

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

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Newsletter: <http://amr.solutions>

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

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1. A common language

Work Package 1A provided

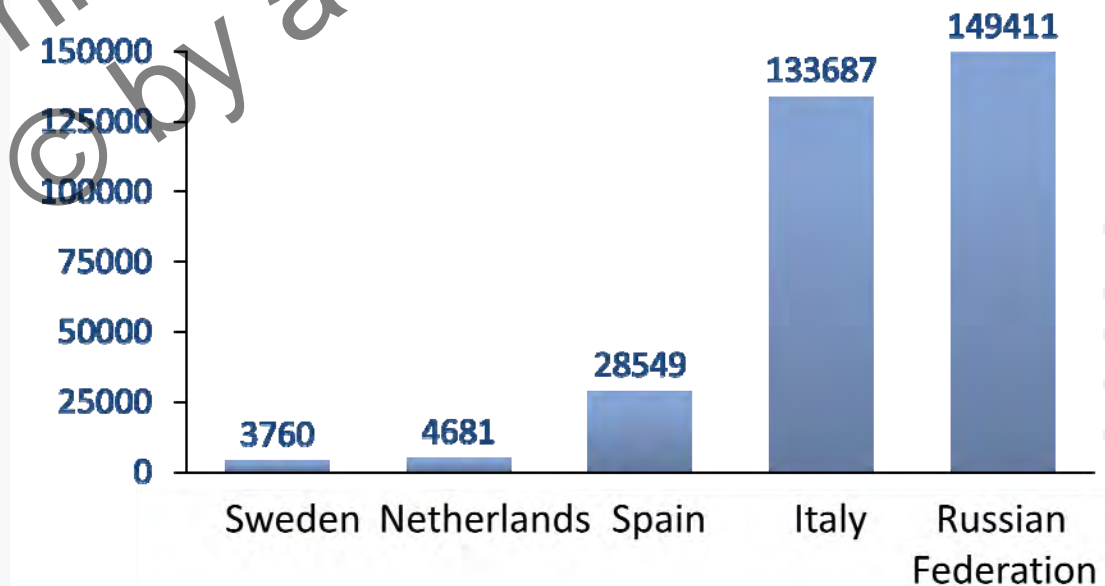
- A common terminology and framework for shared understanding of responsible and sustainable antibiotic use.
- Broadly accepted metrics to monitor responsible use which could be used to inform stewardship programs, improve use of existing antibiotics, and prevent inappropriate use of newly developed 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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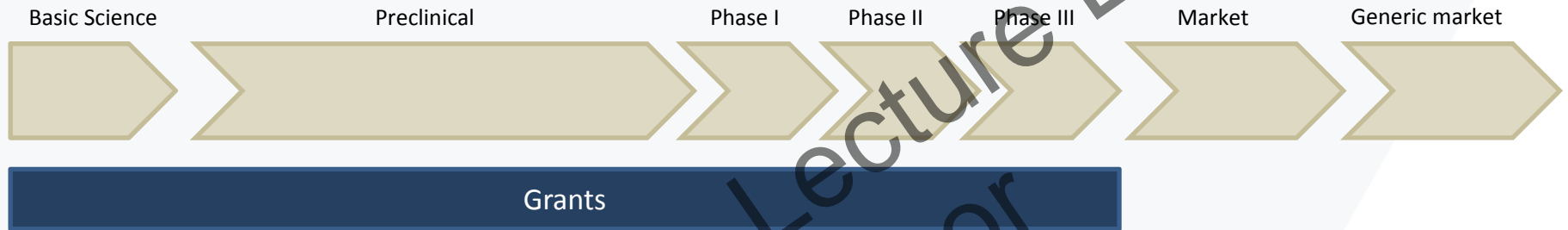
DRIVE-AB: 4 types of incentive tools

Methods:

