Funding, Filing, and Finance

Countering AMR - Nature Conference

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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

Agenda

- Funding and (sometimes) non-dilutive support
  - What's available?
- Filing
  - Recent events & future meetings
  - Three key ideas
- Finance
  - Payor models

Sources (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
  - Round 3 now open, next window is 1-8 June 2018

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

Sources (2 of 3)

- EC: Horizon 2020[1] & IMI[2]
  - Funds broadly but you need to dig deeply into their various calls: IMI Call 8 (Ebola), IMI Call 12 (vaccines)
  - 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
  - 8-9 Nov 17 meeting: Virtual Research Institute proposal
  - Call 8[3] in 2018 will be "Innovation against antibiotic-resistant bacteria: New targets, compounds & tools."
- 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
- Multiple national agencies (too many to list)

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/amr-in-focus-at-g-7-health-ministers-meeting-in-milan/

Sources (3 of 3)

- Novo's REPAIR fund: $165m over 5 years (EU only)
  - https://www.repair-impact-fund.com/
- VALUE-DX: IMI DRIVE-AB-like project for diagnostics
  - I can suggest contacts if you are interested
- VCs (jockey > horse): Path to success
  - 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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Recent events (1 of 2)

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

- 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 use of mortality and mortality-plus as endpoints. Supports study of VABP + ventilated HABP as a single group; non-ventilated HABP is different.
- 2 Aug 2017 FDA Unmet Need Guidance (final)
  - You need to read this one!

Recent events (2 of 2)

See my blog for all of these

- 5-8 Sep 2017 ASM-ESCMID meeting #2
  - CARB-X[ed] + GARDP Bootcamps: “What is a good hit?”, “CMC is pivotal!”, & “Clinical Microbiology”
  - Outstanding presentations by FDA, EMA, and UK NICE
    - Link is here (search for “site:amr.solutions fda ema nice”)
    - UK NICE esp. noteworthy: A major HTA has now made it clear that antibiotics need a different approach to HTA!
- 7 Nov 2017 FDA VRBPAC: Pfizer’s *S. aureus* vaccine
  - Excellent briefing book: Shows challenge of prevention
  - Q: Can one use apply to others? A: Hmm. Maybe not
- 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

http://amr.solutions/blog/updates-from-ema-fda-and-uk-nice-at-the-6-8-sep-2017-asm-escmid-antibiotic-development-conference

Future Meetings of Special Note

- 7-11 Jun 2018 (Atlanta): ASM Microbe
- 4-7 Sep 2018 ESCMID-ASM Conference (#3) on Drug Development for AMR (Lisbon)
  - Don’t miss this one!
- 6-14 Oct 2018 International Course on Antibiotics and Resistance (ICARe, Les Pensières, Annecy, France)
- 7-9 Nov 2018: Better Methods for Clinical Studies in Infectious Diseases and Clinical Microbiology: A Hands-on Workshop (Seville, Spain)
- Please do your homework! Come to these meetings!
  - 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 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 means something bad has happened: Plazomicin and CRE[1]

- In 2012-13, colistin was the only alternative for CRE. 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

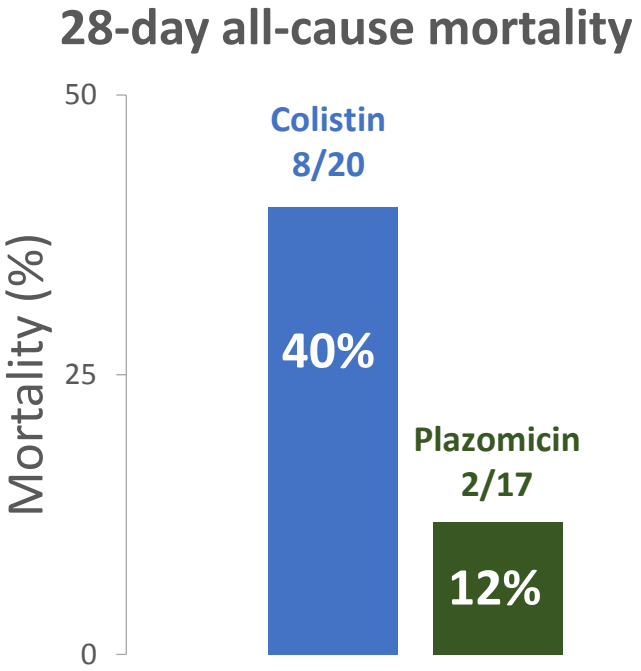

Figure adapted from slide 24 the Jan 2017 Achaogen corporate presentation. Downloaded 24 Feb 2017 from http://files.shareholder.com/downloads/AMDA-2JY46Z/3956962155x0x922829/80C50E00-4B27-4F84-B13F-55DE31AABA28/AKAO-Corporate-Deck-January-2017.pdf

