DRIVE-AB – Driving Re-investment in R&D and Responsible Antibiotic Use *with a brief comment on CARB-X*

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7 Sep 2017: ASM-ESCMID Antibacterial Conference

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Summary of materials from a concurrent meeting in Brussels

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!

- **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 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: Oct 2014 – Sep 2017

- DRIVE-AB overview
- DRIVE-AB workplan: 4 big elements
- Incentive models in detail
- Conclusions

What is/was DRIVE-AB?

- **DRIVE-AB** is/was a 3-year public-private consortium funded by IMI composed of **16 public and 7 private partners from 12 countries**.

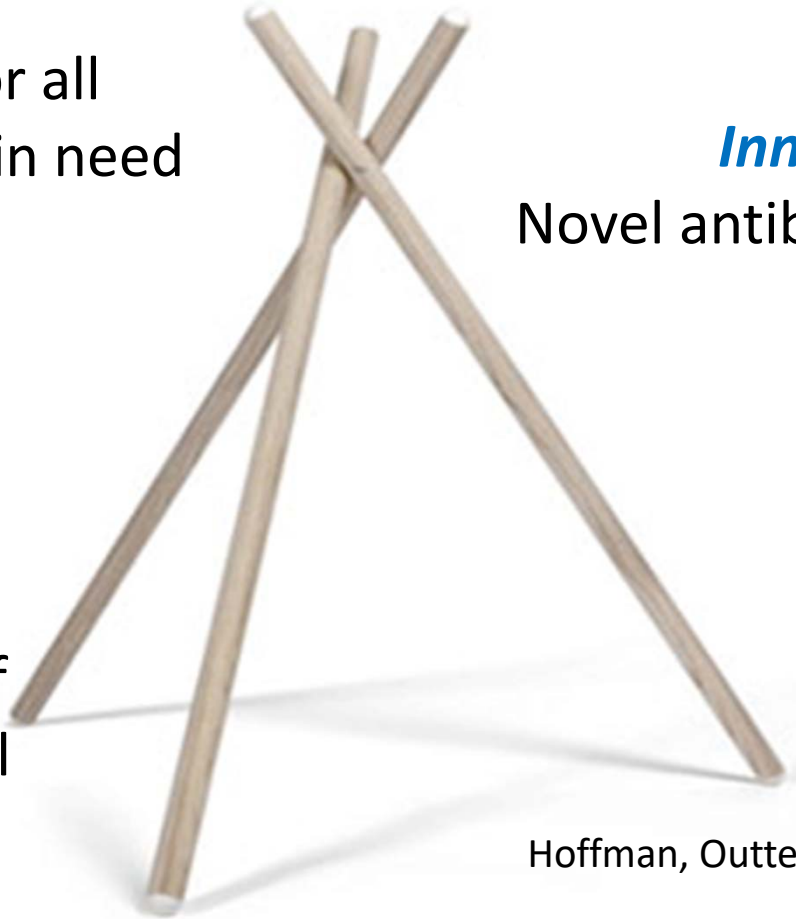
Astellas Pharma Europe
AstraZeneca
Merck
F. Hoffmann-La Roche
GlaxoSmithKline R&D
Pfizer
Sanofi-Aventis R&D

DRIVE-AB: Core principles

The Antibiotic Tripod

Access for all patients in need

Innovation Novel antibacterial drugs



Sustainable use of novel antibacterial drugs

Hoffman, Outterson et al. (2015)

Agenda

- DRIVE-AB overview
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1. A common language

Work Package 1A provided

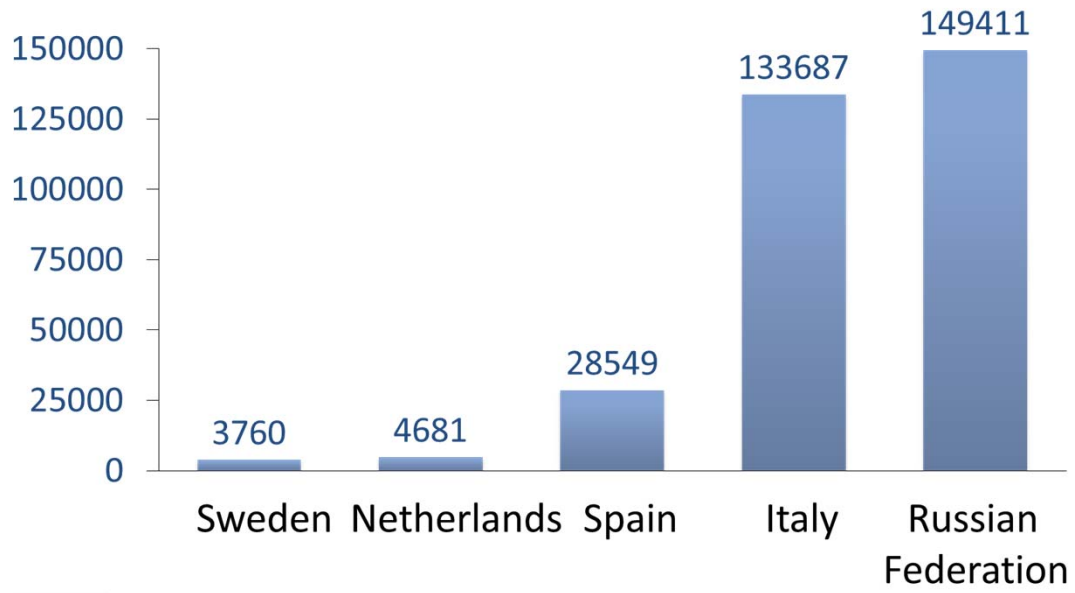
- A common terminology and framework for shared understanding of responsible and sustainable antibiotic use.
- Broadly accepted metrics to monitor responsible use which could be used to inform stewardship programs, improve use of existing antibiotics, and prevent inappropriate use of newly developed molecules

2. Modeling resistance

Work Package 1B developed models to describe

- Early signals for new emerging AMR and
- Predict the spread of resistant organisms

Example: Cases in 2024 of 3rd gen ceph-R *E. coli*



3. The value of an antibiotic

Work Package 1C developed new approaches to antibiotic value that would

- Capture value to patients,
- Capture value to the health care system, and
- Capture value to society.