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



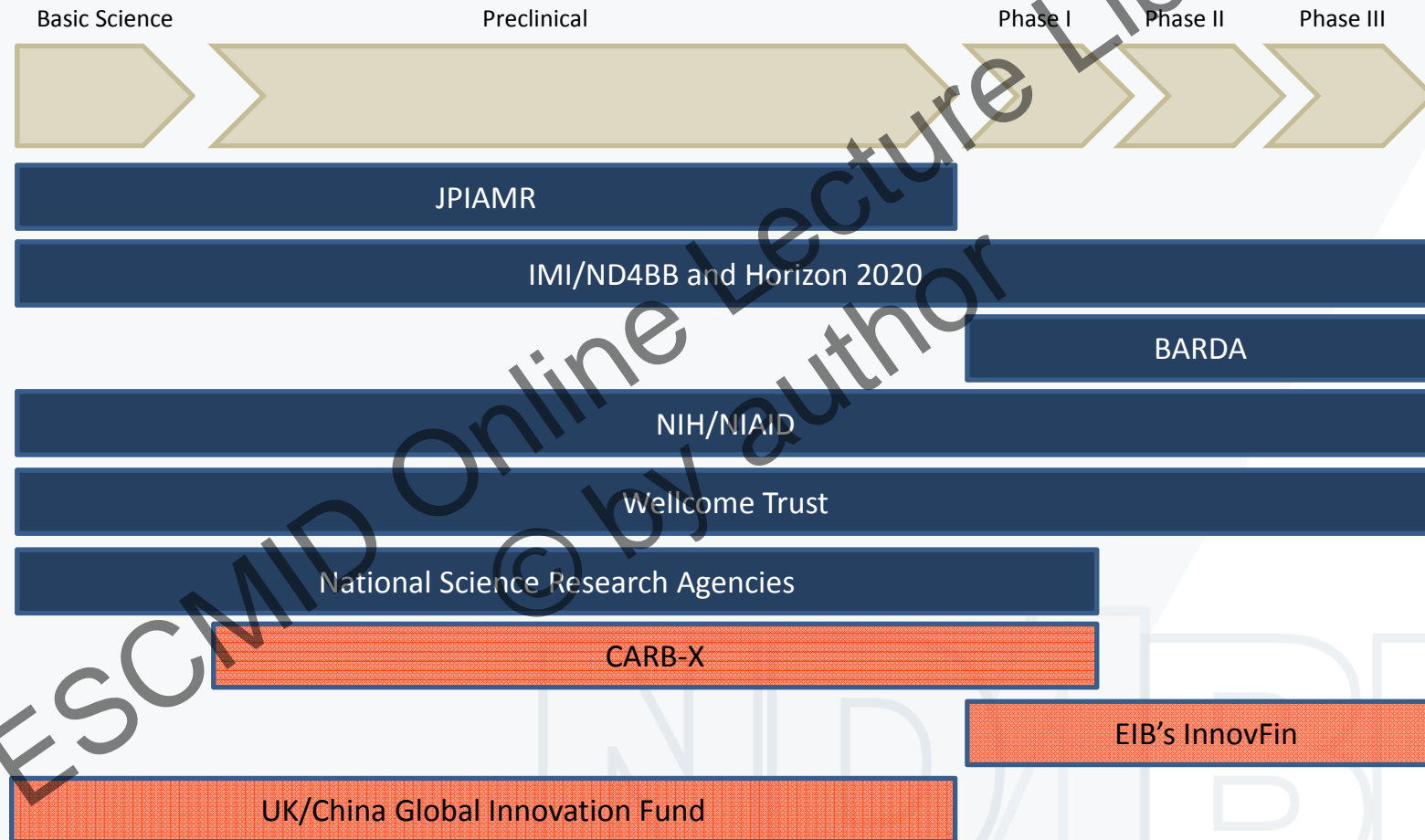
