CARB-X

Combating Antibiotic Resistant Bacteria

Replenishing the antibacterial pipeline with CARB-X

Kevin Outterson

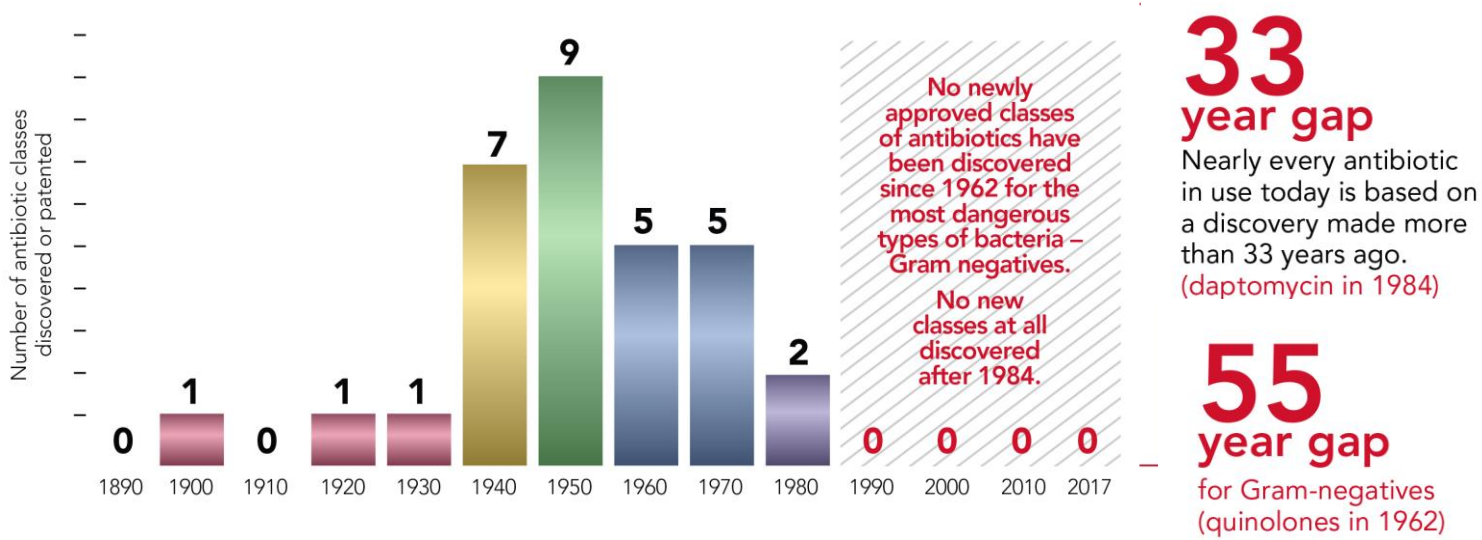
Nature Conference: Countering Antimicrobial Resistance

Beijing, PRC

29 May 2018

Antibiotic science is challenging

Discovery of novel antibiotics is not keeping up with emergence of new superbugs



This chart excludes bedaquiline, which is the first drug in a new class to treat tuberculosis.
Source: Pew Charitable Trusts; Deak D, Powers JH, Outterson K, Kesselheim AS. Progress in the Fight Against Multidrug Bacteria?: A Review of FDA Approved Antibiotics 2010-2015. ANNALS OF INTERNAL MED. 2016 MAY 31. DOI:10.7326/M16-0291.

CARB-X

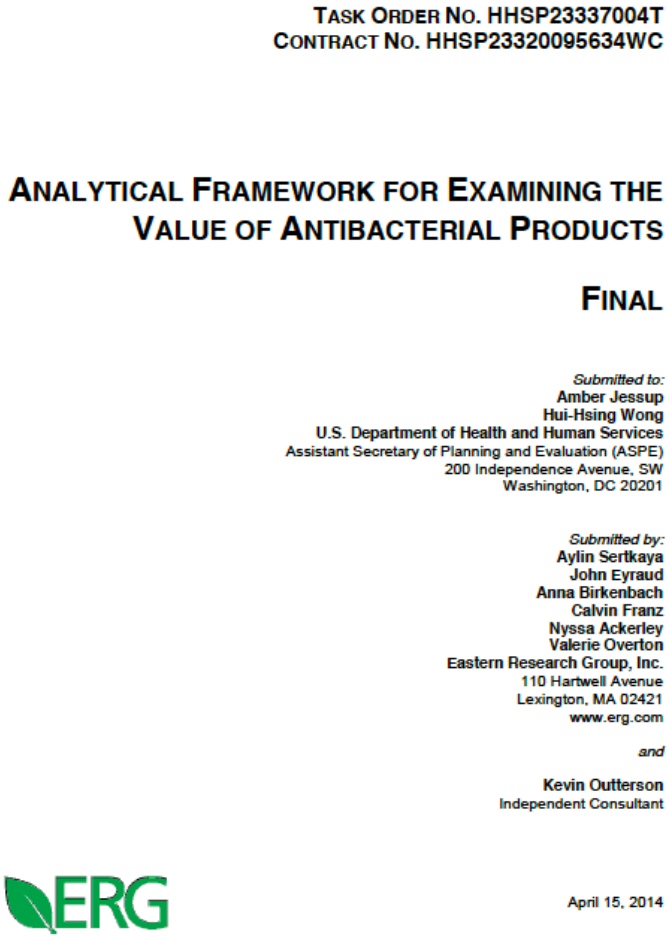
Global antibiotics pipeline is precariously slim

- 48 antibiotics in the global clinical pipeline in September 2017[1]
- but only 12 in development to treat superbugs on the WHO critical threat pathogen list[2]
  - Enterobacteriaceae (CRE)
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*

1 Pew Charitable Trusts, Dec 2017
2 World Health Organization, "Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics" 2017

But the fragile antibiotic clinical pipeline is primarily an economic problem

The ERG Report (2014)



TASK ORDER NO. HHSP23337004T
CONTRACT NO. HHSP23320095634WC

ANALYTICAL FRAMEWORK FOR EXAMINING THE VALUE OF ANTIBACTERIAL PRODUCTS

FINAL

Submitted to:
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U.S. Department of Health and Human Services
Assistant Secretary of Planning and Evaluation (ASPE)
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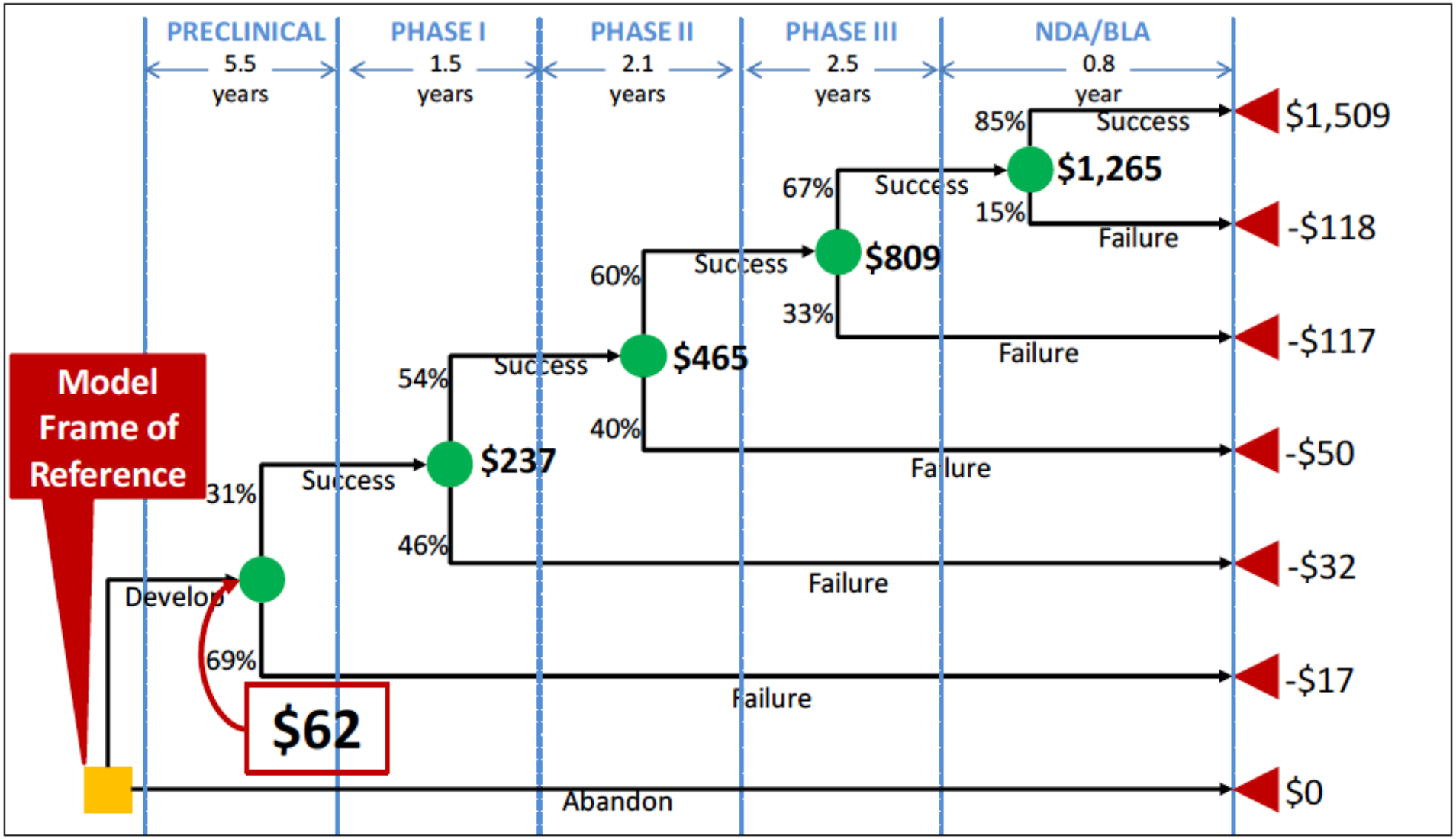
ERG

April 15, 2014

- Funded by US DHHS
- Completely independent of industry
- Economic analysis of both private and social NPV of antibacterial R&D programs

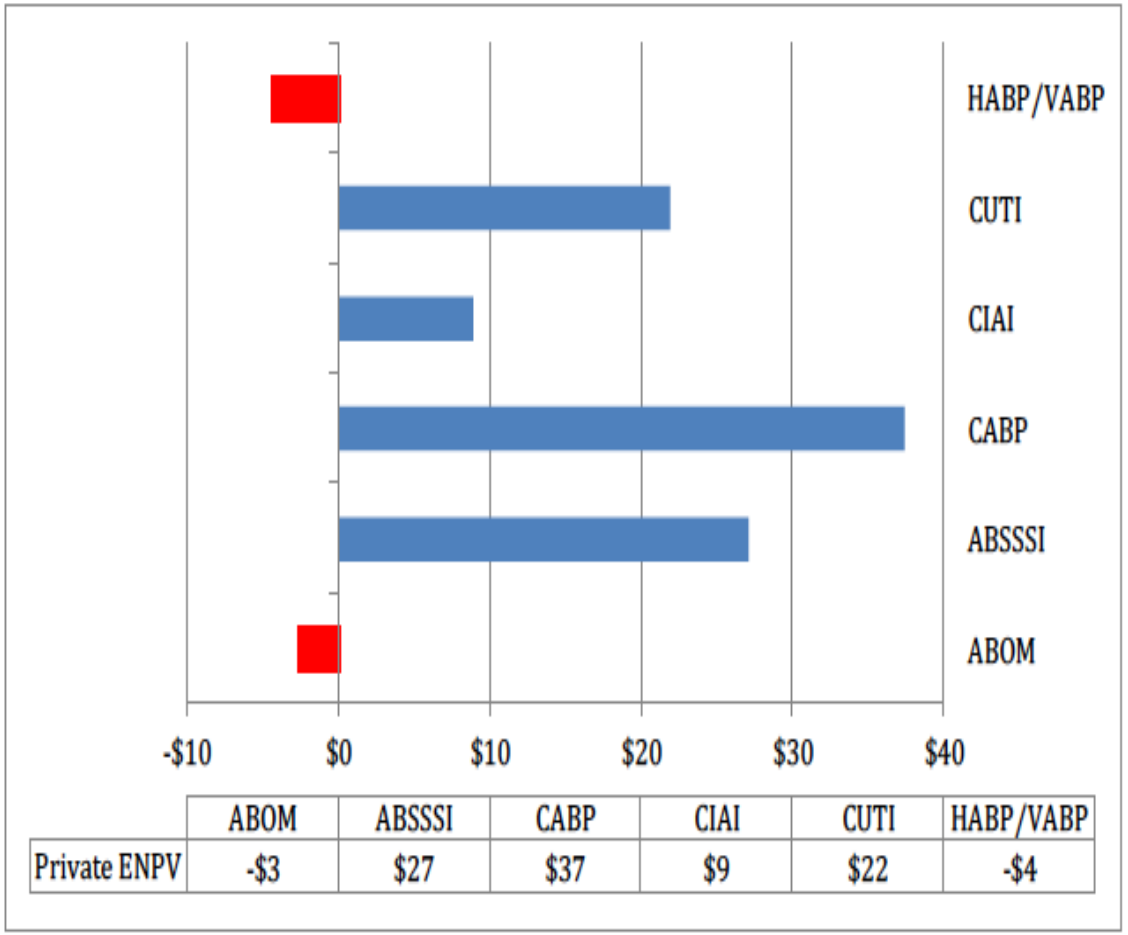
Figure 2: Drug Development Decision Tree Depicting Expected Net Present Value (ENPV) of Private Returns (Values in $ Million) for a Hypothetical New Molecule X



