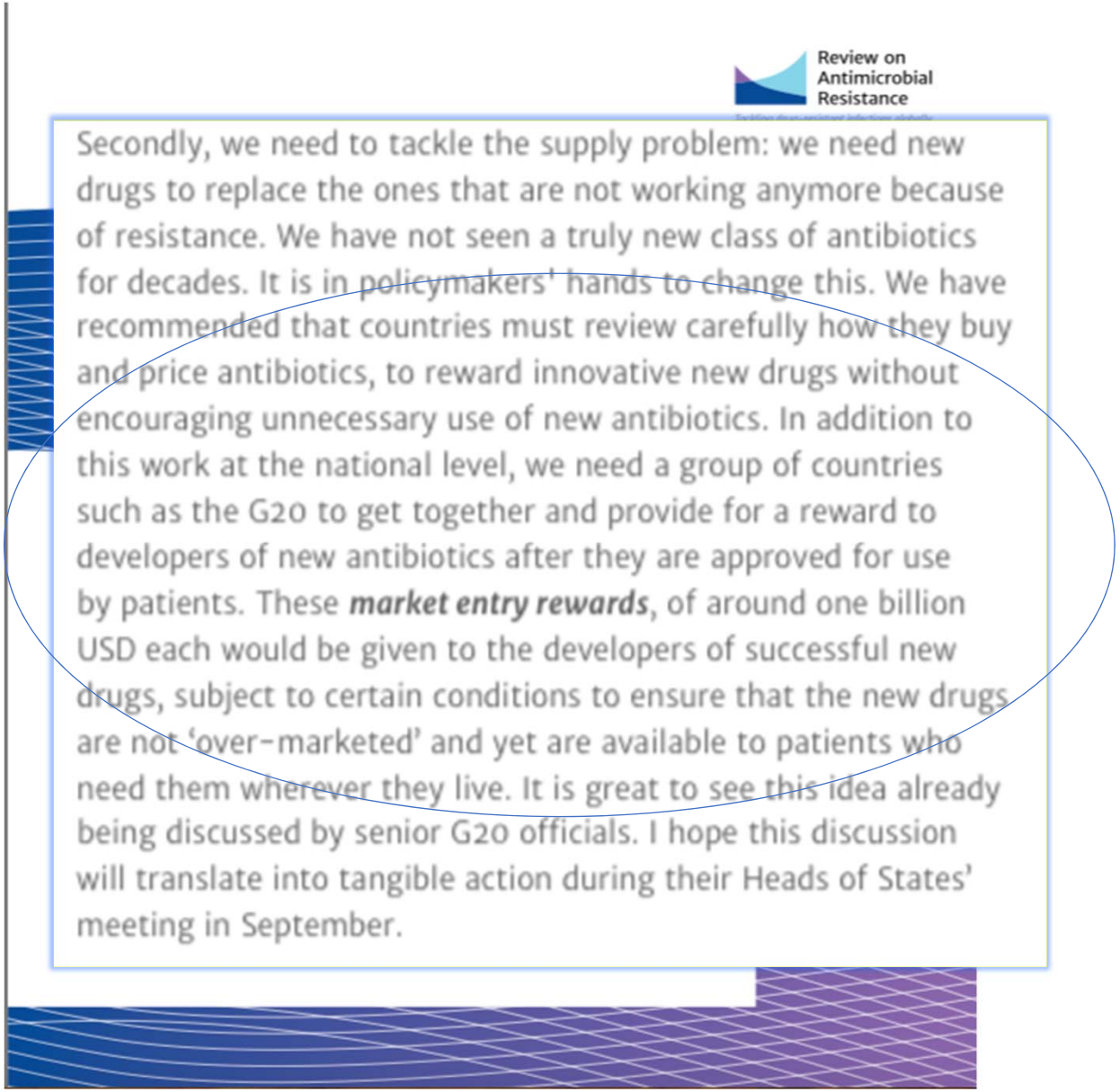
Many efforts to analyse and fix this

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

October 2014 – September 2017

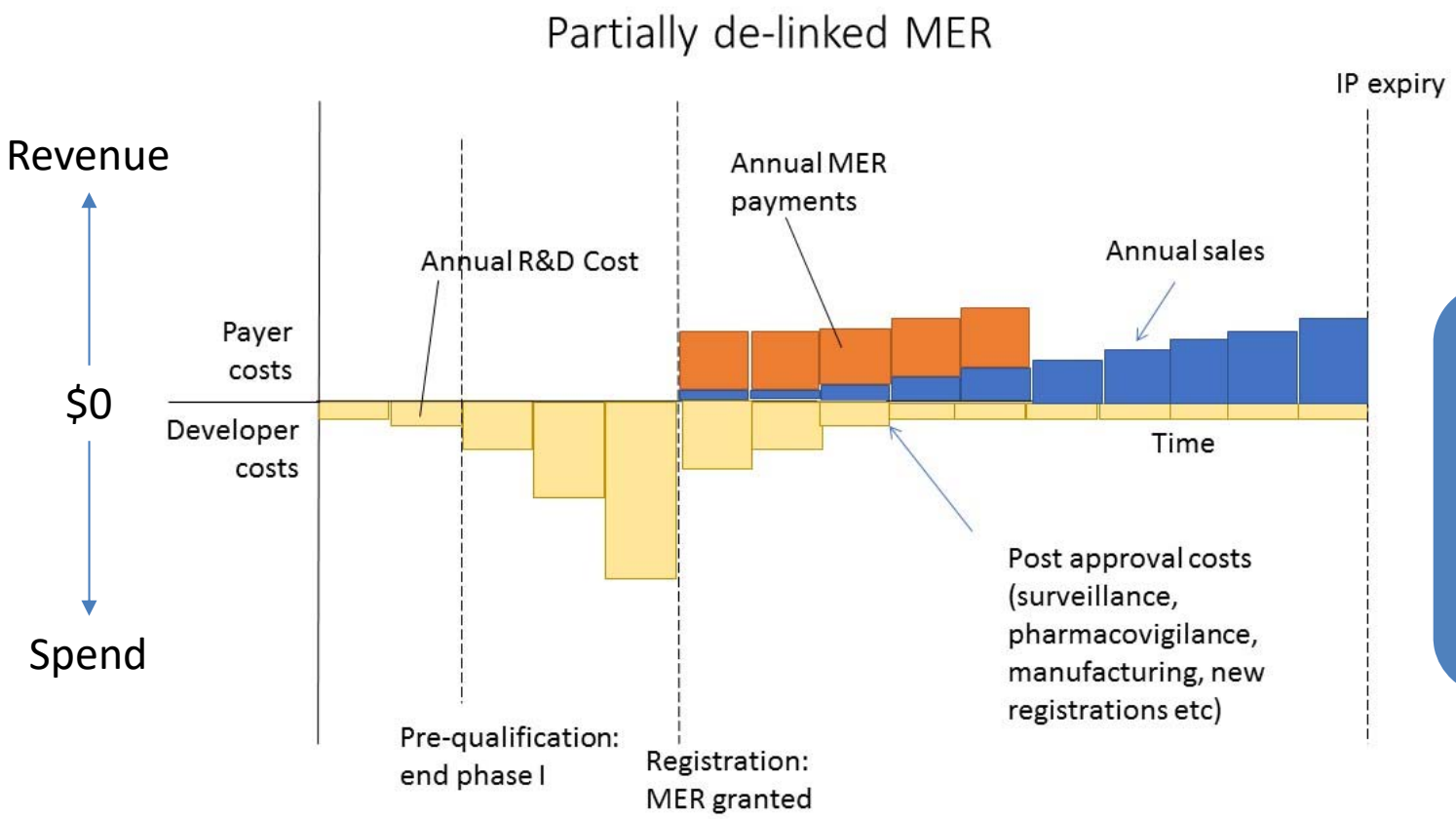
Key Idea:

- Market entry reward
- Payment for registration of an interesting new agent
- Delinks use from income



Slide concept adapted from Colm Leonard

Market entry reward



MER can be implemented via many different funding mechanisms