A. Grants



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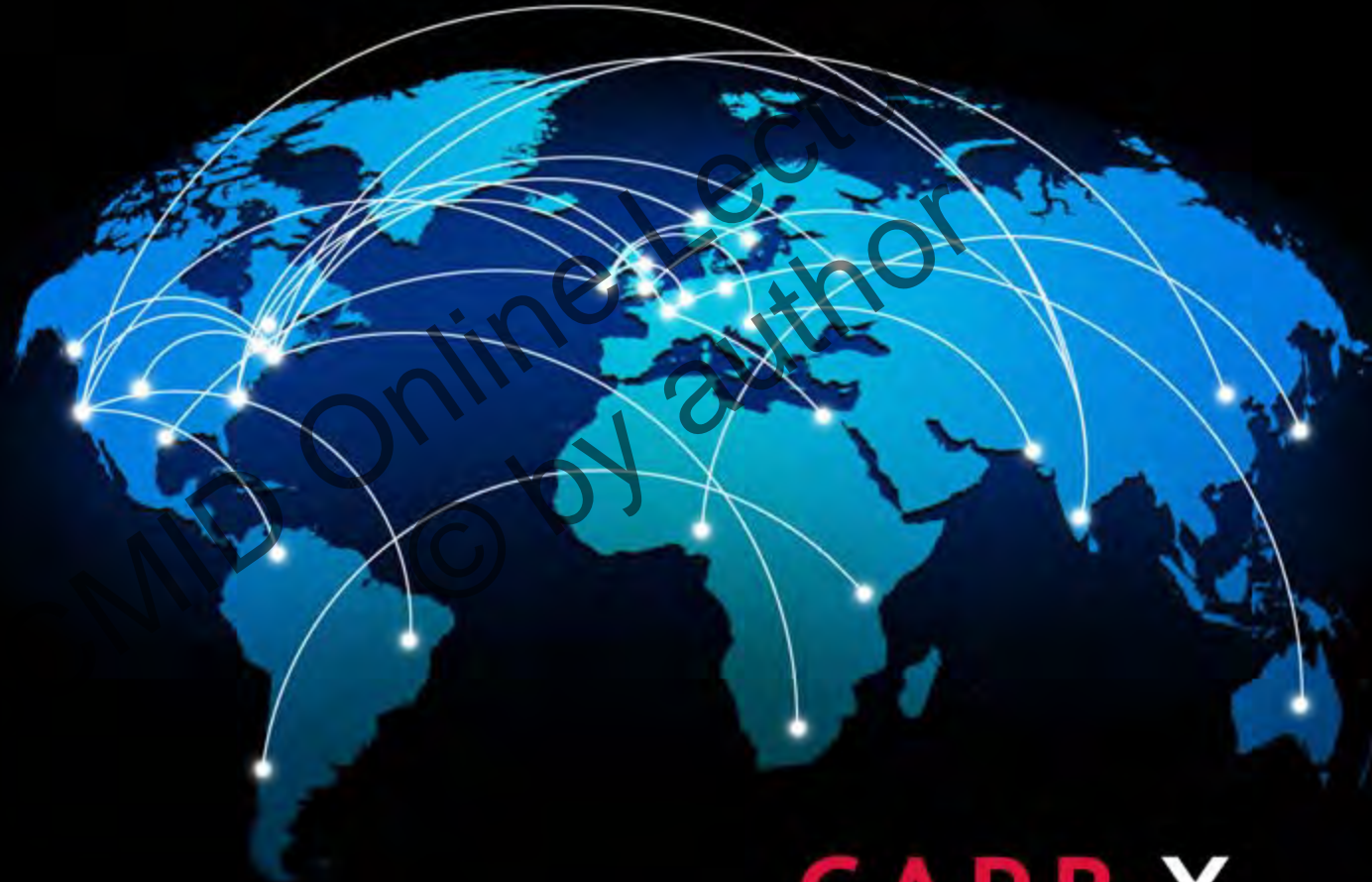