These data

- Inform health technology assessments,
- Underpin the incentive arguments, and
- *Are potentially a very big deal!*

Recommendations for antibiotic HTA

Value assessment should

1. Be at the population level
2. Include a sensitivity analysis of the impact of resistance to the new antibiotic initially and over time
3. Go beyond direct costs & benefits to consider:
   a. Indirect benefits from avoided transmission
   b. Diversity benefits from the protective effects on existing antibiotics currently in use

4. Incentive models

Work Package 2 focused on incentive models

- It built on WPs 1A, 1B, 1C
  - A common language
  - Predictions of resistance
  - Value of an antibiotic
- It used their data 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.
- *Let's look more closely at these results…*

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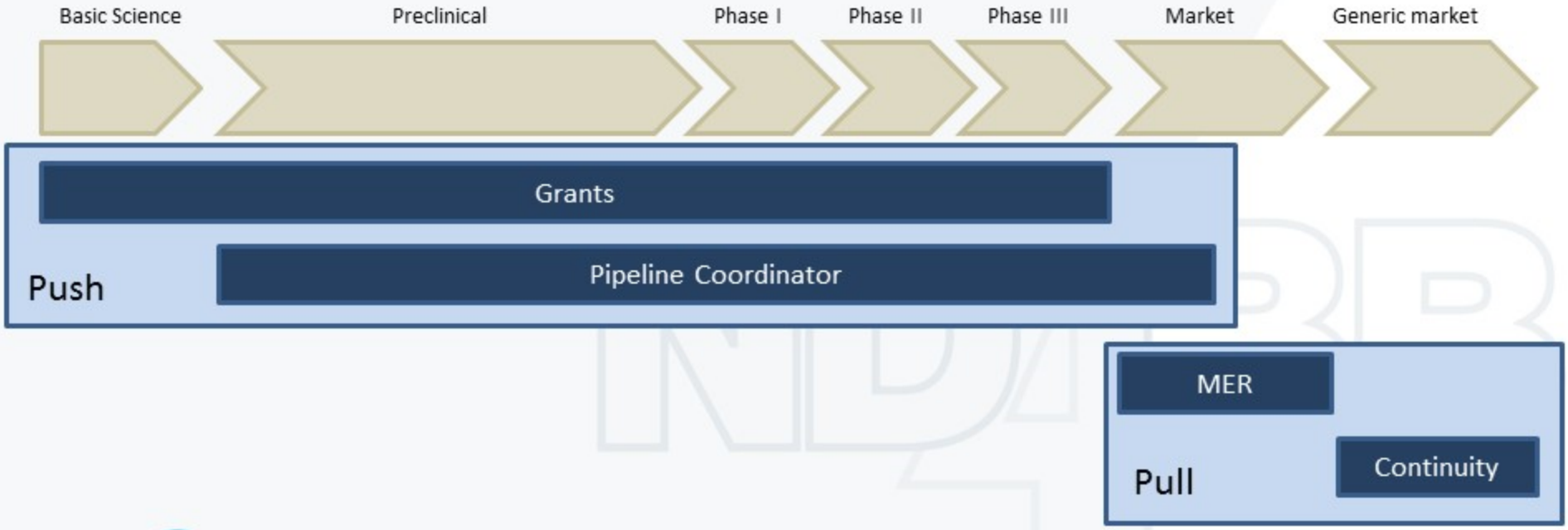
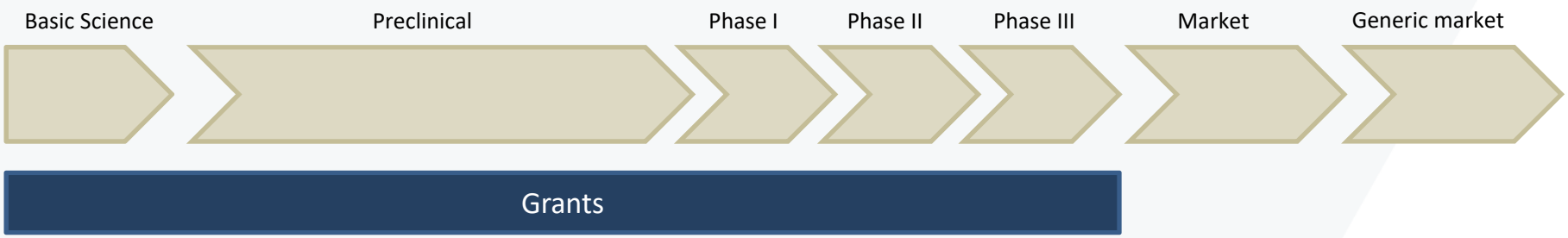
DRIVE-AB: 4 types of incentive tools

Methods:

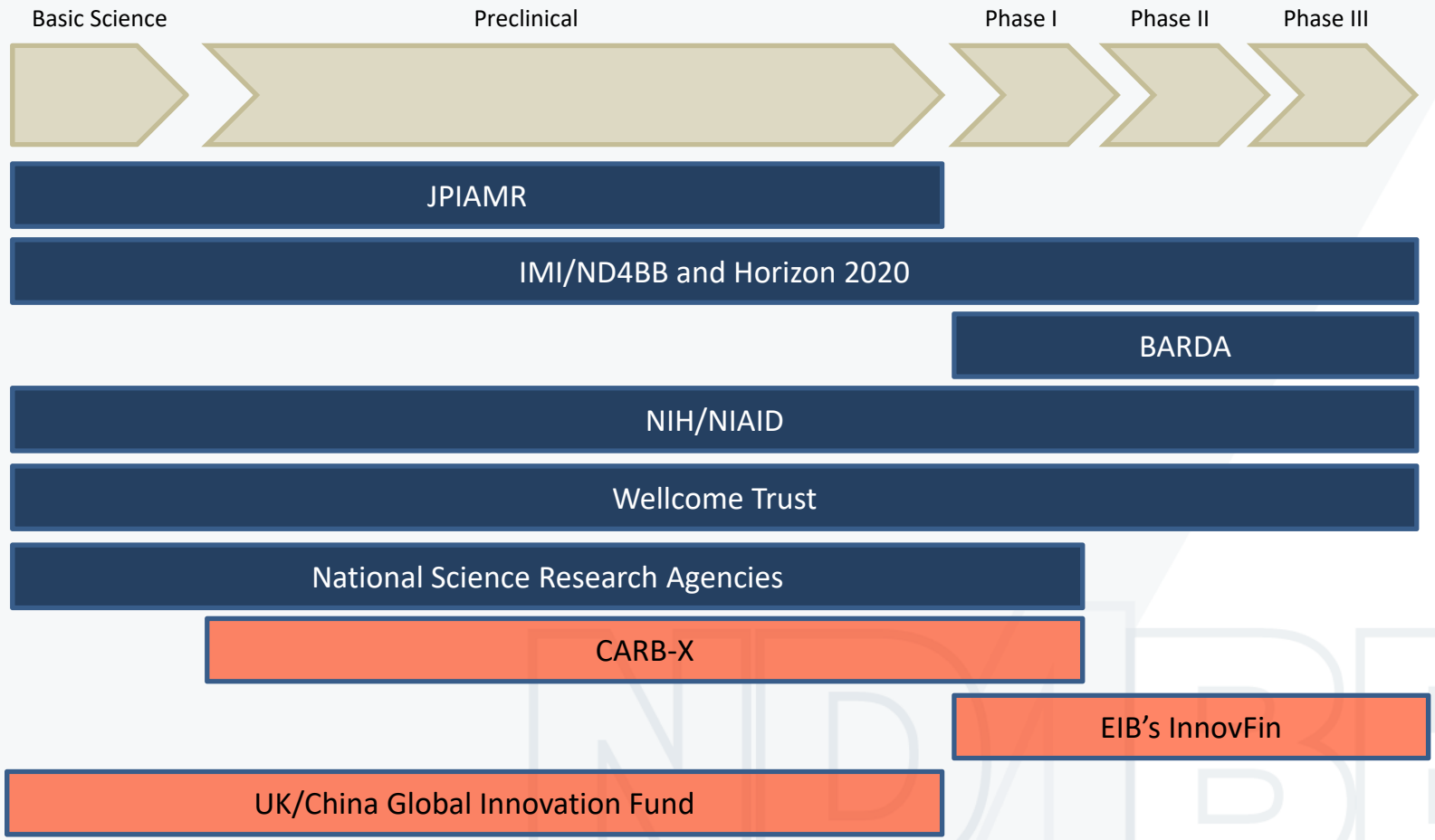
- Model identification (n=35)
- Internal evaluation
- Stakeholder feedback



A. Grants


Basic Science
Preclinical
Phase I
Phase II
Phase III
Market
Generic market
Grants

A. Grants



Existed prior to 2016

Recently launched

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

The race against superbugs

Investing to develop new antibiotics and other life-saving products to treat and prevent drug-resistant bacterial infections

CARB-X

Xccelerating global antibacterial innovation

Global reach at end of Year 1: 368 applications. 18 funded projects. 6 countries. $42m committed. $53m contingent on milestones

North America

Forge Therapeutics
San Diego, CA

Cidara Therapeutics Inc.
San Diego, CA

Achaogen Inc.
South San Francisco, CA

Contrafect Corporation
Yonkers, NY

VenatoRx Pharmaceuticals
Malvern, PA

Spero Therapeutics LLC
Cambridge, MA

Visterra Inc.
Cambridge, MA

Tetraphase Pharmaceuticals Inc.
Watertown, MA

Entasis Therapeutics Inc.
Waltham, MA

Microbiotix Inc.
Worcester, MA

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Europe and Asia

Iterum Therapeutics Ltd.
Dublin, Ireland

Proteus IRC
Edinburgh, Scotland

Redx Pharma Plc
Alderley Park, UK

Oppilotech Ltd.
London, UK

Eligochem Ltd.
Sandwich, UK

Antabio
Labège, France

Debiopharm International S.A.
Lausanne, Switzerland

Bugworks Research India Pvt Ltd.
Bangalore, India

CARB-X

Great science knows no boundaries

Powered by CARB-X

18 projects:

- 8 new classes
- 5 non-traditionals
- 10 new targets
- 1 rapid diagnostic

Company/ Research Team	Project	Novelty*			Project description	Urgency/ Priority**	Bacteria Targeted / Stage of Early Development			
		New Class	Non-traditional	New Target			Hit to Lead	Lead Optimization	Pre-Clinical	Phase 1
Achaogen	AKAO-LpxC	✔		✔	LpxC Inhibitor	✔	*Pseudomonas aeruginosa*			
Antabio	PEI		✔	✔	Pseudomonas Elastase inhibitor	✔	*Pseudomonas aeruginosa*			
Bugworks Research	Gyrox	✔			Gyrase-topoisomerase inhibitor	✔	Gram-negative activity			
Cidara Therapeutics	CD201		✔	✔	Bifunctional immunotherapy	✔	Acinetobacter + *P. aeruginosa* + Enterobacteriaceae			
ContraFect	Gram-negative lysins		✔	✔	Recombinant lysin protein	✔	*P. aeruginosa*			
Debiopharm	Debio 1453	✔		✔	Narrow-spectrum inhibitors of FabI	✔	*Neisseria Gonorrhoeae*			
Eligochem	Helical AMP	✔			Helical Antimicrobial Peptide	✔	Gram-negative activity			
Entasis Therapeutics	ETX0282 CPDP				Oral Gram-negative combination	✔	Gram-negative activity			
Forge Therapeutics	FG-LpxC	✔		✔	LpxC Inhibitor	✔	Gram-negative activity			
Iterum	Sulopenem				Oral and IV penem	✔	Gram-negative activity			
Microbiotix	T3SS Inhibitor		✔	✔	Virulence modifier	✔	*Pseudomonas aeruginosa*			
Oppilotech	LPS	✔		✔	Targets synthesis of LPS	✔	Gram-negative activity			
Redx Pharma	NBTI	✔			Dual-acting topoisomerase inhibitor	✔	Acin. + *P. aerug* + Enterobacteriaceae			
Spero Therapeutics	SPR741			✔	Potentiator	✔	Gram-negative activity			
Tetraphase Pharm	TP-6076				Next-generation tetracycline	✔	Acinetobacter + Enterobacteriaceae			
VenatoRx	VNRX-PBP	✔			ß-lactamase Resistant PBP Inhibitor	✔	Entero-bacteriaceae			
Visterra	VIS705		✔	✔	Antibody-drug conjugate	✔	*Pseudomonas aeruginosa*			