Private NPV

- Private NPV variable across indications
- CABP has the highest private NPV & HABP/VABP the lowest

Figure 3: Estimated Private ENPVs by Indication for a New Antibacterial Drug (in $ Million)

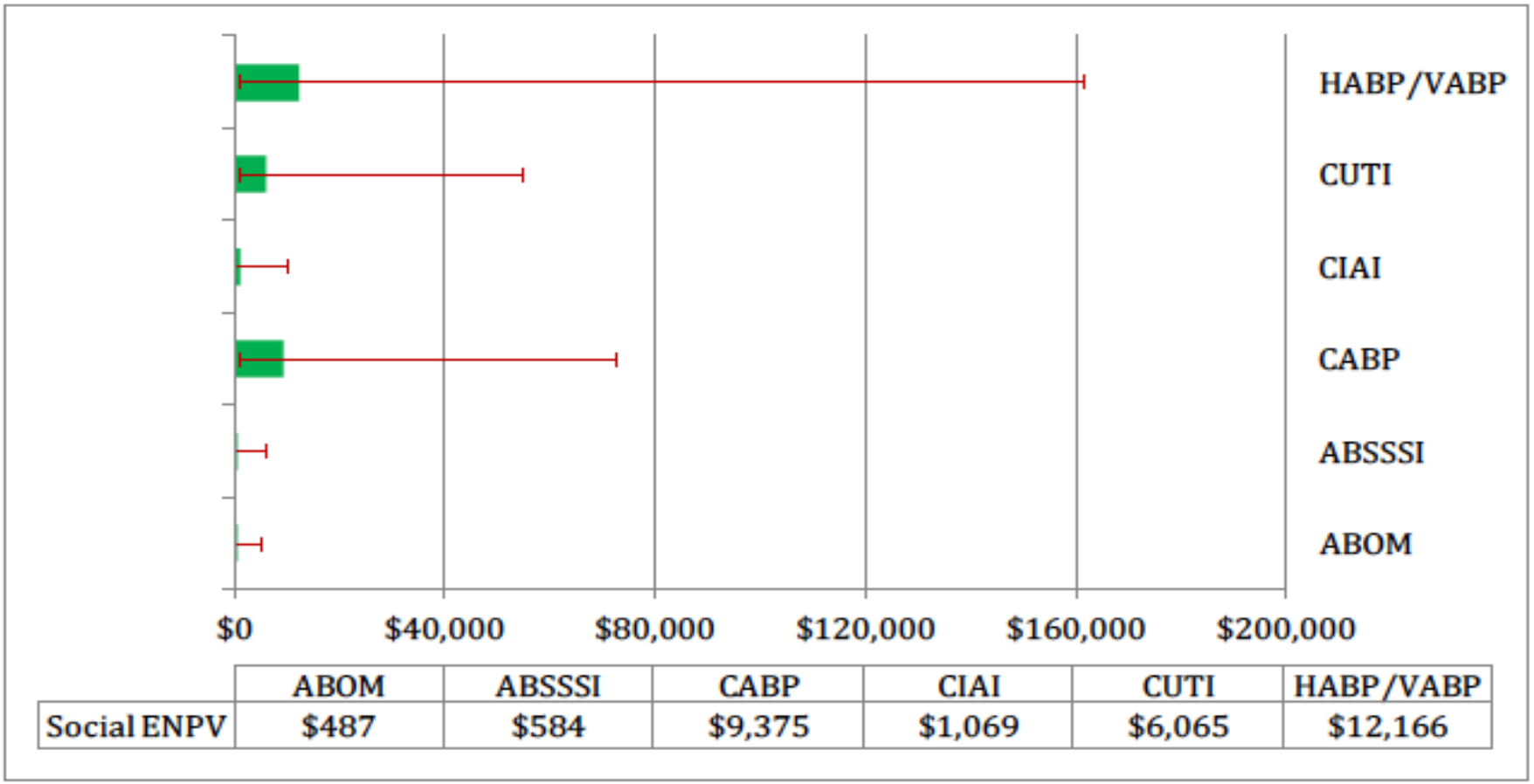


	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Private ENPV	-$3	$27	$37	$9	$22	-$4

ERG Report for DHHS/FDA 2014

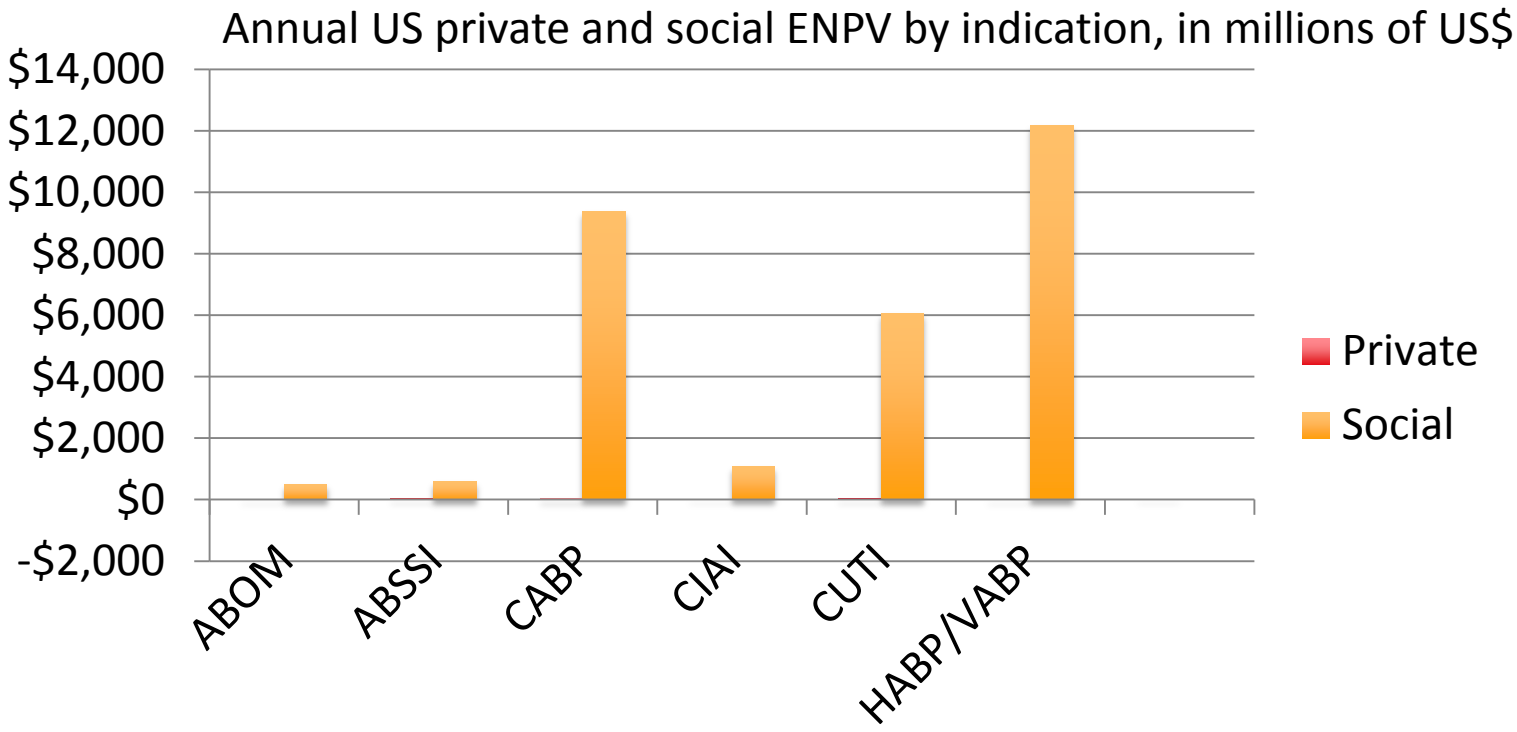
Social NPV

Figure 6: Sensitivity of Estimated Social ENPVs by Indication for a New Antibacterial Drug (in $ Million) - Error Bars Represent 90% Confidence Bounds



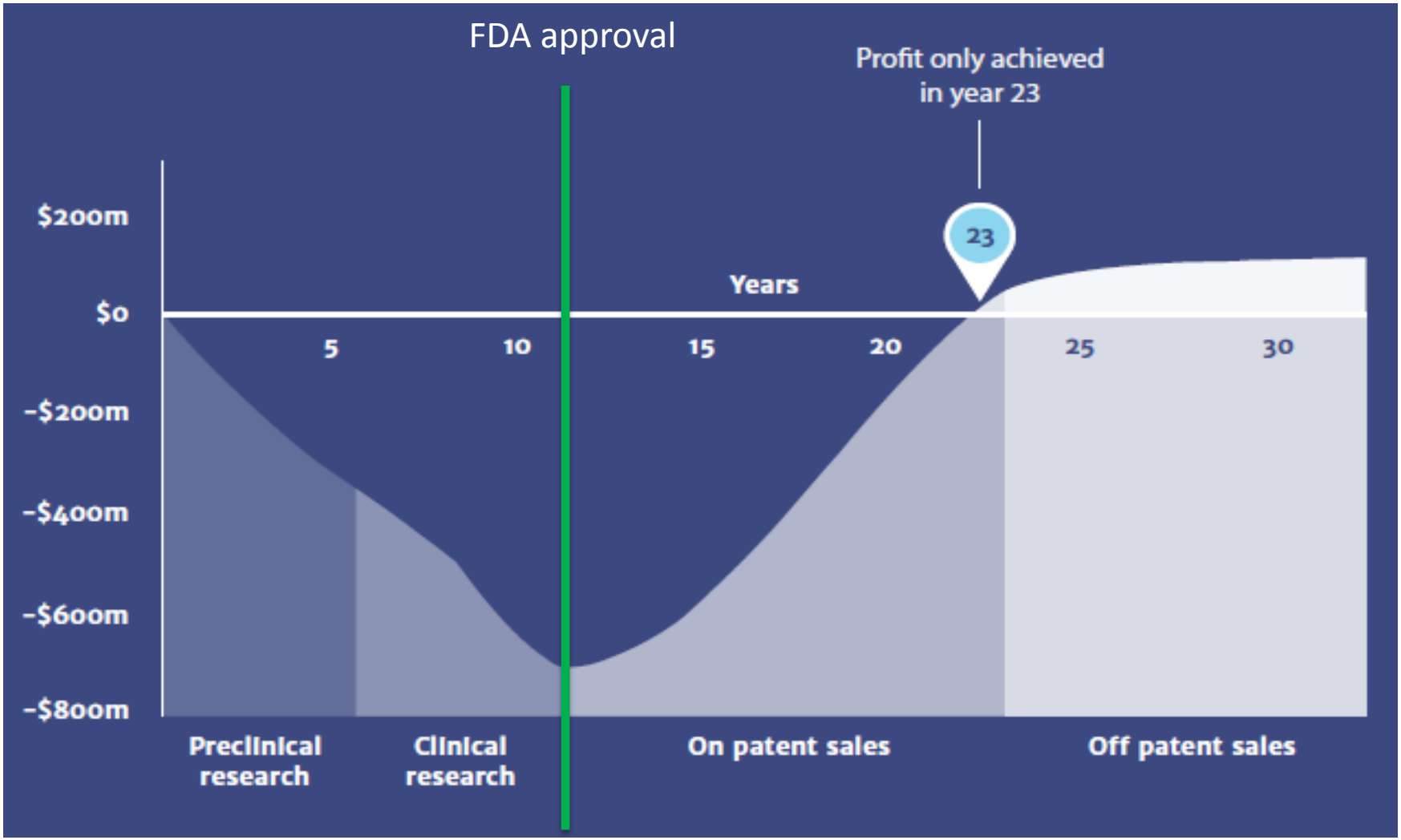
	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Social ENPV	$487	$584	$9,375	$1,069	$6,065	$12,166