A. Grants - recommendation

- 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

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

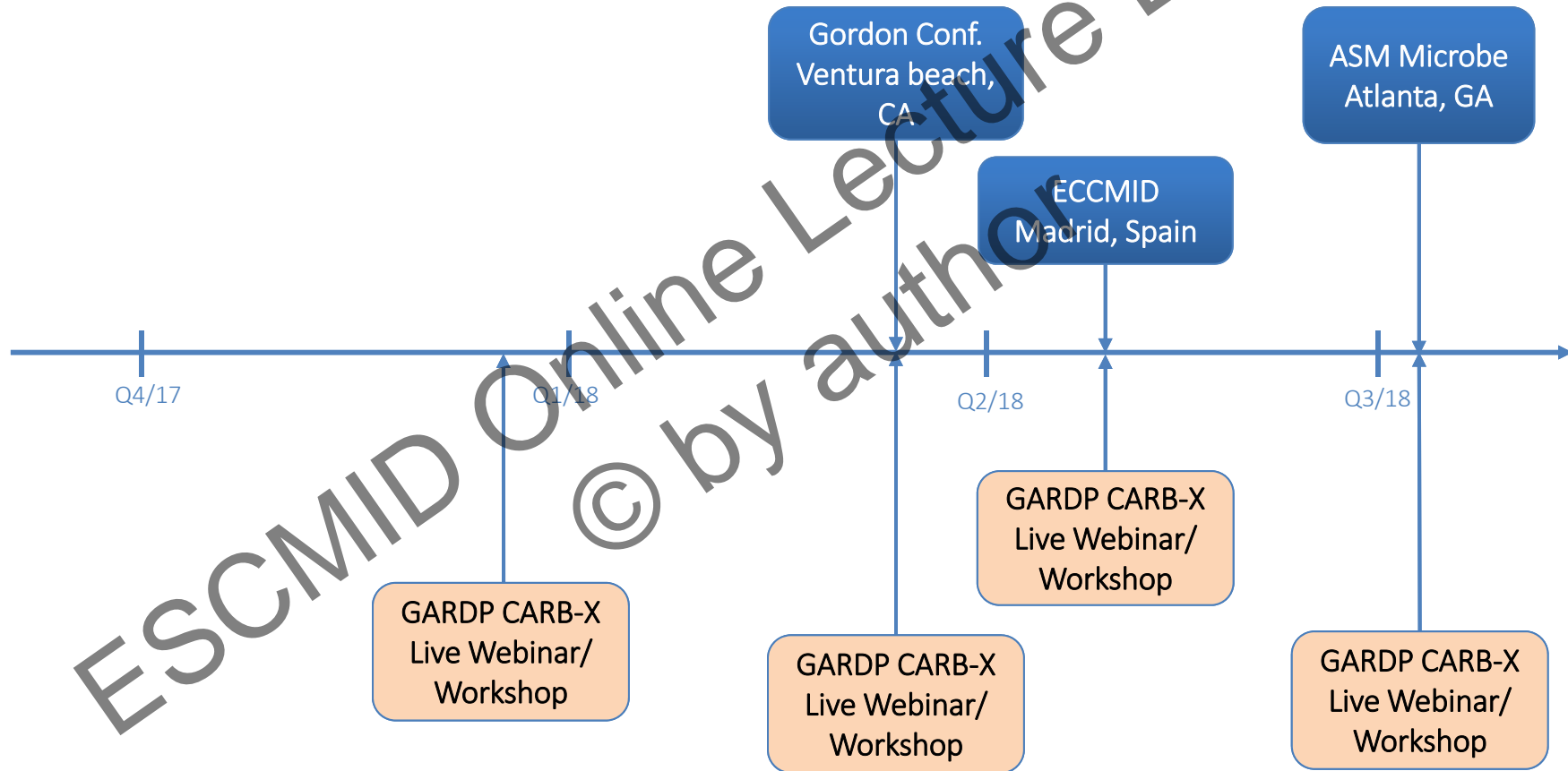
Bugworks Research India Pvt Ltd.
Bangalore, India