Company/ Research Team	Project	Project description	Development Stage			
			Feasability Demonstration	Optimization and Preparation for Development	Product Development	System Integration and Testing
Proteus	Rapid POC Diagnostic	Optical bacterial imaging	POC Diagnostic			

*Novelty characterizations of new class and new target are established by CARB-X following the Pew Charitable Trusts pipeline analysis model. Pew defines a novel chemical class as a group of antibiotics that share a new common core molecular structure. Non-traditional products include lysins and monoclonal antibodies.

** Urgent and priority drug-resistant bacteria are determined by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).
✔ Urgent/Critical priority ✔ Serious/High priority ✔ Serious/Medium priority.
Stage of development is approximate as of July 2017.

CARB-X
Xccelerating global antibacterial innovation

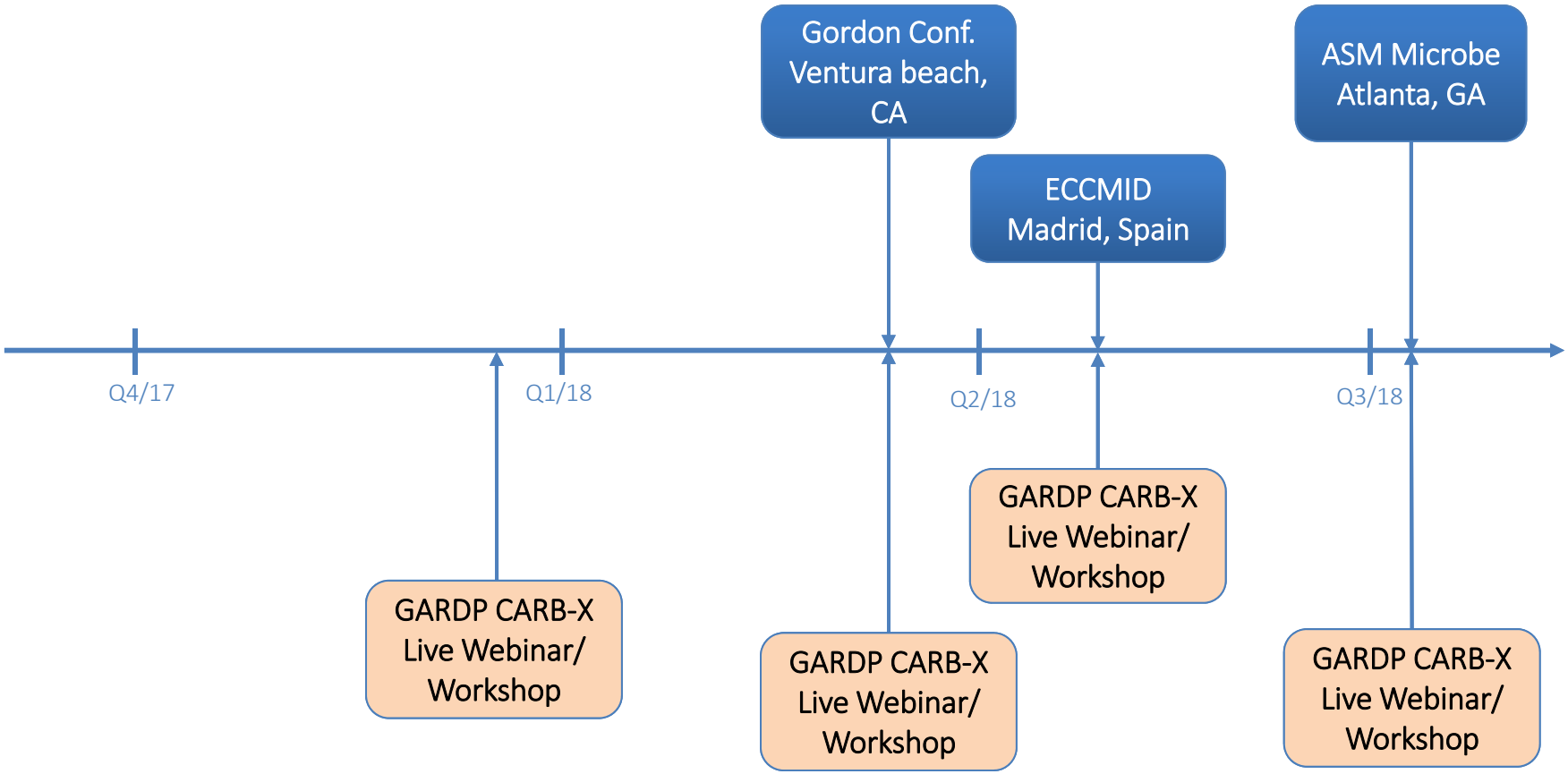
www.CARB-X.org

CARB-X^ed

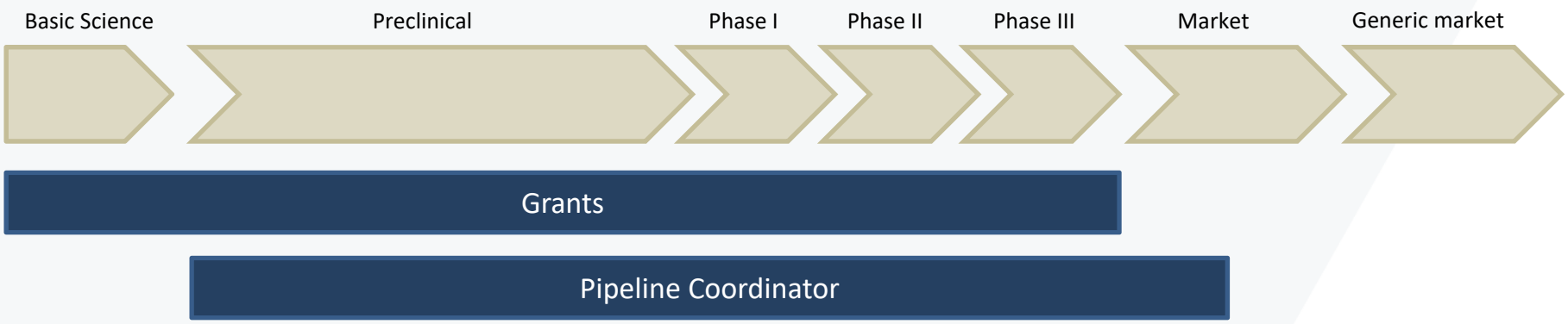
GARDP
Global Antibiotic Research & Development Partnership
A joint DNDi / WHO initiative

- Our goal