Mismatched values



ERG Report for DHHS/FDA 2014

The Current Model…



Modified from O'Neill AMR Review (2016) ; Larsen (BARDA 2016)

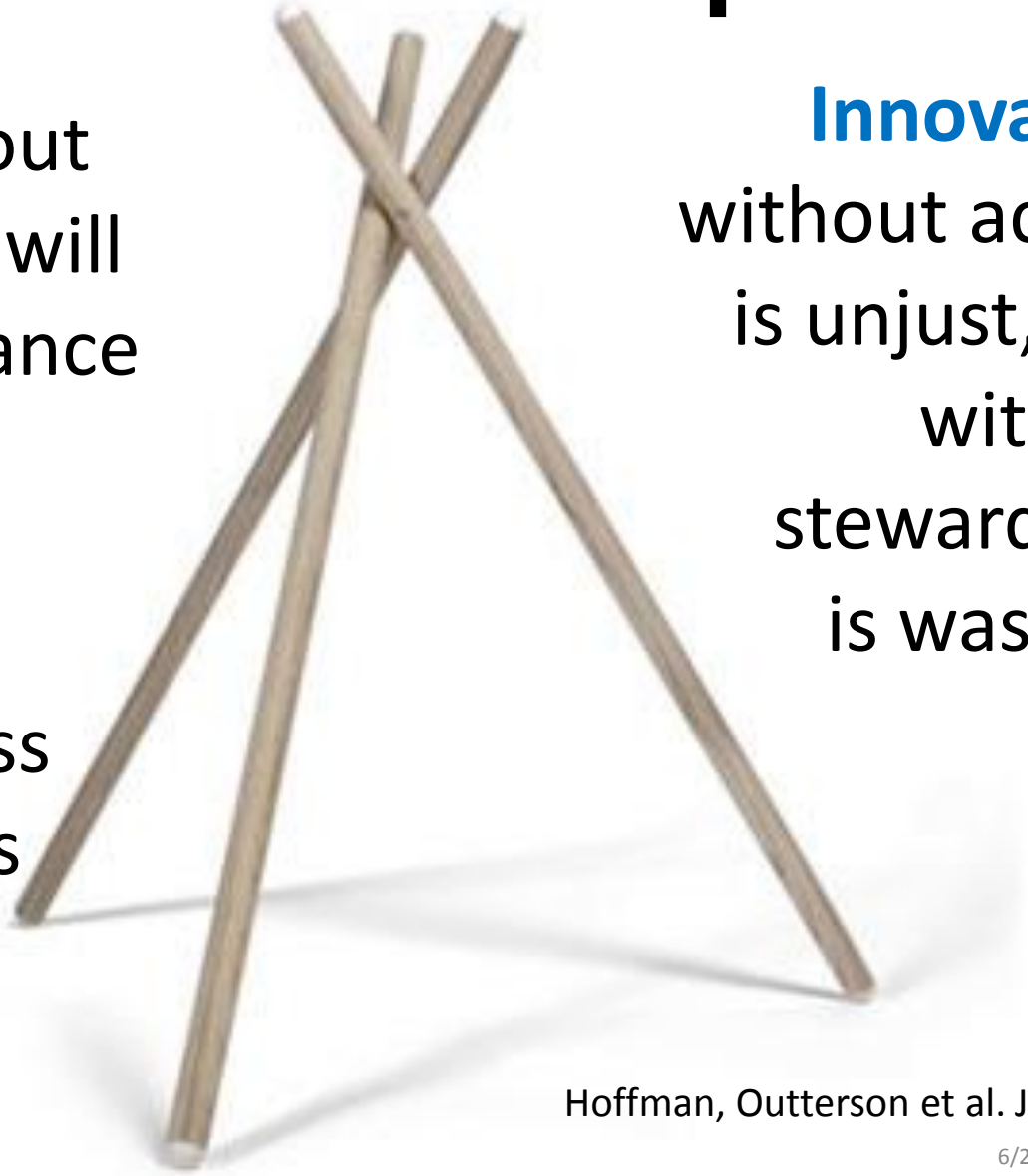
Low sales of new patented antibiotics drive these poor results

The antibiotic tripod

Access without stewardship will speed resistance

Innovation without access is unjust, and without stewardship is wasteful

Stewardship constrains access and undermines innovation



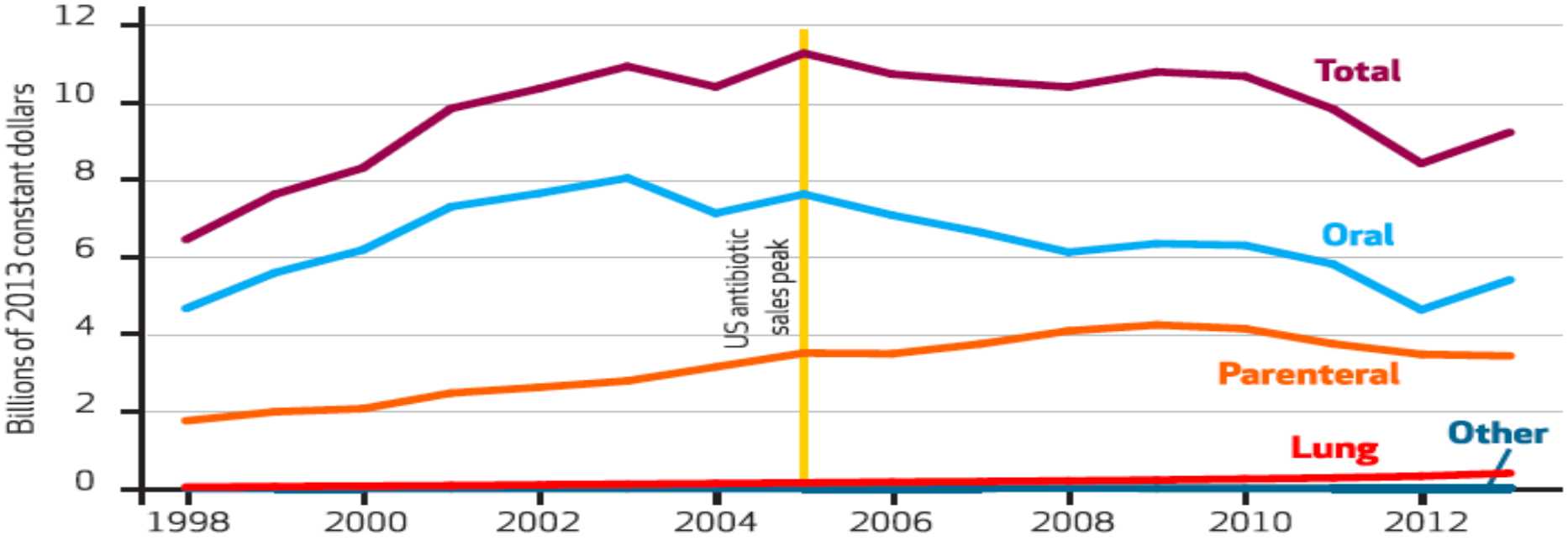
Hoffman, Outterson et al. JLME 2015

Peak antibiotics

Update: US 2017 patented antibiotic market: $1.094B

EXHIBIT 2

US Antibiotic Sales For Human Use, In 2013 Constant Dollars, By Mode Of Administration, 1998–2013

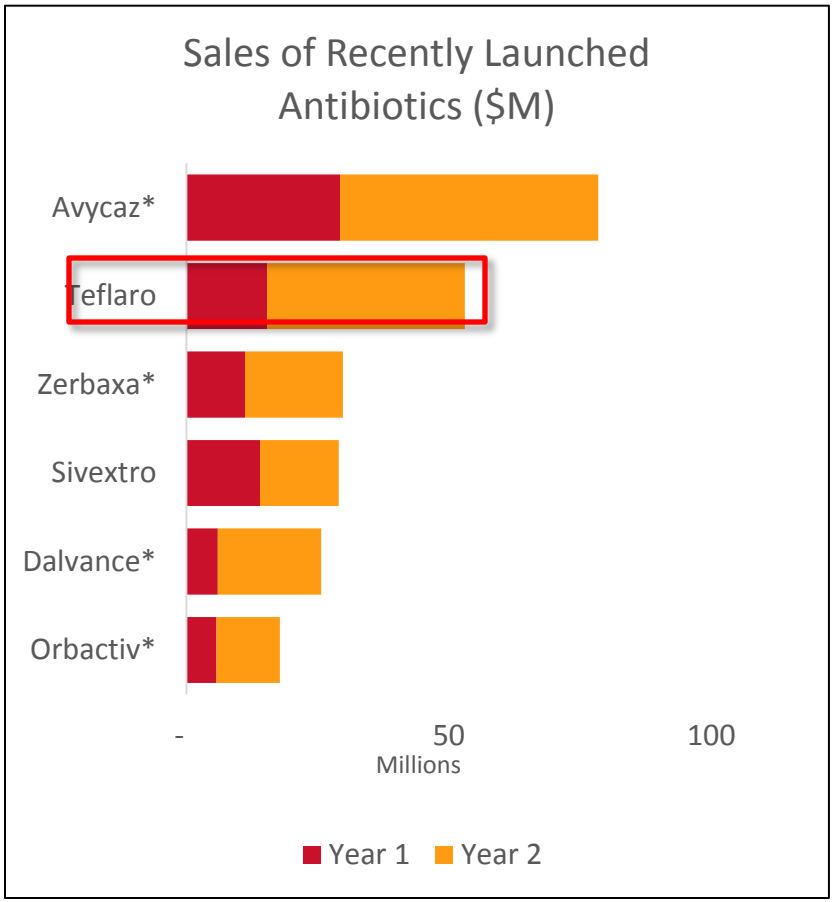


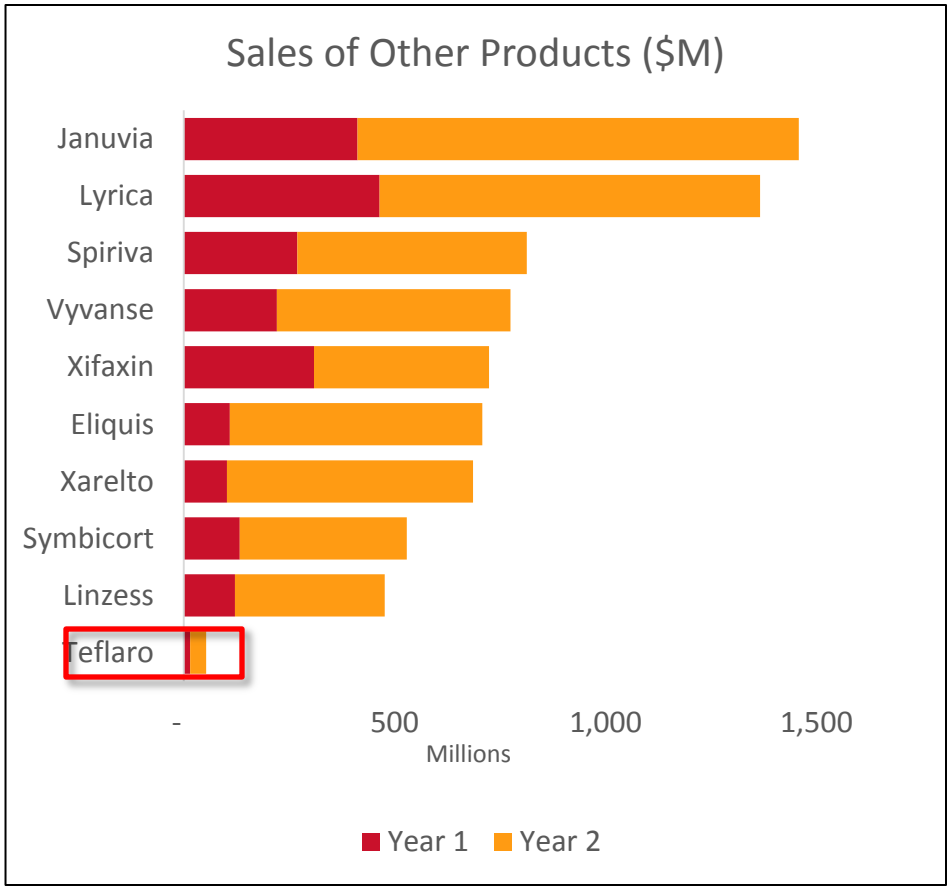
SOURCES IMS Health (US manufacturer US dollar sales at ex-manufacturer prices), and St. Louis Federal Gross Domestic Product deflator (2013 = 100).