CARB-X

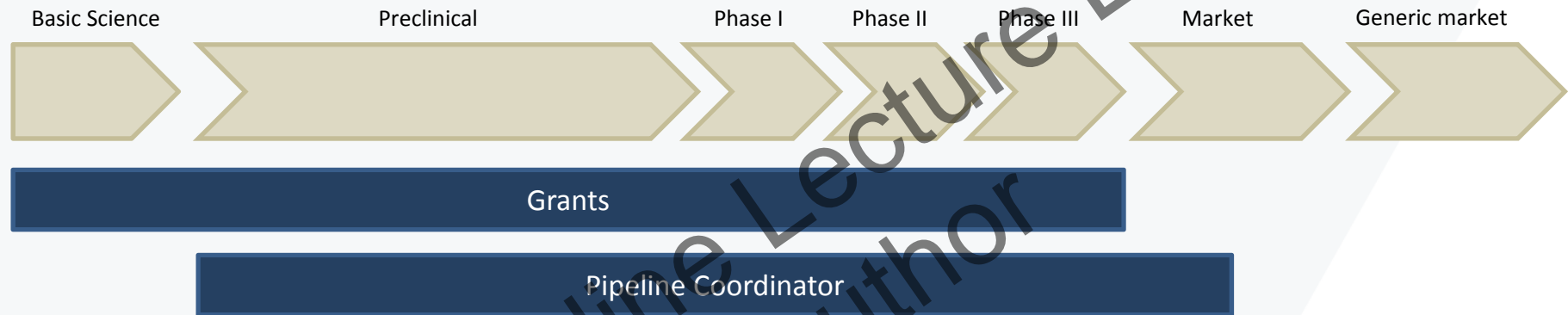
Great science knows no boundaries

- 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

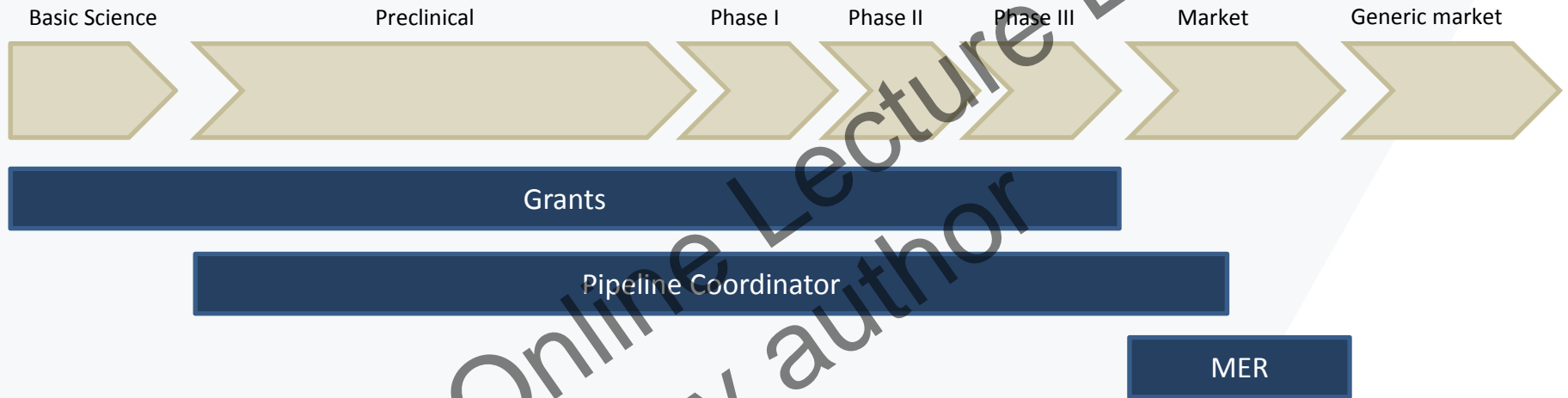
Bacteria (WHO category)	WHO (2017)	# in clinical dev	# likely to register
<i>Acinetobacter baumannii</i> , carbapenem-R	Critical	4	~1
<i>Pseudomonas aeruginosa</i> , carbapenem-R	Critical	3	~1
<i>Enterobacteriaceae</i> , carbapenem-R, 3 rd -gen cep-R (ESBL+)	Critical	9	3-4
<i>Enterococcus faecium</i>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