  - Create ways to share knowledge and insight regarding drug R&D
  - The approach will encompass live events, web-based events, and perhaps more
  - Antibiotic Bootcamps #1 and #2 (Tuesday) were examples. Bootcamp #3 is later today!
  - Events recorded for web-based replay
  - 2018 live events at Gordon Research Conference, ASM Microbe, ESCMID, and perhaps more

Look for GARDP + **CARB-X**[ed] at these events…



B. Pipeline Coordinator



B. Novel antibiotic candidates

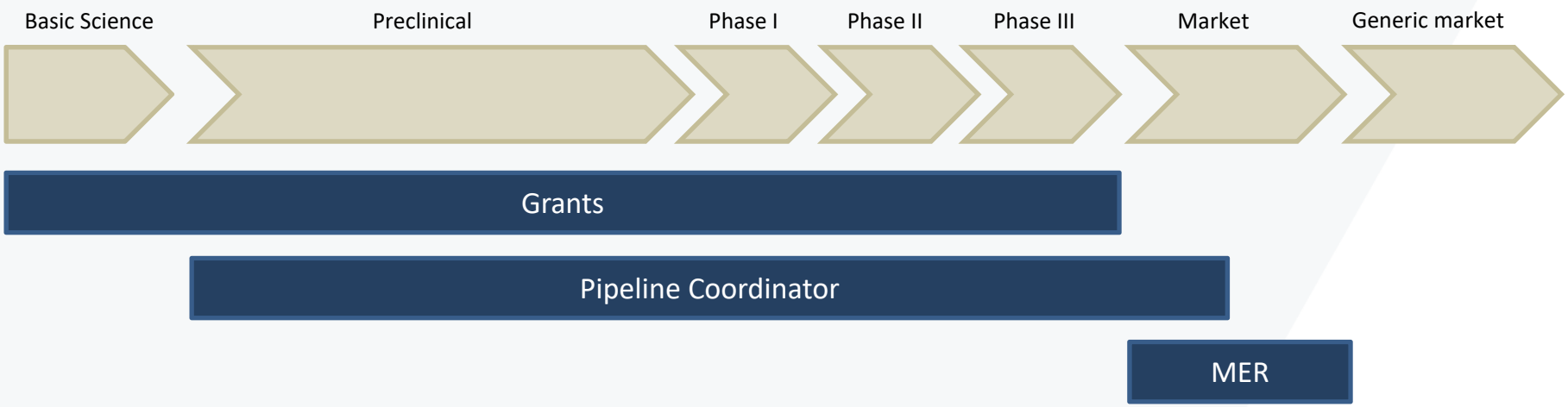
Bacteria (WHO category)	WHO (2017)	# in clinical dev	# likely to register
Acinetobacter baumannii, carbapenem-R	Critical	4	~1
Pseudomonas aeruginosa, carbapenem-R	Critical	3	~1
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	9	3-4
Enterococcus faecium, vancomycin-R	High	9	~4
Staphylococcus aureus, methicillin-R, vancomycin-I/R	High		
Helicobacter pylori, clarithromycin-R	High	0	0
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High	2	~0.6

Candidate tallies per WHO pipeline review (publishing soon). Likelihood of success using industry standard estimates (Czaplewski 2016).