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	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 salvage study for highly Resistant pathogens
  - Randomized vs. Best-Alternative Therapy (BAT) if possible, Open-label if N too small for this
- Example: Plazomicin initial registration program
  - NI RCT: 1x complicated UTI NI RCT vs. meropenem
  - Salvage: 1x study in CRE vs. colistin (prior slide)

*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.

Really narrow-spectrum agents

- This is the concept of "Tier C" pathways[1]
  - Rare pathogens, (only) MDR pathogens, rare diseases
  - Small trial programs, just barely (or not) powered
- Can this be done? Yes, but it's not an easy out
  - Do not think of this as simpler, faster, or cheaper
  - It's not (just) a regulatory hurdle – the strength of evidence will become frustrating
- See recent IDSA whitepaper and FDA workshops
  - Boucher et al. "Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs." J Infect Dis 216: 228-36, 2017
  - My blog notes: 13 Apr 2017 + 5 May 2017 workshops

[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.

Non-traditional products

- Products with interesting potential to augment
  - Virulence factor inhibitors, etc.
  - I would love to see success, but this is hard because…
- Challenge:
  - Must (in general) show NEW + SOC[1] beats SOC alone
- Prevention also has a superiority challenge
  - Again, frustratingly hard, can require very large studies
  - Reducing carriage does NOT work
  - Must show an effect on a subsequent infection
  - Must show this with best available prevention methods
  - See Nov 2017 Pfizer *S. aureus* vaccine FDA VRBPAC

[1]SOC = Standard of Care

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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

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.

DRIVE-AB is/was an effort to fix this

Goal: Develop new economic models to stimulate innovation, sustainable use, and equitable access of novel antibiotics to meet unmet public health needs.

October 2014 – September 2017

DRIVE-AB at a high level

The goal was to build real-world incentive models

- A foundation was laid:
  - A common language
  - Predictions of resistance
  - Value of an antibiotic
- These were used to construct a persuasive argument to undertake the necessary system changes at the national or supranational level.
- **Goal:** drive financing to maintain the necessary levels of antibiotic R&D over time while ensuring rational use.