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

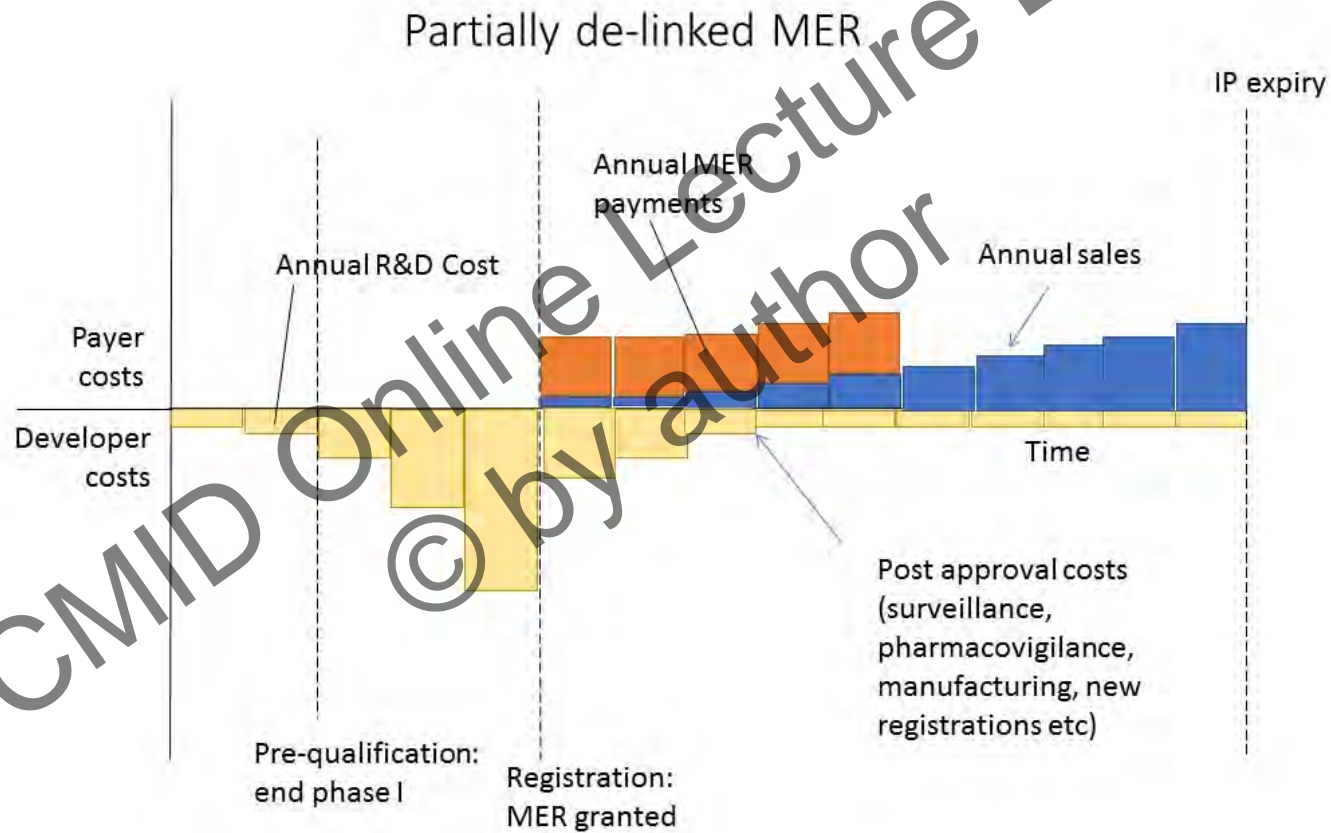
C. Market Entry Reward (MER)



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C. Market entry reward: The idea



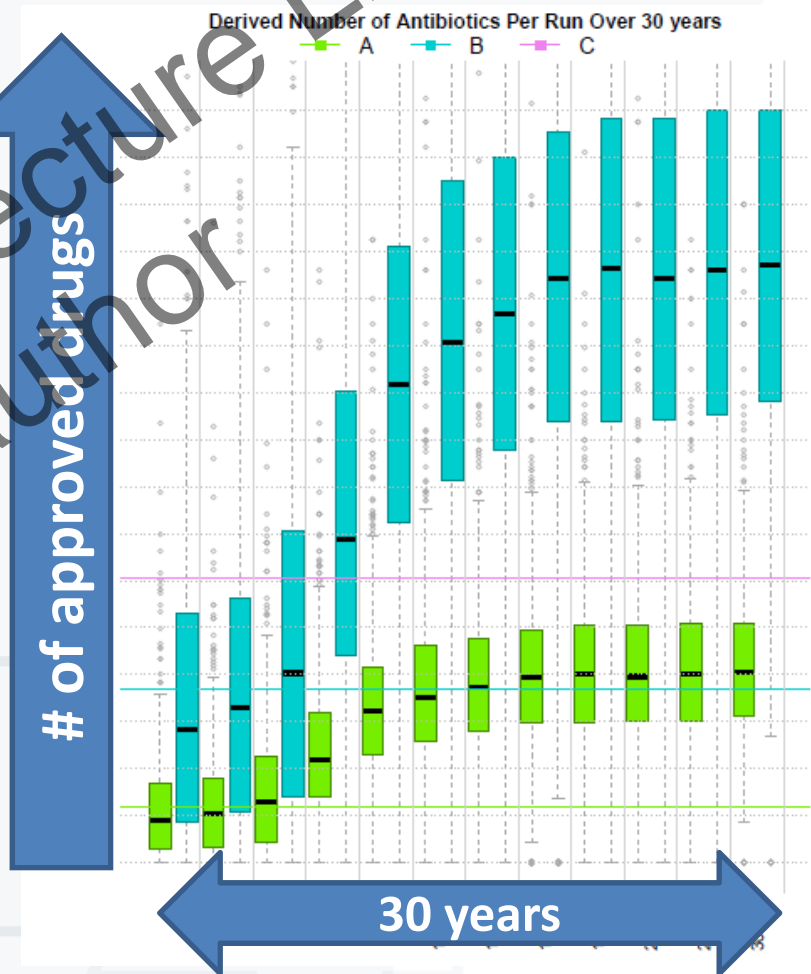
C. Why a market entry reward?