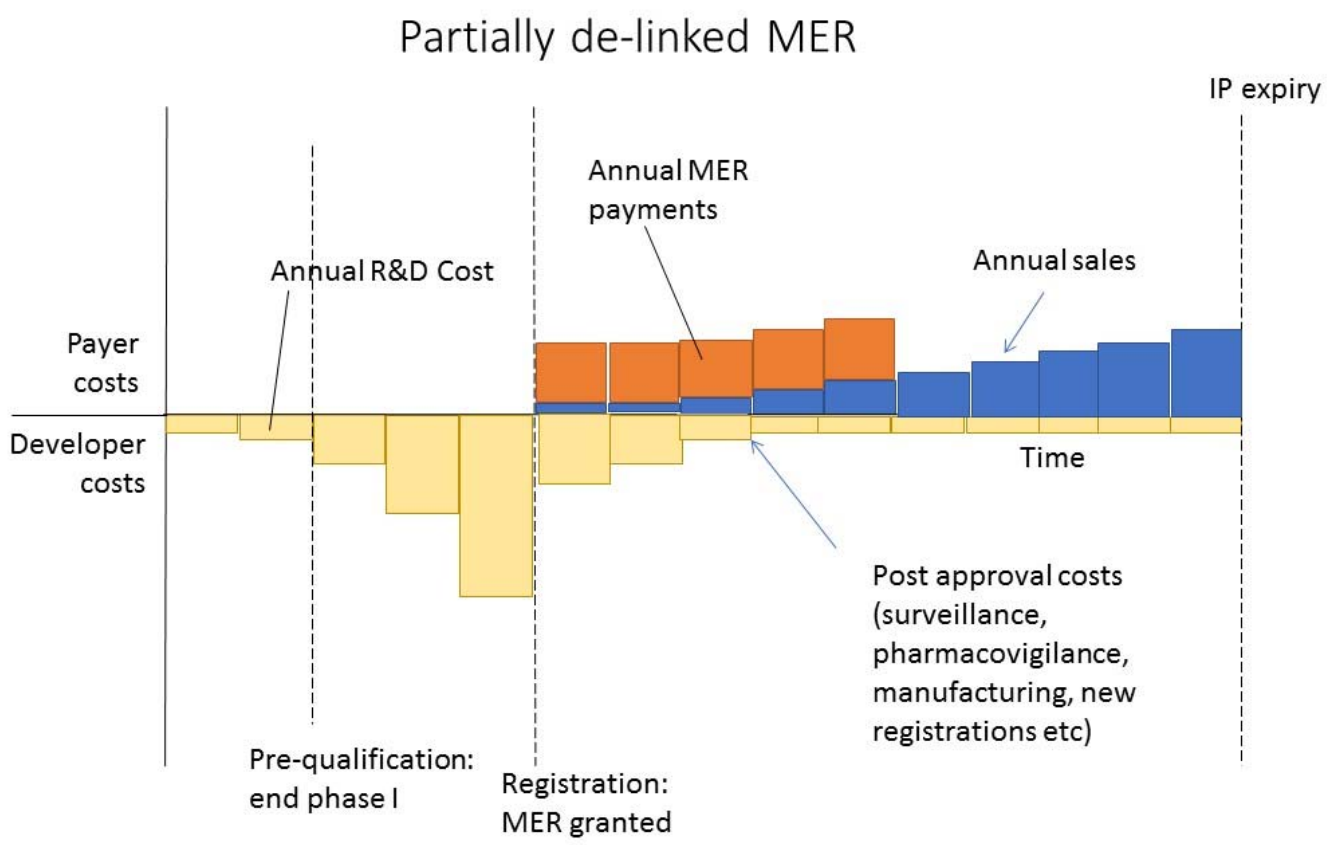
B. Pipeline coordinator - recommendation

- 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 (MER)



C. Market entry reward: The idea



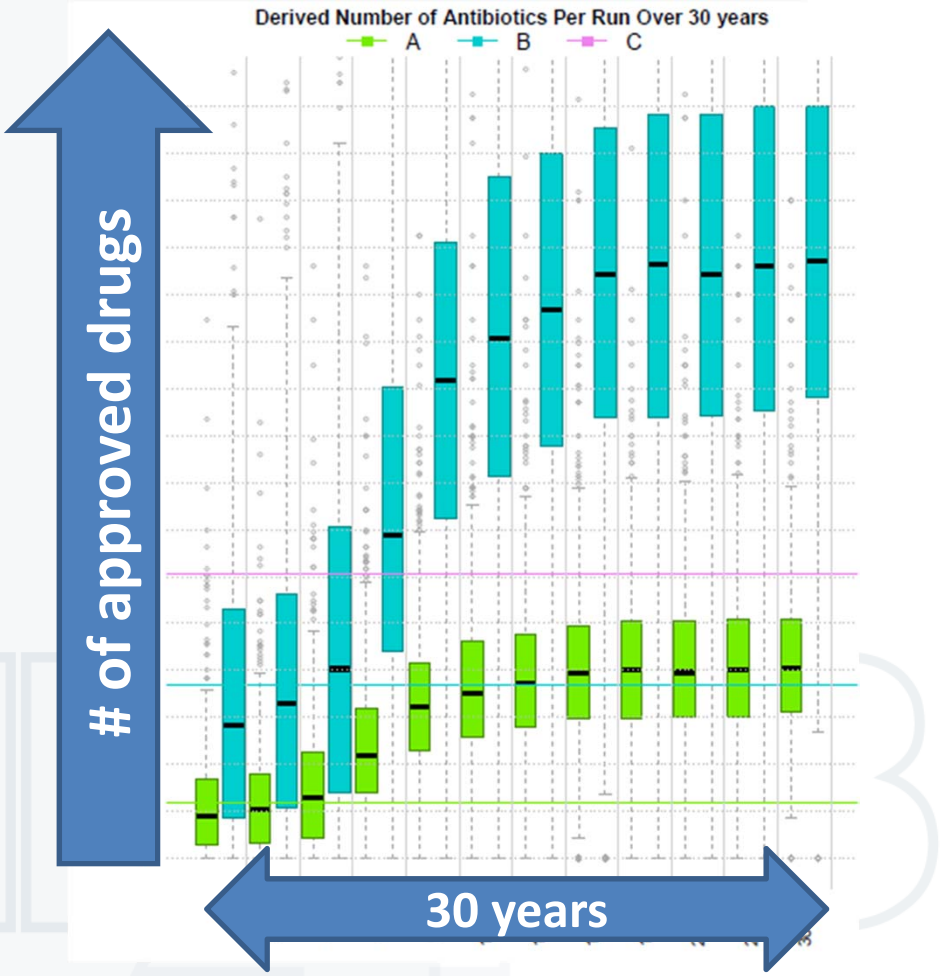
C. Why a market entry reward?