Outterson K et al. 34 HEALTH AFFAIRS 277-85 (Feb. 2015).

Product Launches: New Antibiotics vs. Other Brands

Update: total Avycaz US Sales Apr 15-Jan 18 = $113M

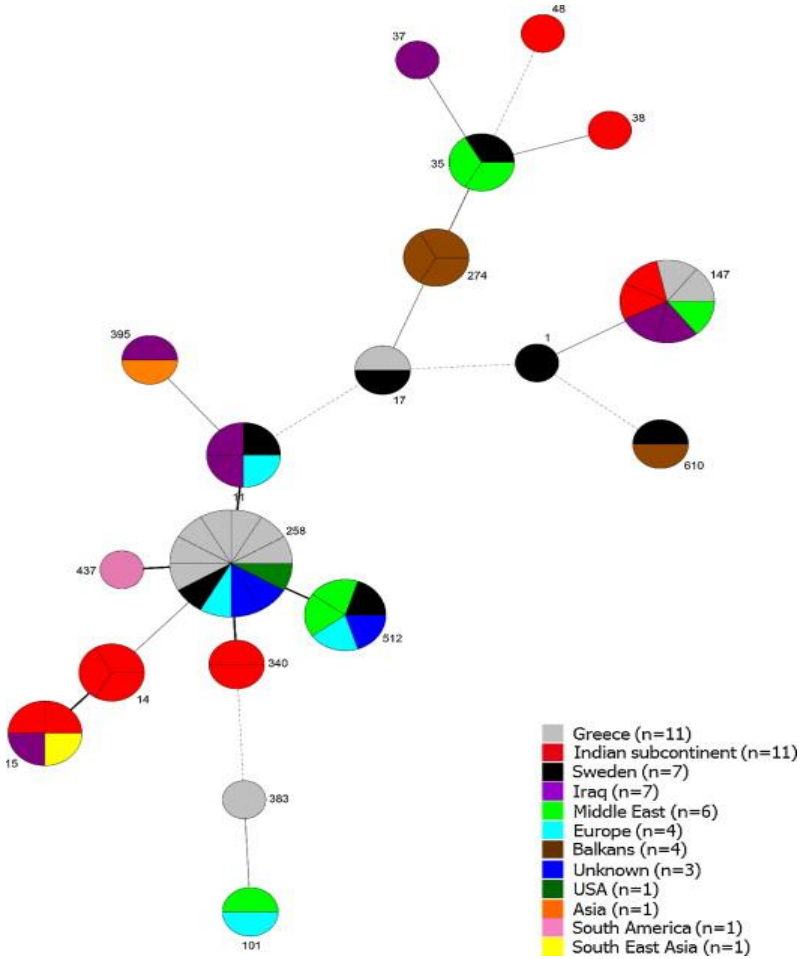




*Projected Sales (year 2)
Source: NSP $ Sales, IMS 2016

Case study: markets for CRE antibiotics

CRE in Sweden



- National mandatory reporting 2007-13
- 24 clinical infections, 70 other colonized
- 81% associated with travel abroad
- 84% with hospitalization abroad
- Only 1 transmission chain in a Swedish hospital
- 28% possibly XDR
- 1 case – colistin only

Löfmark S et al. DRU 2015

Commercial Impact

- Sweden
  - 24 cases over 7 years, every case was susceptible to at least one current abx
  - **Market value of a CRE drug in Sweden = 0**
  - **But insurance/social value might be many millions/year**
- USA
  - 9,000 estimated cases 2011
  - If same pattern as Sweden, expect **<250 US cases in 2020 susceptible to colistin only**

Rex & Outterson, Lancet Infect Dis 2016

CDC strategy

- CRE – target 60% decline by 2020 through aggressive measures
- Similar patterns for other diseases
  - 50% decline in *c. difficile*
  - Nosocomial MDR *Pseudomonas* – ↓35%
  - MRSA BSI – ↓50%
  - Invasive pneumococcal <5 and >65 -- ↓25%

National Strategy for Combatting Antibiotic-Resistant Bacteria
(White House, Sept. 2014, Table 3)

Medicare ASP rules

June 13, 2016

This document is scheduled to be published in the Federal Register on 06/16/2016 and available online at http://federalregister.gov/a/2016-13925, and on FDsys.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Parts 482 and 485

[CMS-3295-P]

RIN 0938-AS21

Medicare and Medicaid Programs; Hospital and Critical Access Hospital (CAH) Changes to Promote Innovation, Flexibility, and Improvement in Patient Care

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS.

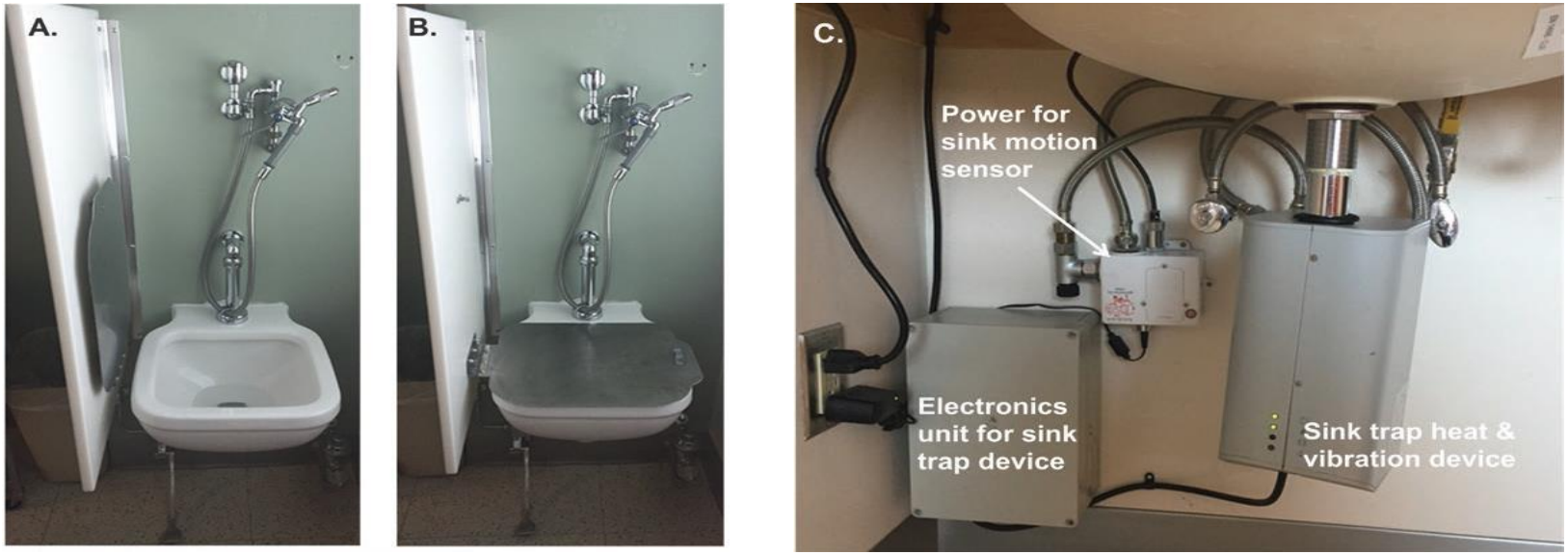
ACTION: Proposed rule.

Clinical Infectious Diseases
MAJOR ARTICLE

Intensive Care Unit Wastewater Interventions to Prevent Transmission of Multispecies *Klebsiella pneumoniae* Carbapenemase–Producing Organisms

Amy J. Mathers,[1,2] Kasi Vegesana,[3] Ian German Mesner,[3] Katie E. Barry,[1] Aaron Pannone,[4] Josh Baumann,[3] Derrick W. Crook,[5,6] Nicole Stoesser,[5,6] Shireen Kotay,[1] Joanne Carroll,[2] and Costi D. Sifri[1,7]

[1]Division of Infectious Disease and International Health, Department of Medicine, University of Virginia, Charlottesville, [2]Clinical Microbiology Laboratory, Department of Pathology, University of Virginia Health System, Charlottesville, and [3]Health Information & Technology, University of Virginia Health System, and [4]Department of Public Health Sciences, University of Virginia, School of Medicine, Charlottesville; [5]Modernizing Medical Microbiology Consortium, Nuffield Department of Clinical Medicine, University of Oxford, and [6]National Institute for Health Research (NIHR) Health Protection Research Unit in Healthcare Associated Infection and Antimicrobial Resistance at University of Oxford in partnership with Public Health England, United Kingdom; and [7]Office of Hospital Epidemiology, University of Virginia Health System, Charlottesville



Mathers AJ et al. Clin Infect Dis. 2018 Feb 2.

Table 1. Patients Who Were in a Hopper Unit Before Acquisition of *Klebsiella pneumoniae* Carbapenemase–Producing Organism

Patient characteristics	Preintervention August 2014-January 2016	Intervention May 2016-October 2017	Odds Ratio[‡]	95% Confidence Interval	*P* Value
KPCO acquisition	56	30	…	…	…
Clinical culture	20	9	…	…	…
Colonization	36	21	…	…	…
Total patient days[#]	25332	26417	…	…	…
Total patient admissions[*]	7427	7783	…	…	…
Total perirectal cultures[†]	5783	7088	…	…	…
Acquisitions per 10000 patient-days	22.10	11.36	0.51	0.31–0.81	.003
Acquisitions per 1000 patient admissions	7.54	3.85	0.51	0.31–0.81	.003
Clinical cultures per 1000 patient admissions	9.15	2.69	0.29	0.17–0.48	<.001
New perirectal colonizations per 1000 surveillance screens	8.4	3.52	0.41	0.24–0.68	<.001

Abbreviation: KPCO, *Klebsiella pneumoniae* carbapenemase–producing organism.

[#]Total patient days for patients admitted to a hopper unit.

[*]Patient admission to a hopper unit.

[†]Peri-rectal screening culture for KPCO on patients exposed to a hopper unit.

[‡]Fisher's Exact test.

Mathers AJ et al. Clin Infect Dis. 2018 Feb 2.

Intervention reduced acquisition by 51%

- great news for public health
- terrible news for product market estimates

The view from Wall Street

Allergan launched Avycaz into the CRE space in mid-2015 w/ 14-day WAC price $11970 (now $13,762). Avycaz has had a negative impact on colistin TRX, but not polymyxin B TRX. Given that polymyxin B is also used to treat other infections, our interpretation is that the bulk of the CRE market is captured by Avycaz and colistin. We have two observations from TRX data: 1) current annual rate of infections is between ~30,000 (w/o polymyxin B) and ~50,000 (w/ polymyxin B) and 2) annual infection rate fell 10-15% from early 2016, but now appears to have stabilized.

Our new 2030 U.S. CRE market size estimate is $800M (was $950M). We assume number of CRE infections annually has stabilized and will begin growing 1%. Based on Avycaz launch pattern and strength of plazomicin profile, we assume peak penetrations of 32% for plazomicin (was 35%). We have reduced our launch ramp and our new plazomicin U.S. peak sales estimate is $250M (was $300M).