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

Source: Duke Margolis, 2017

C. Market entry reward – simulated results

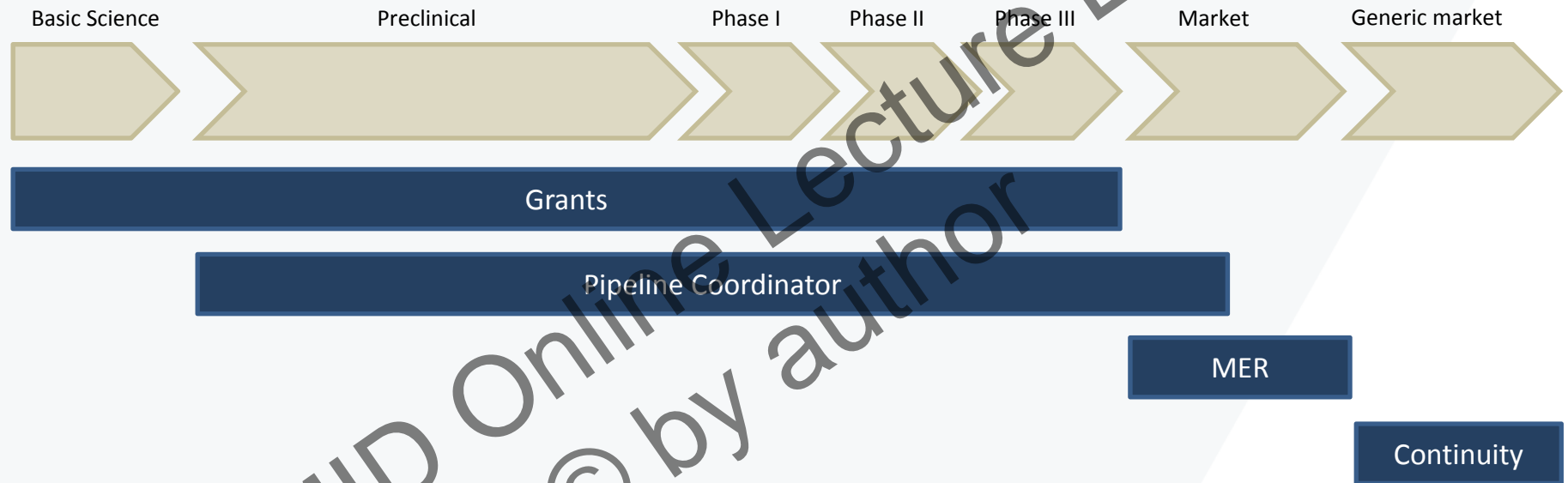
- Exhaustive simulations
- Example at right
 - Green: Situation as is
 - Blue: \$1B MER per antibiotic
- Effect
 - Quadruples number of new anti-Gram-negative antibiotics over 30 years



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



“In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of ‘forgotten antibiotics’ has worsened since 2011.”

From previous work we estimated that the availability of 17 common bacterial antimicrobials increased 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.