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

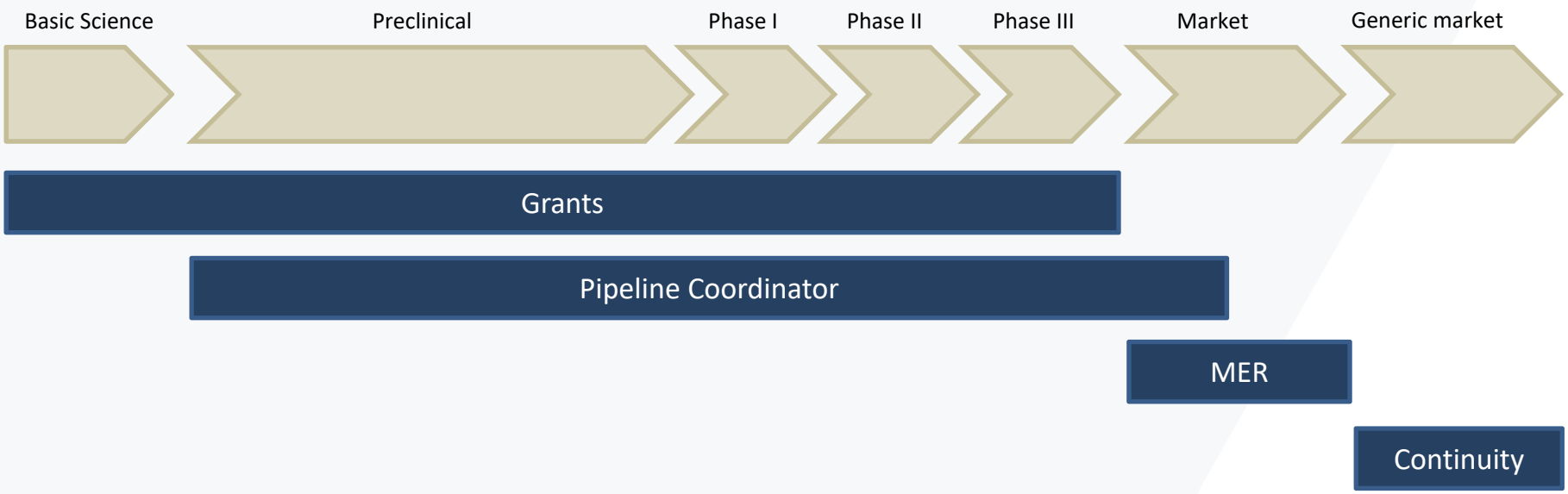
- Exhaustive simulations
- Example at right
  - Green: Situation as is
  - Blue: $1B MER per antibiotic
- Effect
  - Quadruples number of new anti-Gram-negative antibiotics over 30 years



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



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]

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.

"In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of 'forgotten antibiotics' has worsened since 2011."

Pop quiz

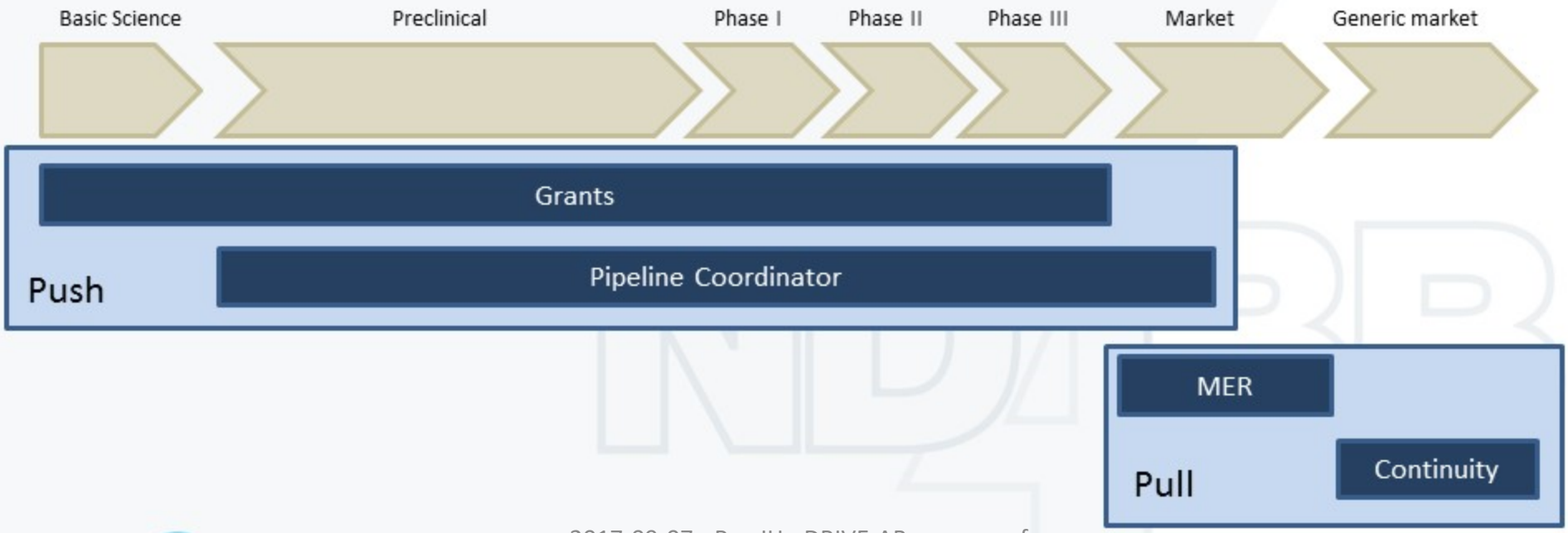
- What does it cost per year to maintain the plant that makes a sterile injectable so that you can make at least 1 vial per year?
- Please consider
  - Cost for the building
  - Cost for the staff
  - Cost for record-keeping
  - Cost for destroying unused materials that go beyond their expiration date