Alan Carr, Needham, Achaogen Feb 28, 2018

Bottom line

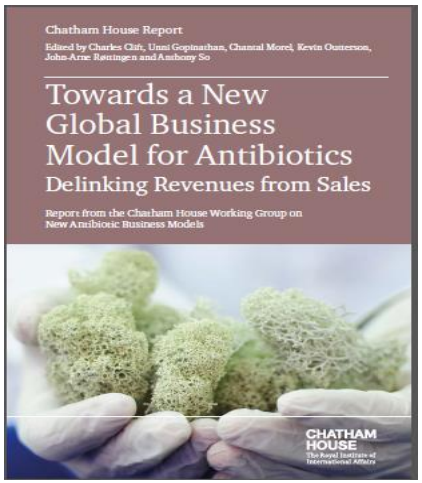
Shrinking market for innovative, targeted abx

(Unless marketing)

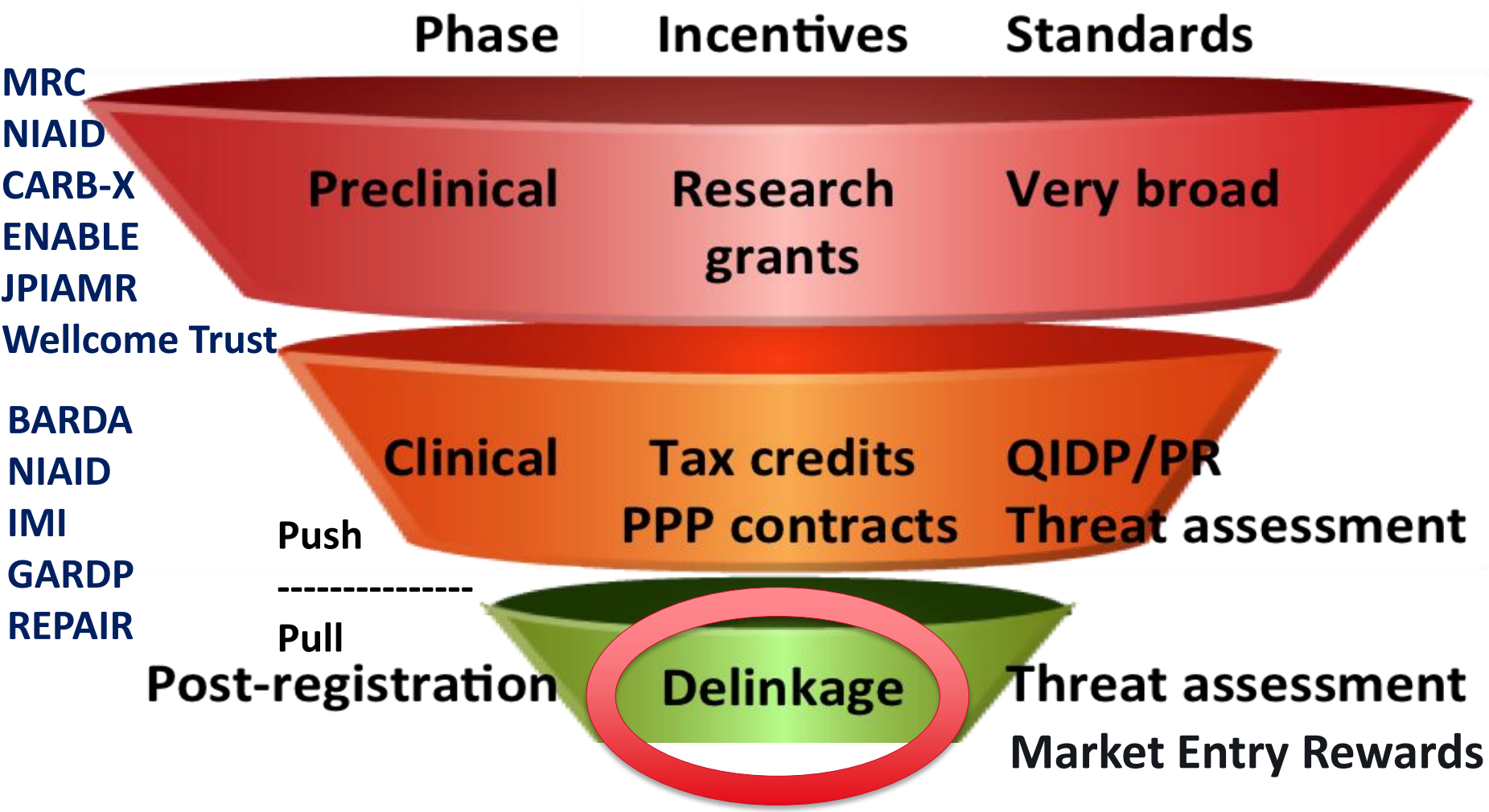
Solutions

Convergence of principles

- Need for both “push” and “pull” mechanisms
- Delinkage (i.e., revenues delinked from volumes sold)
- Access and stewardship are integral
- Global collaboration and financing necessary



Antibiotic R&D Incentives



Chatham House, Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales Oct. 2015

Network of major AMR development push initiatives

	CARB-X Combating Antibiotic Resistant Bacteria	GARDP Global Antibiotic Research & Development Partnership A joint DNDi / WHO initiative	repair impact fund novo holdings	ND4BB ENABLE
Budget	USD 455m (2016-21)	Euro 270m (2017-23)	USD 165m (2018-23)	Euro 85m (2014-20)
Products	Novel therapeutics, diagnostics, preventatives, devices	Novel therapeutics, Optimize antibiotics, Develop combinations	Novel therapeutics, companion diagnostics	Novel therapeutics
Pathogens	High priority defined by WHO and CDC, largely Gram-negatives	WHO priority pathogen list, especially Gram-negatives	High priority defined by WHO and CDC	*E. coli, K. pneumoniae, P. aeruginosa and A. baumannii*
Stages of development	Hit-to-lead through end of Phase 1	Any stage of development to patient access	Lead optimization through end of Phase 1	Hit-to-lead through end of Phase 1
Geography	Global	Global	Europe & U.S.	Europe
Funding instruments	Non-dilutive funding and expert support	Sponsor role (preclinical studies & clinical trials)	Convertible loans and royalty-based	Financial, in-kind and expertise support
Funding allotments	Flexible, with milestones; >30% cost share	Direct funding and flexible partnerships	USD 1m to 15m	Flexible
Conditions	Stewardship and market access requirements	Stewardship and access. Consider in/out licencing	Stewardship and access requirements *(in progress)*	Limited compensation when value generated

6/2/2018

CARB-X push incentives

CARB-X

Combating Antibiotic Resistant Bacteria

A non-profit partnership accelerating the best science from around the world to fight drug resistant infections

FUNDERS

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

BARDA
BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY

wellcome

NIH National Institute of Allergy and Infectious Diseases

UKaid
from the British people

ALLIANCE PARTNER

BILL & MELINDA GATES foundation

ACCELERATORS

BOSTON UNIVERSITY

RTI INTERNATIONAL

CLSI
California Life Sciences Institute

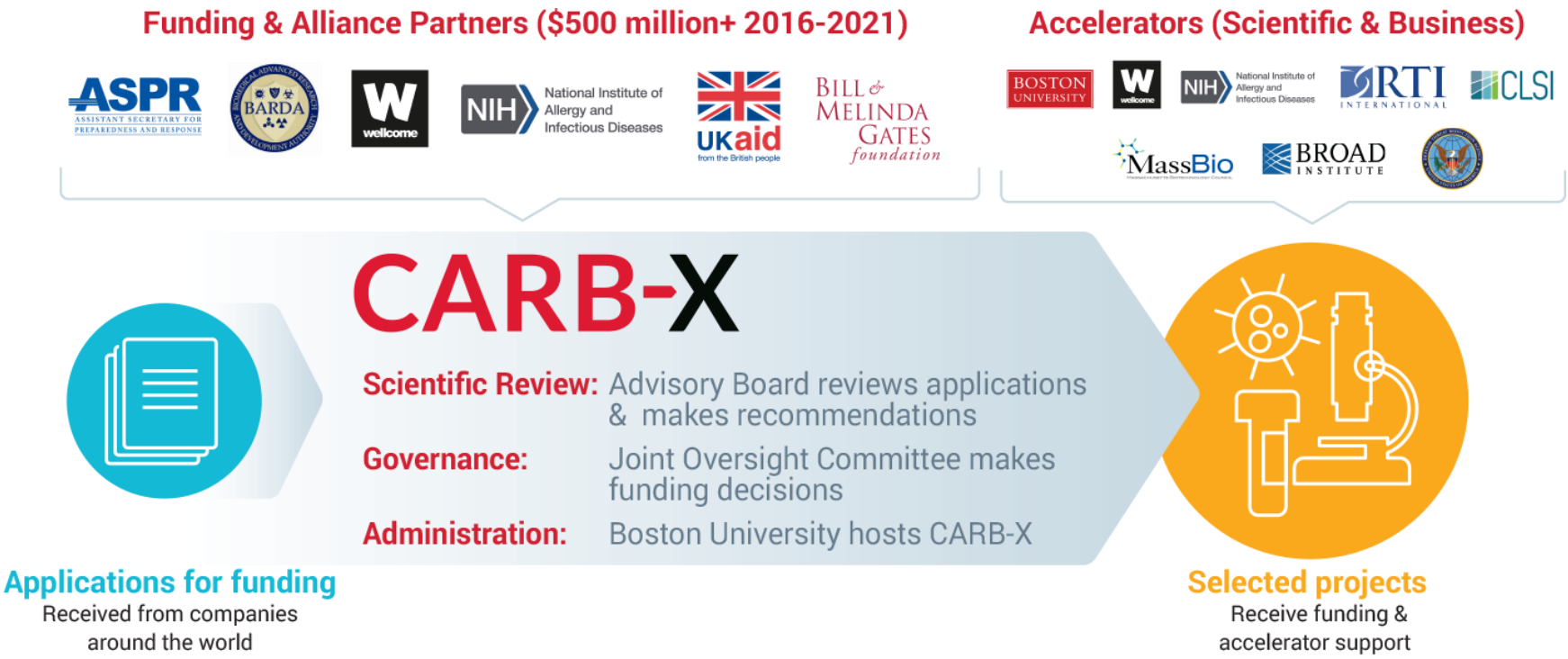
MassBio
MASSACHUSETTS BIOTECHNOLOGY COUNCIL

BROAD INSTITUTE

Geneva 22 May 2018

How CARB-X works

CARB-X welcomes applications from around the world. Projects are selected through a competitive process by panels of experts. Funded projects are supported by a network of world-class accelerators



CARB-X funds R&D to combat the rising threat of serious drug-resistant bacteria

Urgent public health need

Antibiotic resistance kills an estimated 700,000 people each year world-wide. No new antibiotic classes for drug-resistant Gram-negative bacteria have been approved in decades.

Investing globally

CARB-X is a non-profit public-private partnership investing more than $500M in 2016-2021 to accelerate the early development of life-saving antibiotics, vaccines and rapid diagnostics.

Turning science into products

CARB-X provides non-dilutive funding and accelerator support for projects that target Gram-negative resistant bacteria on the WHO and CDC priority lists.

Partnering for results

CARB-X is funded by BARDA and the Wellcome Trust, the UK Government and the Bill & Melinda Gates Foundation. NIAID provides pre-clinical services. Partners include the Broad Institute of MIT and Harvard, MassBio, California Life Sciences Institute and RTI International. CARB-X is based at Boston University.

Global Reach: CARB-X Funds 33 Projects in 7 Countries*

North America

Forge Therapeutics
San Diego, CA

Cidara Therapeutics
San Diego, CA

MicrobeDx
Los Angeles, CA

Inhibrx
La Jolla CA

Amicrobe Inc.
Calsbad, CA

Talis Biomedical
Menlo Park, CA

MicuRx Pharmaceuticals
Hayward, CA

Achaogen
San Francisco, CA

Specific Diagnostics
Mountain View, CA

Curza
Salt Lake City, UT

VenatoRx Pharmaceuticals
Malvern, PA

Integrated Biotherapeutics
Rockville, MD

Contrafect Corporation
Yonkers, NY

Melinta Therapeutics
New Haven, CT

Seres Therapeutics
Cambridge, MA

Vedanta Biosciences
Cambridge, MA

T2 Biosystems
Lexington, MA

Helixbind Inc.
Marlborough, MA

Spero Therapeutics
Cambridge, MA

Visterra Inc.
Cambridge, MA

Tetraphase Pharmaceuticals
Watertown, MA

Macrolide Pharmaceuticals
Watertown, MA

Entasis Therapeutics (2)
Waltham, MA

Microbiotix Inc.
Worcester, MA

Europe and Asia

Iterum Therapeutics Ltd.
Dublin, Ireland

Proteus IRC
Edinburgh, Scotland

Oppilotech Ltd.
London, UK

Eligochem Ltd.
Sandwich, UK

Antabio
Labège, France

Idorsia
Allschwil, Switzerland

Debiopharm International S.A.
Lausanne, Switzerland

Bugworks Research India Pvt Ltd.
Bangalore, India

Shionogi & Co., Ltd
Osaka, Japan

* As of 26 May, 2018

Great science knows no boundaries

33 active PD subawards

Powered by CARB-X

- 33 early development projects targeting serious drug resistant bacteria
- 9 new classes of antibiotics
- 10 non-traditional antibiotics
- 11 new molecular targets
- 6 rapid diagnostics