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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

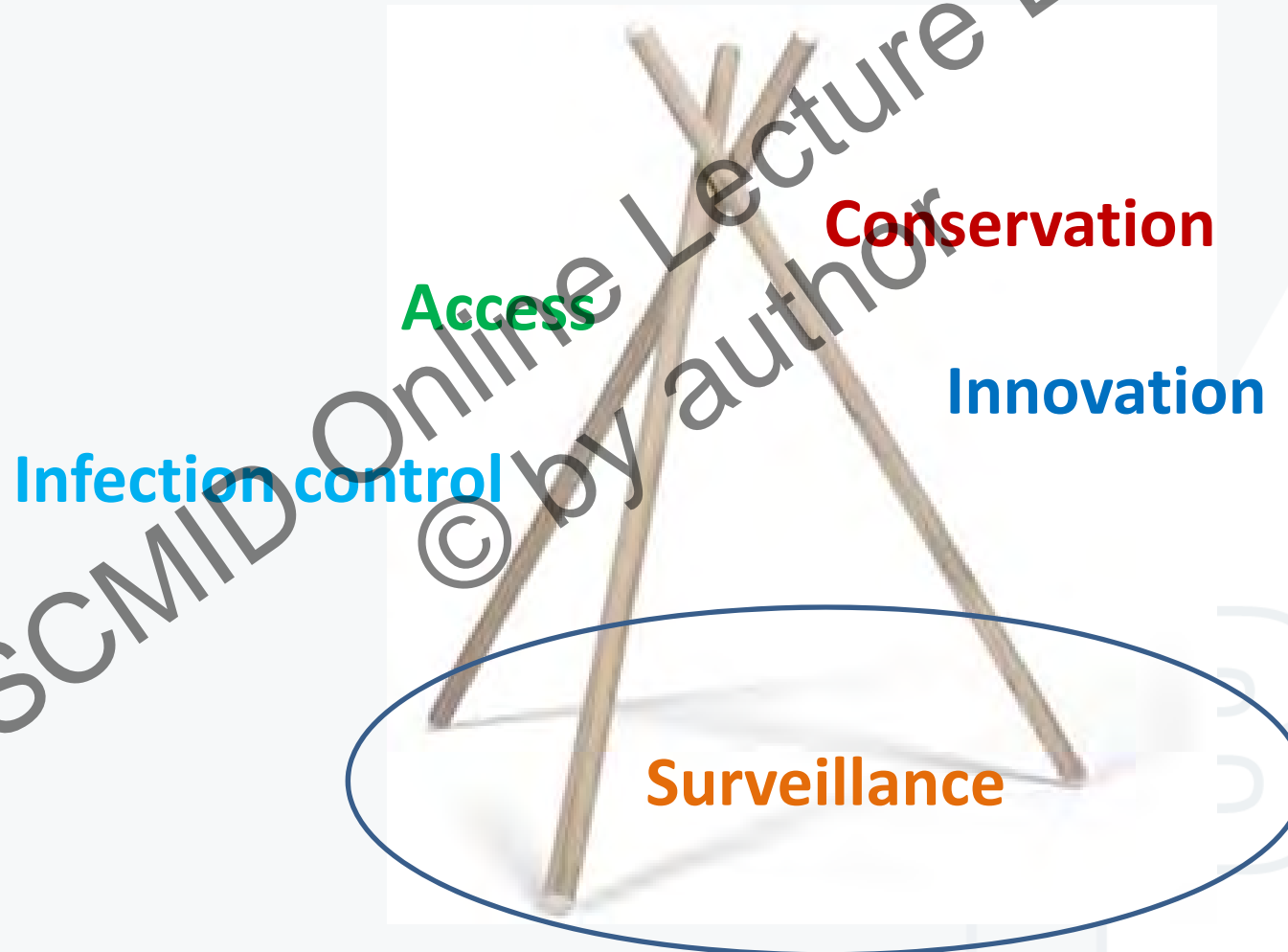


How much financing is needed?

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...



NDA BBB

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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



Image: 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

KNOW YOUR FIRE EXTINGUISHER

CHOOSING THE RIGHT EXTINGUISHER CAN PREVENT PROPERTY DAMAGE AND SAVE LIVES

Extinguisher Type →	Water	Foam	CO ₂	Dry Chemical
Type of Fire ↓				
A Paper, Wood & Plastic	✓	✓	X	✓
B Flammable & Combustible Liquids	X	✓	✓	✓
C Electrical Equipment	X	X	✓	✓

Thank you!

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