DRIVE-AB: 4 types of incentive tools

These 4 were selected via an in-depth process

- Model identification (n=35)
- Internal evaluation
- Stakeholder feedback

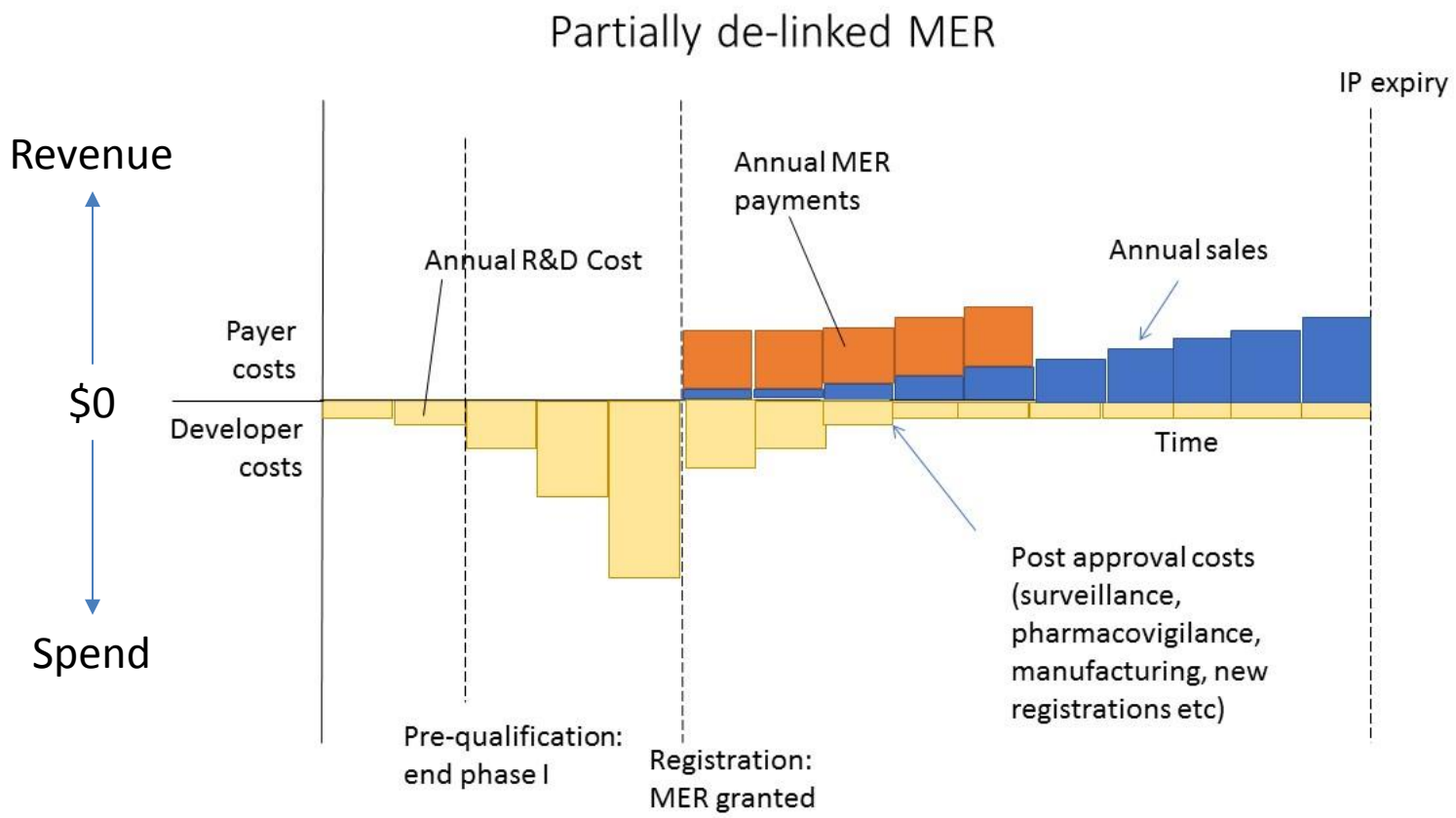
A. Grants - recommendation

- Continue to finance @ the current rate of ~USD 550 million per year and ideally increase by 50% to ~$750m/year
- Target early- and mid-stage grants until the pipeline becomes more robust
- Focus on priority pathogens
- Coordinate efforts

B. Pipeline coordinator - recommendation

- Continue to support (and expand support) for organizations like BARDA, CARB-X, and GARDP that target and eliminate priority, public health R&D gaps
- We should as a global community seek to balance and diversify the portfolio

C. Market entry reward: The idea



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.

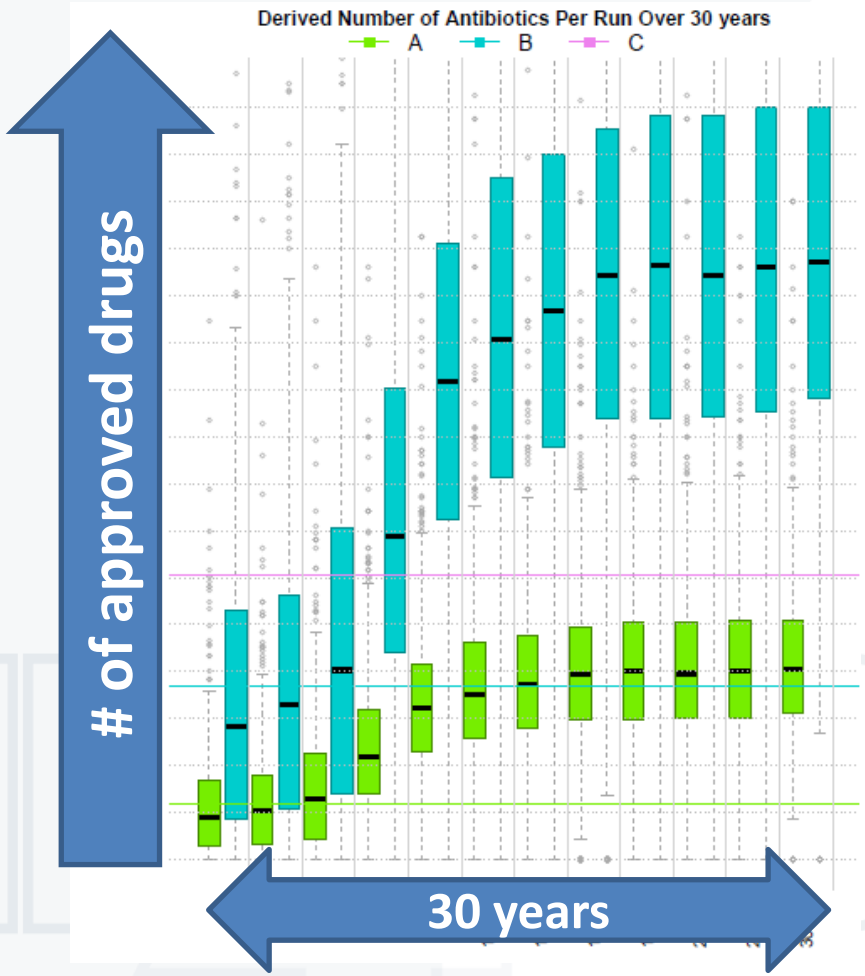
C. Why a market entry reward?