Ardal, C., J. A. Rottingen, A. Opalska, A. J. Van Hengel and J. Larsen (2017). "Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance." Clin Infect Dis 65(8): 1378-1382.

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:

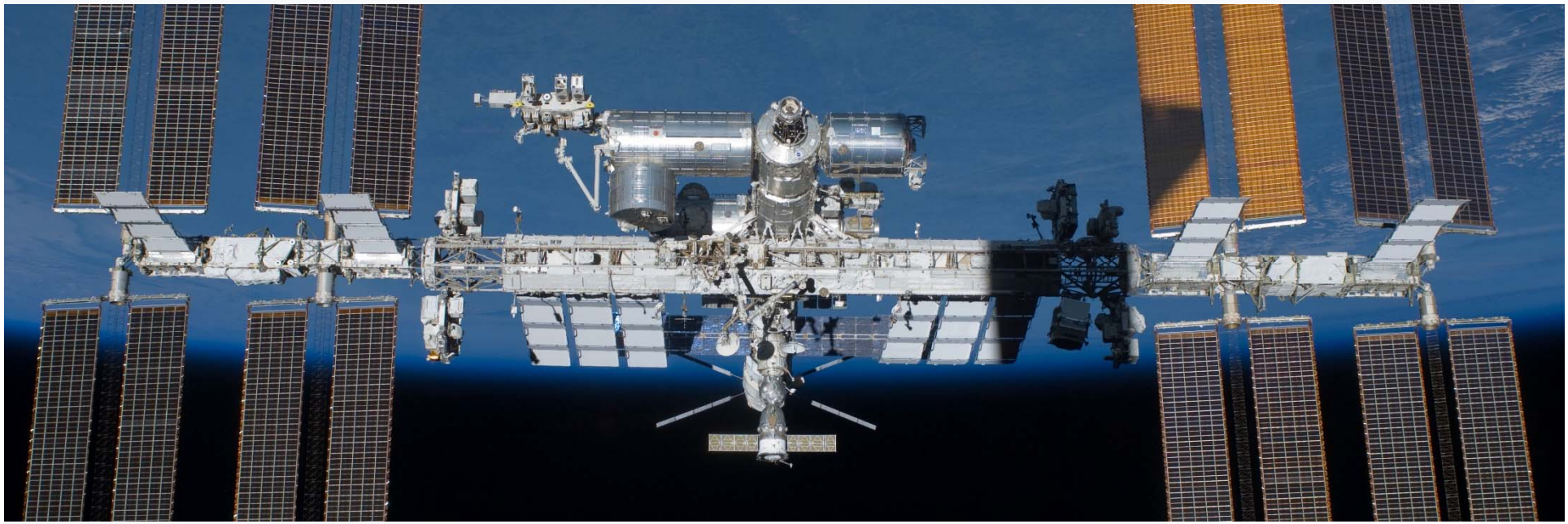
- to start at **USD 800 million per year in 2018,**
- increasing to **USD 1 billion per year in about 2020,** and
- to **USD 1.2 billion in about 2021,** including the USD 550 million/year spent as of 2017

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.