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

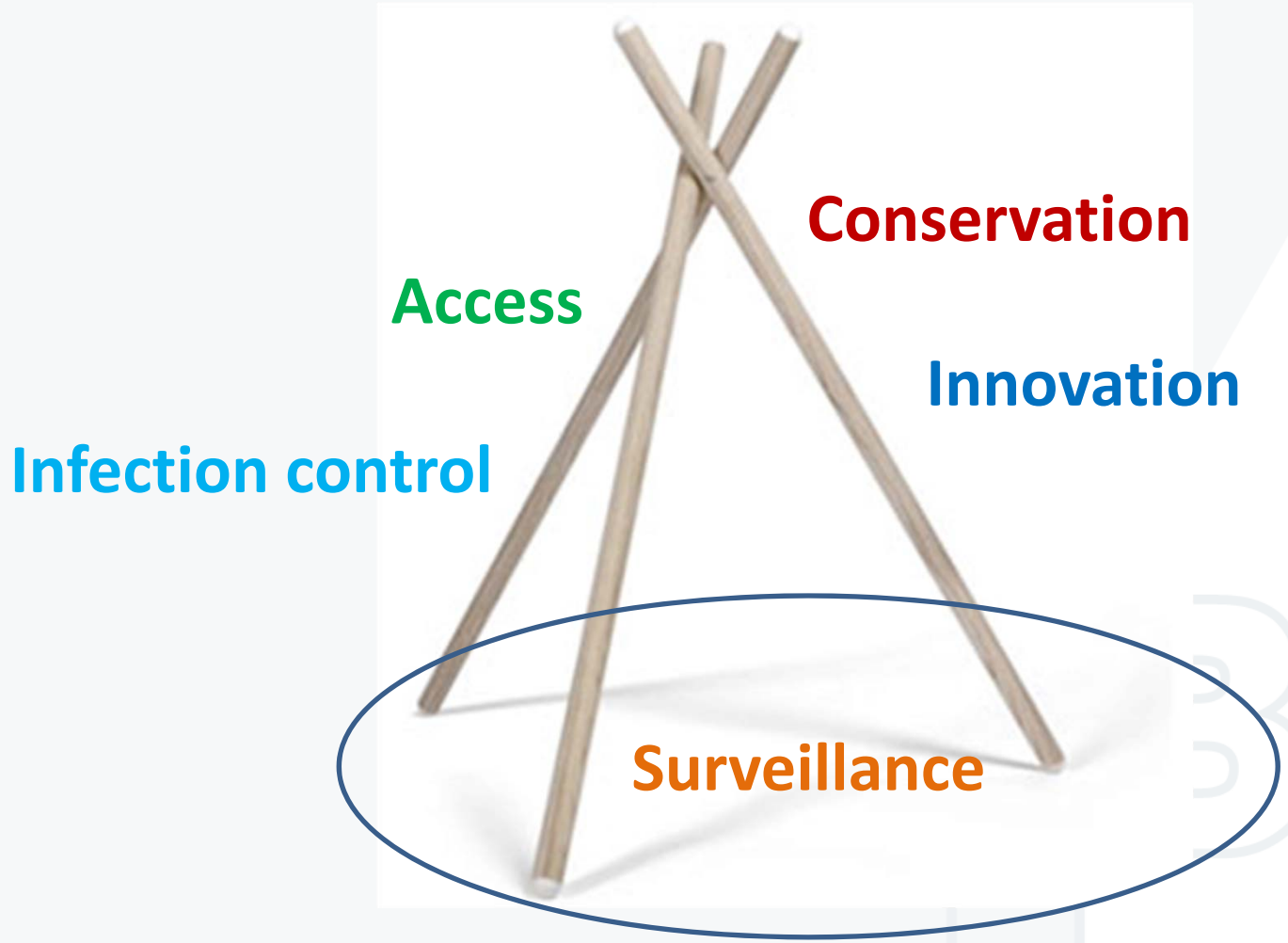


How much financing is needed?

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.

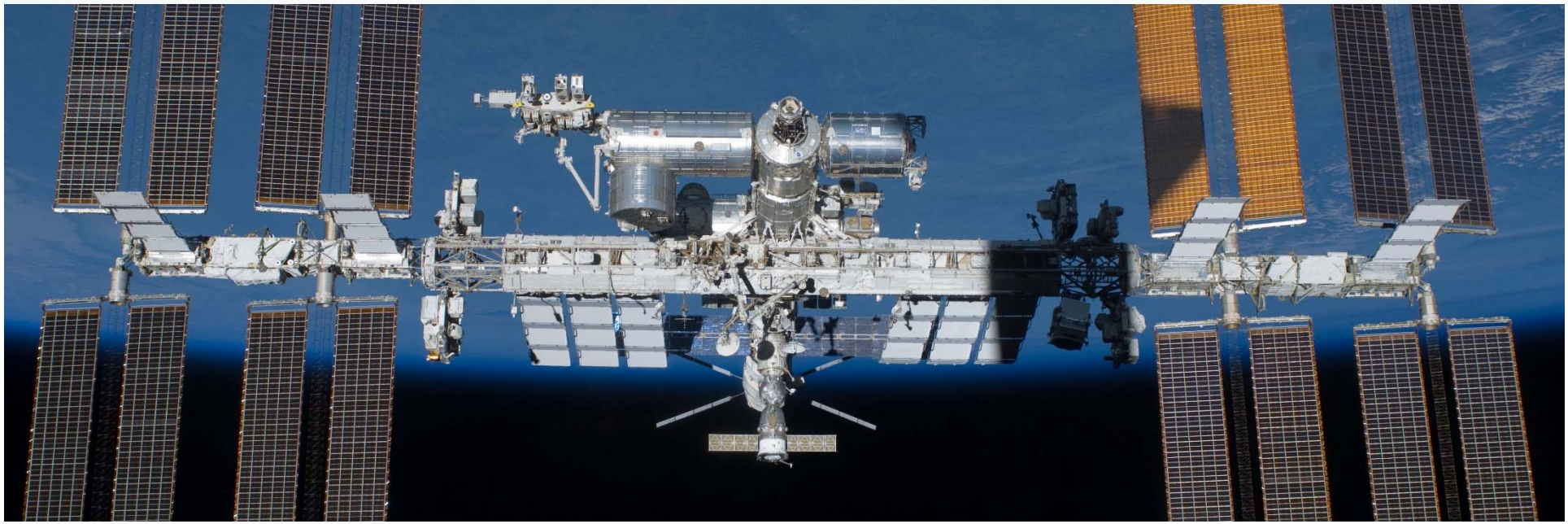
Must continue other funding…



Adapted from Hoffman S, Outterson K et al JLME 2015

Can this be done?

Example – International Space Station



- No pooled budget
- Bilateral agreements with US
- $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

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Change is coming (we hope!)

- 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
  - Reward will not be based on volume
  - Not all antibiotics have equal value
  - Choose your projects wisely…

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

Thank you!

John H. Rex, MD
7 Sep 2017: ASM-ESCMID Antibacterial Conference
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Newsletter: http://amr.solutions

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