Antibiotic	Regulatory approval (US)	Sales in US in 2015 (millions)
Ceftazidime/avibactam	2015	35.8
Tedizolid phosphate	2014	37
Dalbavancin	2014	20.3
Oritavancin	2014	9.1
Fidaxomicin	2011	39.8
Ceftaroline fosamil	2010	118.5
Telavancin	2009	9.4

Source: Duke Margolis, 2017

C. Market entry reward – simulated results

- Exhaustive simulations
- Example at right
  - Green: Situation as is
  - Blue: $1B MER per antibiotic
- Effect
  - Quadruples number of new anti-Gram-negative antibiotics over 30 years



C. Market entry reward - recommendation

- Implement a market entry reward for a 20-year time period
- Can start with a three- to five-year pilot
- Big debates
  - What is an antibiotic worth? Why?
  - Are all antibiotics worth the same amount? If not, what creates value within a MER-based scheme?
  - These questions are not (yet) fully answered, but serious conversations are happening now

D. Long-term continuity model

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia ☆

Céline Pulcini [a,*], Simone Mohrs [b], Bojana Beovic [c], Inge Gyssens [d,e], Ursula Theuretzbacher [f], Otto Cars [b] on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP), ReAct Working Group on Old Antibiotics [1]

The availability of 'forgotten antibiotics' has worsened since 2011.

in 13 countries and decreased in 17. In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of 'forgotten antibiotics' has worsened since 2011. Urgent measures are needed to ensure better availability of these antibiotics on a global scale as a conservation measure to ensure sustainable and responsible use of antibiotics.

Pop quiz

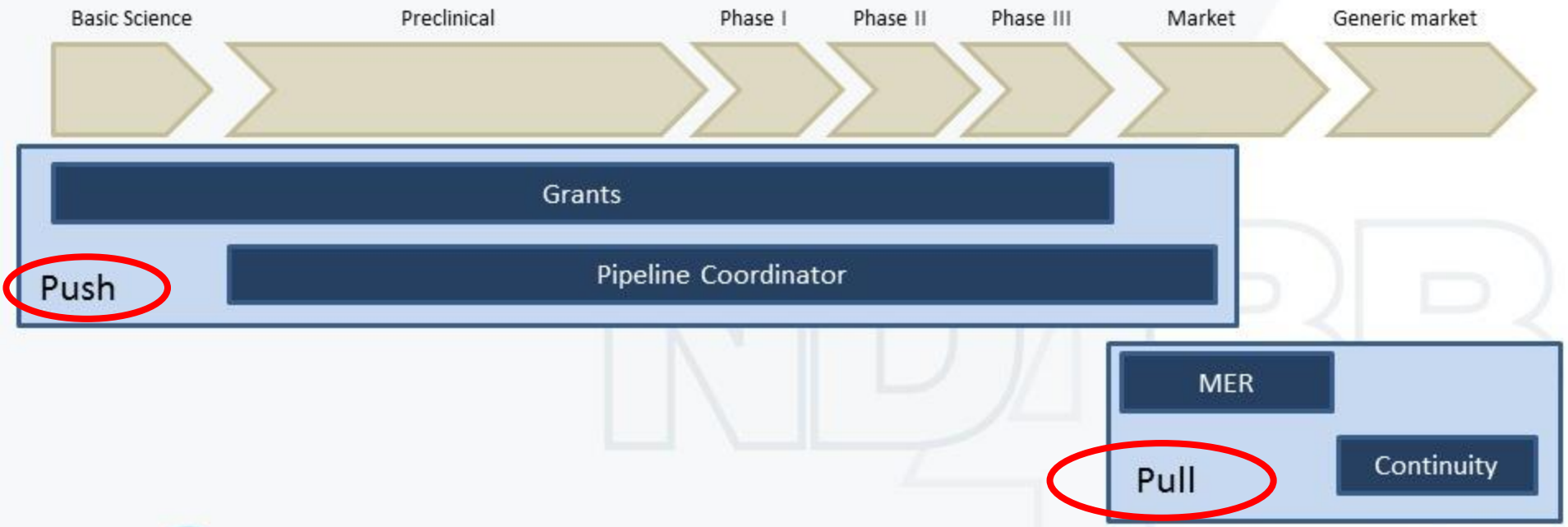
- What does it cost per year to maintain the plant that makes a sterile injectable so that you can make at least 1 vial per year?
- Please consider
  - Cost for the building
  - Cost for the staff
  - Cost for record-keeping
  - Cost for destroying unused materials that go beyond their expiration date