CARB-X Antibacterial Treatment and Prevention Product Portfolio

Sponsor	Product	Novelty: New Abx Class	Novelty: New Non-traditional Product	Novelty: New Target	Description	Priority: CDC	Priority: WHO	Development Stage: Hit to Lead	Development Stage: Lead Optimization	Development Stage: Pre-Clinical	Development Stage: Phase I
Achaogen	Next-Generation AG				Next-gen AG with extended Gram-negative coverage (Pseudomonas)	✓	✓	Gram-neg activity including *Pseudomonas*			
Amicrobe	Amicidin-β		✓		Next-generation local antimicrobial	✓	✓	Broad spectrum			
Antabio	PEI		✓	✓	Pseudomonas elastase inhibitor	✓	✓	*P. 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*			
Curza	CZ-02	✓		✓	Novel class Gram-negative	✓	✓	*Broad Spectrum*			
Debiopharm International SA	Debio1453	✓		✓	Narrow-spectrum inhibitors of FabI	✓	✓	*Neisseria Gonorrhoeae*			
Eligochem	Helical AMP	✓			Helical antimicrobial peptide	✓	✓	Gram-negative activity			
Entasis Therapeutics	ETX0282CPDP				Oral Gram-negative combination	✓	✓	Gram-negative activity			
Entasis Therapeutics	Non-BL PBPi	✓			Non-beta-lactam PBPi	✓	✓	Gram-negative activity			
Forge Therapeutics	FG-LpxC	✓		✓	LpxC inhibitor	✓	✓	Gram-negative activity			
Idorsia	TopESKAPE	✓			Dual-acting topoisomerase inhibitor	✓	✓	*Acinetobacter, Pseudomonas, and Enterobacteriaceae*			
Inhibrx	INBRX-111		✓	✓	Multi-specific antibody	✓	✓	*P. aeruginosa*			
Integrated BioTherapeutics	IBT-V02		✓		Multi-valent toxoid vaccine	✓	✓	*S. aureus*			
Iterum	Sulopenem				Oral and IV penem	✓	✓	Gram-negative activity			
Macrolide	Novel Macrolides				Novel macrolide antibiotics with Gram-negative activity	✓	✓	Gram-negative activity			
Melinta	Pyrrolocytosine	✓		✓	Novel class, MDR ESKAPE	✓	✓	*Broad spectrum*			
Microbiotix	T3SS Inhibitor		✓	✓	Virulence modifier	✓	✓	*P. aeruginosa*			
MicuRx	MRX-8				Soft drug polymyxin	✓	✓	Gram-negative activity			
Seres Therapeutics	SER-155		✓		Microbiome - transplant patients	✓	✓	Broad spectrum activity vs CRE/VRE			
Shionogi	AGN-BL				Novel gram-negative lactam	✓	✓	*Enterobacteriaceae*			
Spero Therapeutics	SPR741			✓	Potentiator	✓	✓	Gram-negative activity			
Tetraphase Pharmaceuticals	TP-6076				Next-generation tetracycline	✓	✓	*Acinetobacter* + Enterobacteriaceae			
Vedanta	VE303		✓		Microbiome	✓		*C.difficile*			
VenatoRx	VNRX-PBP	✓			β-lactamase resistant PBP inhibitor	✓	✓	Entero-bacteriacae			
Visterra	VIS705		✓	✓	Antibody-drug conjugate	✓	✓	*P. aeruginosa*			

CARB-X Antibacterial Devices and Diagnostic Product Portfolio

Sponsor	Type	Technology	Description: Feasibility Demonstration	Description: Optimization and Preparation for Development	Description: Product Development	Description: System Integration and Testing
Helixbind	Hospital Dx	Automated culture-free pathogen ID	Bloodstream Infections			
MicrobeDx	Near care Dx	CD based microfluidics	Urinary Tract Infection			
Proteus	Rapid POC Dx	Optical bacterial imaging	POC Diagnostic			
Specific Diagnostics	Hospital Dx	Colorimetric Sensor Array to detect VOCs	Bloodstream Infections			
Talis	Point of care Dx	Pathogen ID; Phenotypic AST	AST *Neisseria gonorrhoeae*	NID NG and *Chlamydia trachomatis*		
T2 Biosystems	Hospital Dx	Expanded bacteria and resistance panels for T2Dx	Bloodstream Infections			

CARB-X

As of May 26, 2018

Powered by CARB-X

- CARB-X has announced more than $87 million in awards, plus an additional $118 million if project milestones are met.
- More awards to come in 2018, including a significant number of additional vaccines and other preventatives

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Antabio	PEI		✓	✓	Pseudomonas elastase inhibitor	✓	✓	*P. aeruginosa*			
Bugworks Research	GYROX	✓			Gyrase-topoisomerase inhibitor	✓	✓	Gram-negative activity			
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Eligochem	Helical AMP	✓			Helical antimicrobial peptide	✓	✓	Gram-negative activity			
Entasis Therapeutics	ETX0282CPDP				Oral Gram-negative combination	✓	✓	Gram-negative activity			
Entasis Therapeutics	Non-BL PBPi	✓			Non-beta-lactam PBPi	✓	✓	Gram-negative activity			
Forge Therapeutics	FG-LpxC	✓		✓	LpxC inhibitor	✓	✓	Gram-negative activity			
Idorsia	TopESKAPE	✓			Dual-acting topoisomerase inhibitor	✓	✓	*Acinetobacter, Pseudomonas, and Enterobacteriaceae*			
Inhibrx	INBRX-111		✓	✓	Multi-specific antibody	✓	✓	*P. aeruginosa*			
Integrated BioTherapeutics	IBT-V02		✓		Multi-valent toxoid vaccine	✓	✓	*S. aureus*			
Iterum	Sulopenem				Oral and IV penem	✓	✓	Gram-negative activity			
Macrolide	Novel Macrolides				Novel macrolide antibiotics with Gram-negative activity	✓	✓	Gram-negative activity			
Melinta	Pyrrolocytosine	✓		✓	Novel class, MDR ESKAPE	✓	✓	*Broad spectrum*			
Microbiotix	T3SS Inhibitor		✓	✓	Virulence modifier	✓	✓	*P. aeruginosa*			
MicuRx	MRX-8				Soft drug polymyxin	✓	✓	Gram-negative activity			
Seres Therapeutics	SER-155		✓		Microbiome - transplant patients	✓	✓	Broad spectrum activity vs CRE/VRE			
Shionogi	AGN-BL				Novel gram-negative lactam	✓	✓	*Enterobacteriaceae*			
Spero Therapeutics	SPR741			✓	Potentiator	✓	✓	Gram-negative activity			
Tetraphase Pharmaceuticals	TP-6076				Next-generation tetracycline	✓	✓	*Acinetobacter* + Enterobacteriaceae			
Vedanta	VE303		✓		Microbiome	✓		*C.difficile*			
VenatoRx	VNRX-PBP	✓			β-lactamase resistant PBP inhibitor	✓	✓	Entero-bacteriacae			
Visterra	VIS705		✓	✓	Antibody-drug conjugate	✓	✓	*P. aeruginosa*			

CARB-X Antibacterial Devices and Diagnostic Product Portfolio

Sponsor	Type	Technology	Description: Feasibility Demonstration	Description: Optimization and Preparation for Development	Description: Product Development	Description: System Integration and Testing
Helixbind	Hospital Dx	Automated culture-free pathogen ID	Bloodstream Infections			
MicrobeDx	Near care Dx	CD based microfluidics	Urinary Tract Infection			
Proteus	Rapid POC Dx	Optical bacterial imaging	POC Diagnostic			
Specific Diagnostics	Hospital Dx	Colorimetric Sensor Array to detect VOCs	Bloodstream Infections			
Talis	Point of care Dx	Pathogen ID; Phenotypic AST	AST *Neisseria gonorrhoeae*	NID NG and *Chlamydia trachomatis*		
T2 Biosystems	Hospital Dx	Expanded bacteria and resistance panels for T2Dx	Bloodstream Infections			

As of May 26, 2018

CARB-X Clinical Investments

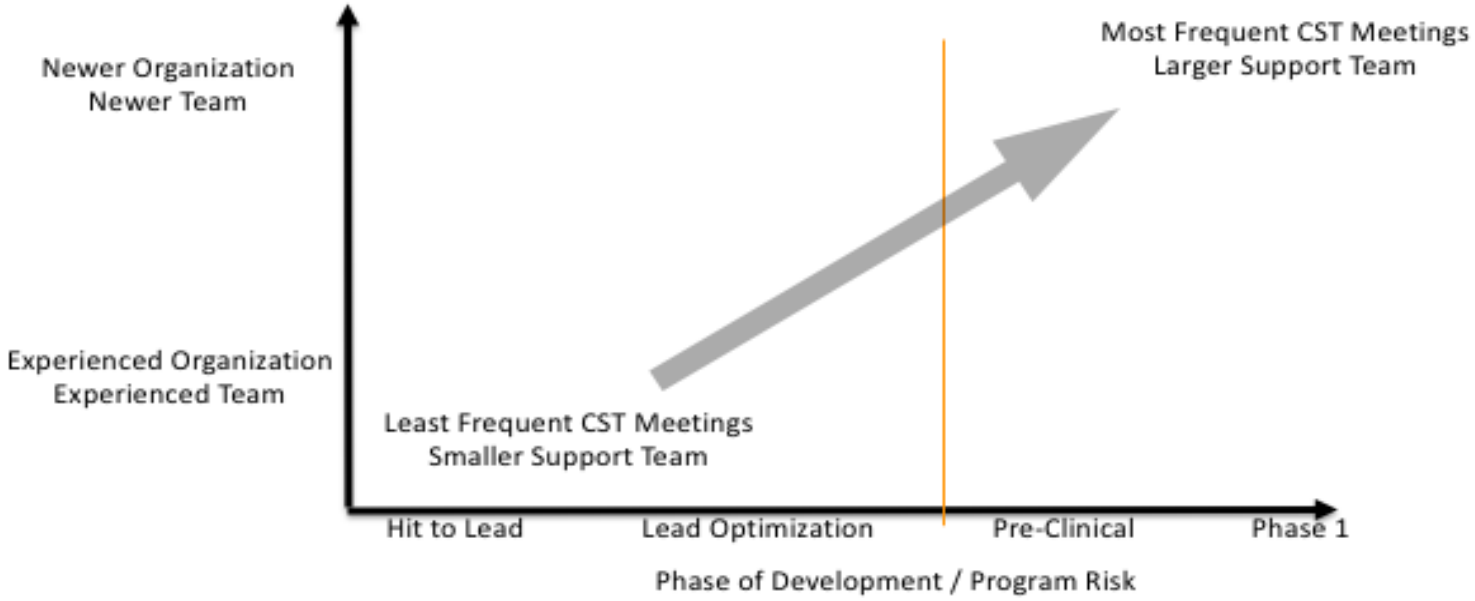
- 5 funded projects in Phase I (ending at SAD/MAD)
- Total CARB-X Phase I investment: $15.825M
- Company cost share: $13.775M

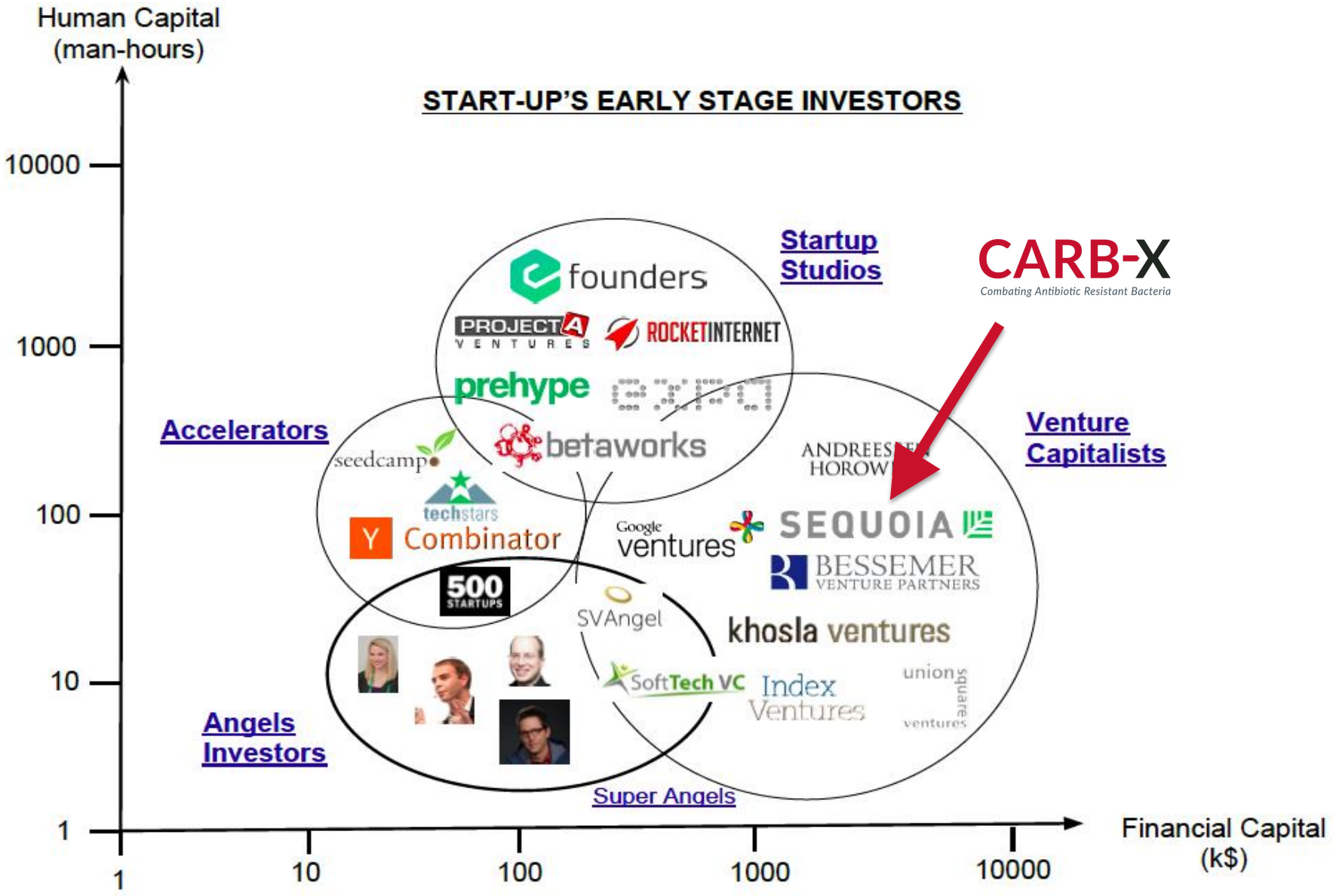
CARB-X MRB Decisions (as of 28 May 2018)