D. Continuity model - recommendation

- Test a joint procurement process of an antibiotic with a fragile supply chain but included as an “access” antibiotic on WHO’s Essential Medicine List (e.g., benzylpenicillin)
- Aside: Testing a long-term supply continuity model can also test the implementation of a national market entry reward.

DRIVE-AB: Summary of incentives

- It's a balanced ecosystem
- Push & pull are needed



Implication: Novelty above all

- 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?

We estimate the global cost of implementing our recommendations

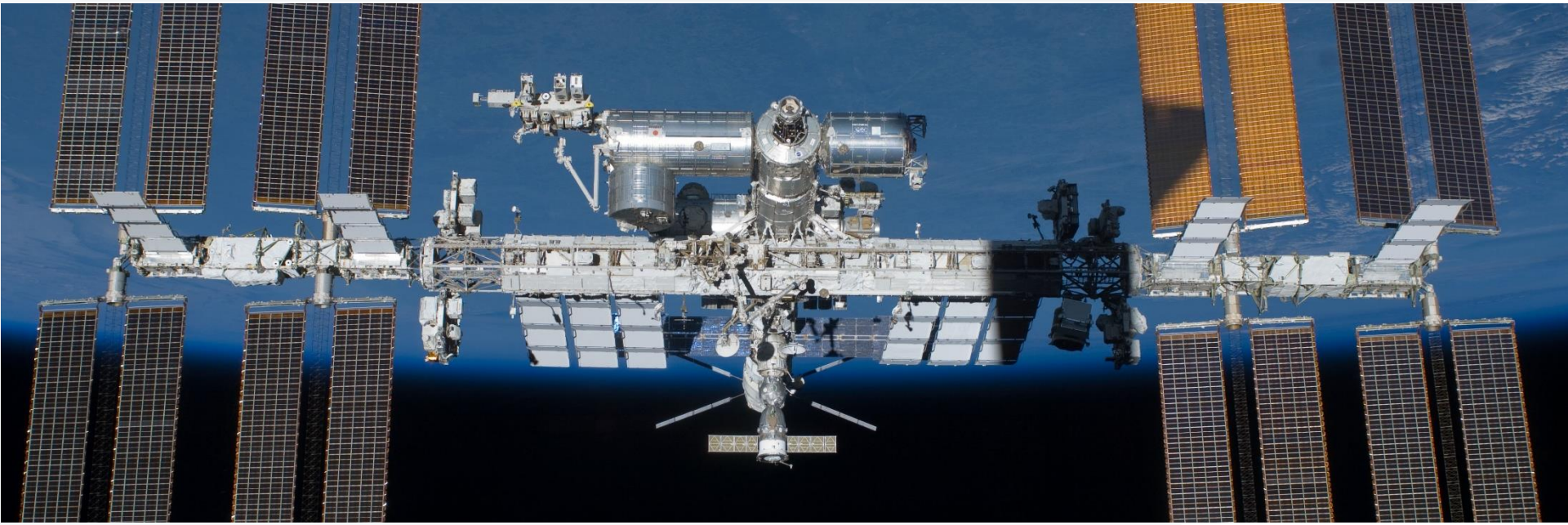
- to start at **USD 800 million per year in 2018,**
- increasing to **USD 1 billion per year in about 2020,** and
- to **USD 1.2 billion in about 2021,** including the USD 550 million spent today.

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 antibiotics have equal value
  - Program design must also be carefully considered

Thank you!

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13 Nov 2017 Superbugs & Superdrugs USA (Iselin, NJ)

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Slides happily shared – just drop me a note