- First MRB meeting was Oct 2017
- 10 decisions thus far
  - Terminations: 2
  - No cost extensions: 3
  - Budget modifications within stage: 1
  - Milestones met and progress to funding next stage: 4
- We have no quotas; the process is driven by whether the projects meet the pre-determined milestones

Post-award services

- In addition to funding, CARB-X also provides wrap-around support services through accelerators and experts on our AdBoard
- Business, scientific, technical, regulatory support
- Based on company need & stage of development
- FDA workshops 14 June / 21-22 Aug




Human Capital
(man-hours)
START-UP'S EARLY STAGE INVESTORS
10000
1000
100
10
1
1
10
100
1000
10000
Financial Capital
(k$)
Startup
Studios
CARB-X
Combating Antibiotic Resistant Bacteria
founders
PROJECT A VENTURES
ROCKETINTERNET
prehype
Accelerators
seedcamp
betaworks
techstars
Y Combinator
500 STARTUPS
Venture
Capitalists
Google ventures
SEQUOIA
BESSEMER VENTURE PARTNERS
SVAngel
khosla ventures
SoftTech VC
Index Ventures
union square ventures
Angels
Investors
Super Angels

CARB-X^ed

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

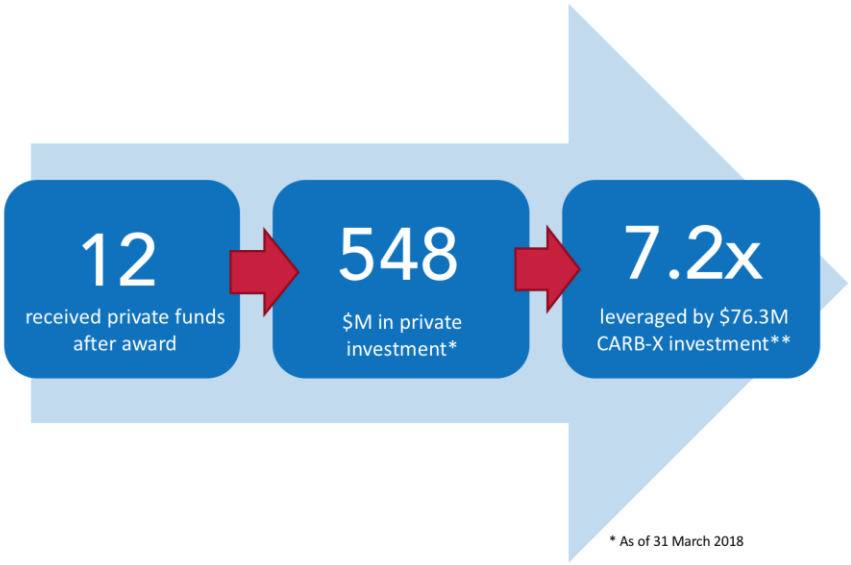
- We hosted 3 Bootcamps
  - What is a TPP; CMC; Microbiology for an NDA
- ~190 people at each
- VERY positive feedback

CARB-X (and funders) …. are at the forefront of innovative funding in AMR and have proven it is possible to take action within a few months to make the difference….

BEAM Alliance Position Paper 2017,
urging 'push-pull' incentives for SMEs

- November 16, 2017

Private investment following CARB-X funding



ACHAOGEN	ANTABIO Developing tomorrow's antibacterials	CIDARA THERAPEUTICS
$50.0M	$8.9M	$20.0M
ContraFect	ENTASIS THERAPEUTICS	FORGE Therapeutics
$40.0M	$31.9M	$15.0M
ITERUM Therapeutics	MICURX PHARMACEUTICALS	SPERO THERAPEUTICS
$78.1M	$15.5M	$135.3M
TETRAPHASE PHARMACEUTICALS	VenatoRx PHARMACEUTICALS	Visterra
$65.0M	$42.0M	$46.7M

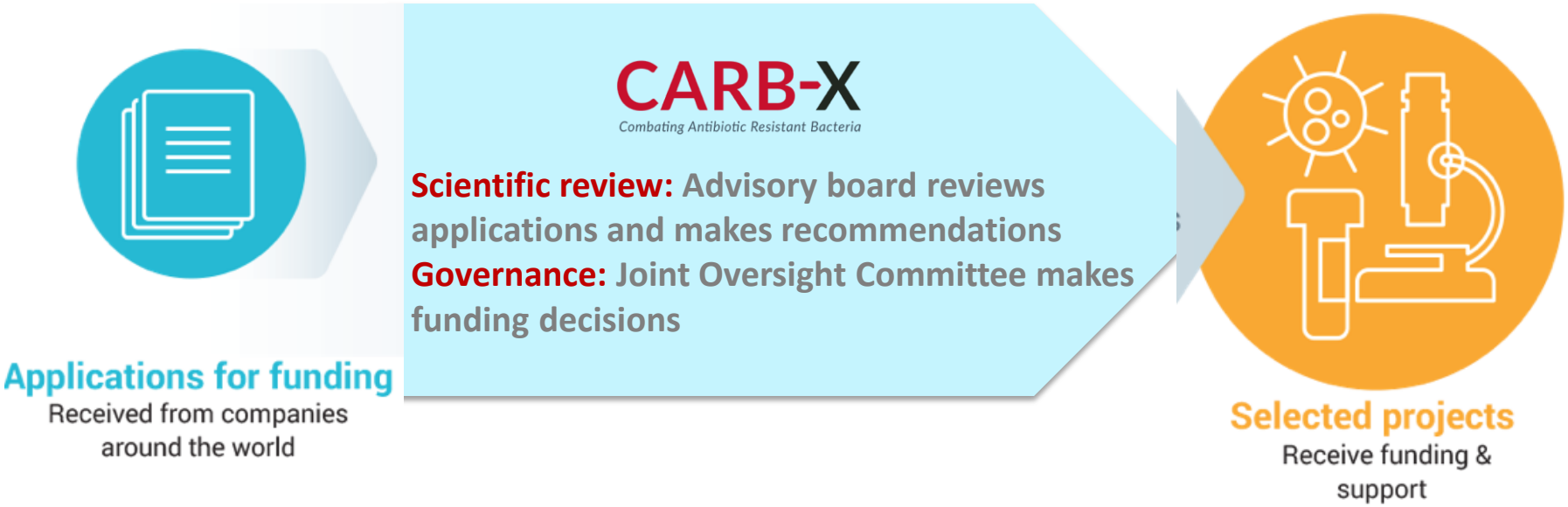
Every $1 that CARB-X invested in *Powered by CARB-X* projects was followed by more than $7.2 in private funding

*As of 31 March 2018; does not include $18M in non-CARB-X grants.

** Total CARB-X Base investments announced as of 31 March 2018. Does not include uncontracted Options.

Applying to CARB-X

How Funding Decisions are Made



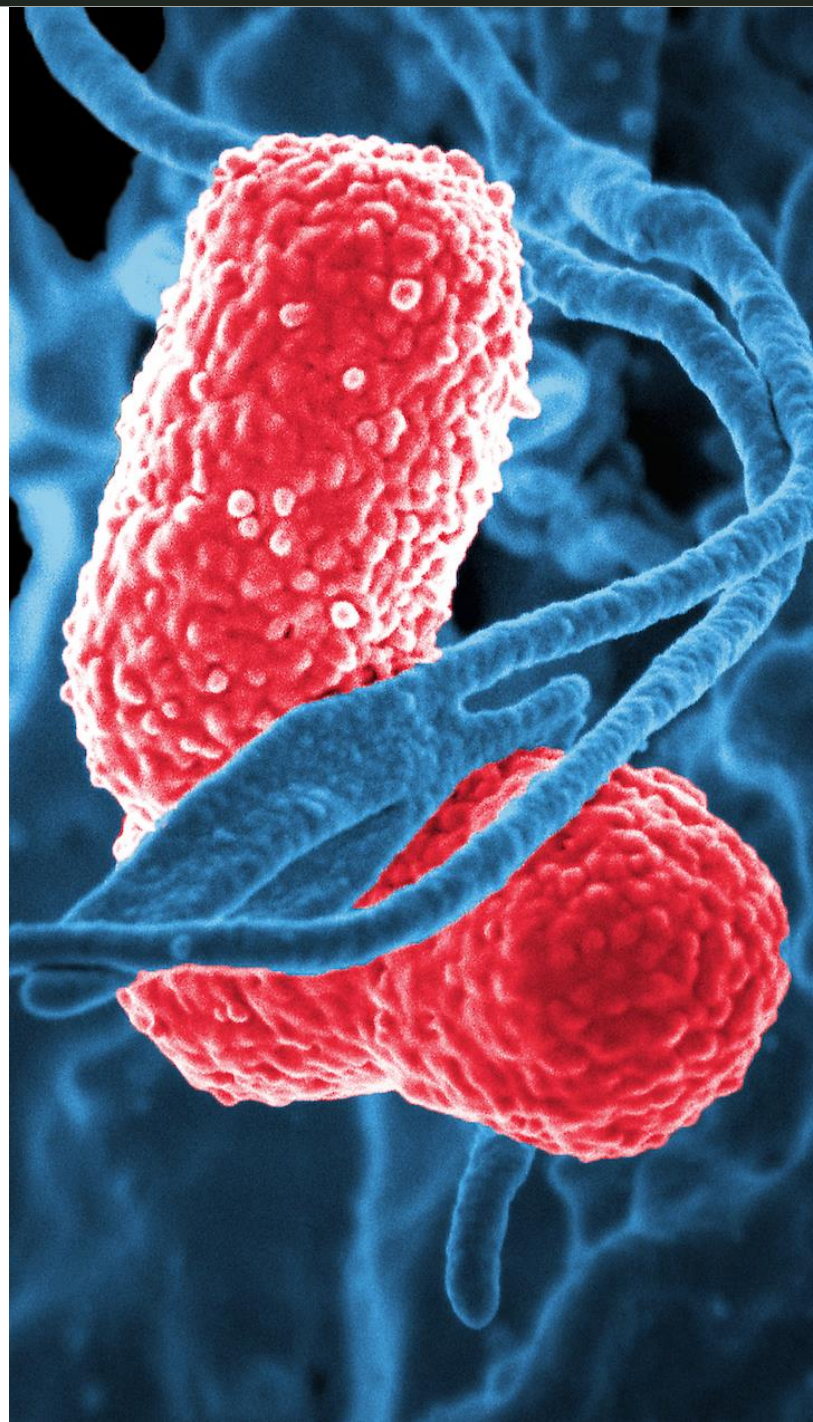
What to Expect When You Apply

About 8 months from EOI to decision

1	2	3	4	5	6	7	8
Cycle begins	**Expression of Interest**	**Review by CARB-X**	**Short Form**	**Review by CARB-X**	**Long form**	**Final Review**	**Funding**
CARB-X sets the scope and timing of funding cycle, and opens the application period.	Companies submit Expressions of Interest summarizing the product proposed as a candidate for support. EOIs should not include confidential information.	CARB-X evaluates the application. and selects qualifying projects. CARB-X invites selected applicants via email to provide more detail in a confidential Short Form.	Selected companies submit confidential Short Forms.	CARB-X evaluates the Short Form and invites selected applicants via email to provide more detail in a confidential Long Form.	Selected applicants submit Long Form and a detailed budget.	Long Form applicants are invited to present their project proposals in person to an Advisory Board panel. Applicants undergo due diligence.	Final funding decisions made by CARB-X's JOC. Sub-award negotiations begin on project plan, milestones and budgets. Applicants must agree contractually to certain standards and conditions. Project support begins.

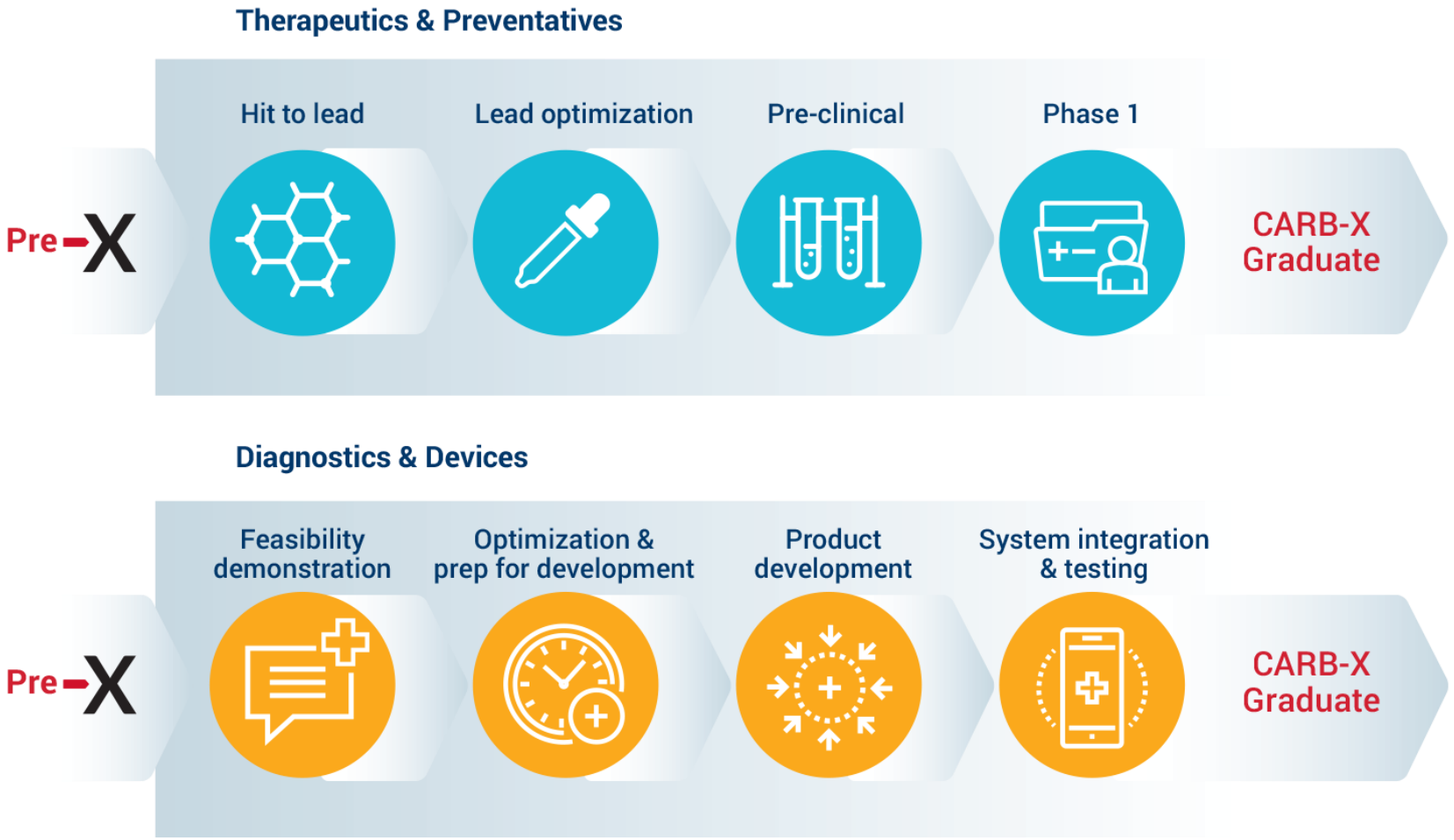
What CARB-X Funds

- Early development projects that address serious bacterial threats
  - antibiotics and therapeutics of all types
  - rapid diagnostics
  - prevention such as vaccines, microbiome, devices
- Projects must target specific bacteria on the Antibiotic Resistance Threats List issued by the Centers for Disease Control and Prevention (CDC) in 2013 or on the Priority Bacterial Pathogens list published by the World Health Organization (WHO) in 2017



CARB-X

CARB-X Funds Projects in Early Development



Who Can Apply for CARB-X Funding?

CARB-X welcomes applications from around the world

- Projects must be in scope – CARB-X and specific round
- Applicants must have a legal entity and be considered a going concern – solvent with funding in place for operations for at least 12 months
- Applicants must own or have rights to the intellectual property and reasonable expectation of freedom to operate required to carry out the project
- Applicants must be able to contribute at least 30% of the cost of the program/project
  - Applicants from larger or better-resourced companies are encouraged to propose higher amounts of cost share where feasible, as this demonstrates financial commitment to the project
- Applicants must have appropriate operations or capabilities in place to support product development, at least through proposed project phases
- Applicants from noncommercial drug development centers or academic institutions must meet additional requirements (next slide)

CARB-X Welcomes Applications from Academic and Non-commercial Developers

Organization must be able to demonstrate R&D/business capabilities, including

- Capabilities similar to those expected of a drug development industry partner, particularly through the development stages in scope for CARB-X.
- Access to and use of relevant experts (internal and/or external) to advance projects toward clinical investigation within the framework of a major regulatory agency, e.g. FDA, EMA, PMDA
- Active management of IP supporting the project
- Well-developed strategy for advancement to human clinical with options for 'exit strategy' from organization (e.g. spin out, licensure to biotech)
- Capabilities in commercial (business) development and technology transfer (if IP is controlled by a university, is the project supported by the Technology Transfer office?)
- Financial commitment and stability to cover cost share of at least 30% of the total cost of the project

Please note: CARB-X does not fund basic research/drug discovery including screening for novel targets

CARB-X 2018 Funding Round 2

- Scope of Round 2
  - **Broad scope** of therapeutics, vaccines, microbiome, diagnostics and devices
- Expressions of Interest (EOI) accepted on-line only https://carb-x.org/apply/
- EOI must be submitted **June 1 - June 8, 2018, 5 pm EST**

Applying for Round 2?
Mark your calendar
June 1 - 8

CARB-X 2018 Funding Round 2 – Scope

Only projects in scope will be considered for funding by CARB-X
To be considered, Expressions of Interest for Round 2 must be submitted on-line June 1 through June 8, 2018, 5 pm EST

Pathogen Scope	Area Scope				Other requirements (if direct Tx)
	Diagnostics	Prevention	Indirect Tx	Direct Tx	
Acinetobacter baumannii, carbapenem-R	YES	YES	YES	YES	
Pseudomonas aeruginosa, carbapenem-R	YES	YES	YES	YES	
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	YES	YES	YES	YES	
Enterococcus faecium, vancomycin-R	YES	YES	YES	YES	Must also target at least one Gram-negative bacteria listed to be in scope
Staphylococcus aureus, methicillin-R, vancomycin-I/R	YES	YES	YES	YES	Must also target at least one Gram-negative bacteria listed to be in scope
Helicobacter pylori, clarithromycin-R [1]	YES	YES	YES	NO	
Campylobacter spp., fluoroquinolone-R[1]	YES	YES	YES	NO	
Salmonellae spp., fluoroquinolone-R[1]	YES	YES	YES	YES	
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	YES	YES	YES	YES	
Streptococcus pneumoniae, penicillin-NS	YES	YES	YES	YES	Must also target at least one Gram-negative bacteria listed to be in scope
Haemophilus influenzae, ampicillin-R [1]	YES	YES	YES	NO	
Shigella spp., fluoroquinolone-R[1]	YES	YES	YES	YES	
Clostridium difficile	YES	YES	NO	NO	
Group A Streptococcus	YES	YES	YES	NO	
Group B Streptococcus	YES	YES	YES	NO	

[1]*Applications for these pathogens should include a discussion of intended/potential routes for sourcing of funding for later stages of clinical development.*

Mode of administration preference guidance:
For Enterobacteriaceae offerings: If Tx is only for ESBL (eg. lacks CRE), PO options are higher priority than IV only
For ***Salmonellae spp., Shigella spp.*** **and** ***Neisseria gonorrhoeae*** **offerings** – if Tx(direct or indirect), oral delivery is strongly preferred
Non-systemic modes of delivery are in scope generally but would require well-reasoned justification for clinical utility/benefit

Tx = therapeutic

UK Government Official Development Assistance (ODA)

- £20 million over 3 years
- Focused on development of alternatives to traditional antibiotics[1] including vaccines for infection prevention in low and middle income countries (LMICs)
- UK funds for CARB-X projects will also meet ODA eligibility criteria
  - ODA is government aid for activities with the primary intention to promote the welfare and economic development of LMICs
  - ODA-eligible research and development:
    - Has to target problems directly and primarily relevant to LMICs
    - Should investigate a specific problem or seek a specific outcome which will impact LMICs in the immediate or longer-term
    - Demonstrate appropriate pathways to impact that ensure the LMIC benefits from the research
    - While LMICs should be the primary beneficiaries, the research can also be relevant and have secondary benefits for HICs
- Complete details at https://carb-x.org/apply/

[1] as defined in Czaplewski et al, Lancet 2016

UKaid
from the British people

Prevention

- Vaccines, microbiome, mAbs and non-traditional approaches are also in scope
- Can spend approximately $75M in this category over next 4 years

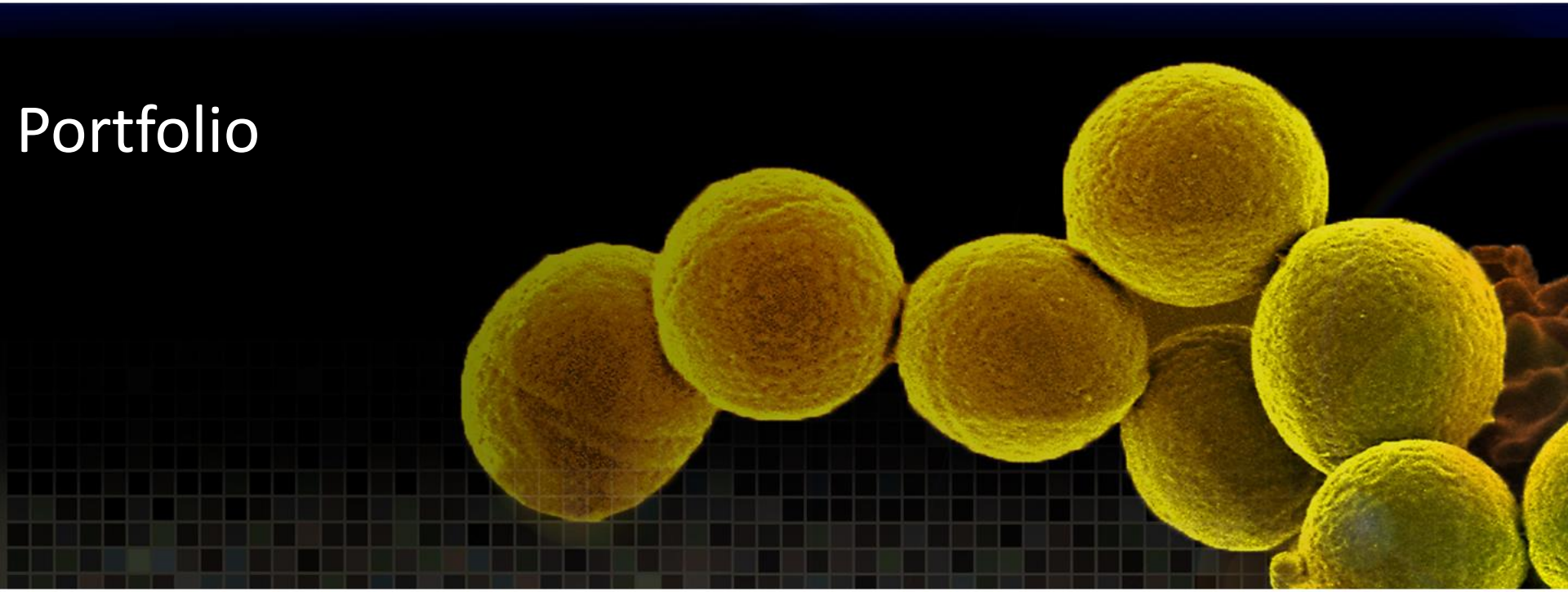
Recap

CARB-X 2018 Funding Round 2 will open for Expressions of Interest from June 1 through June 8, 2018 at 5 pm EST

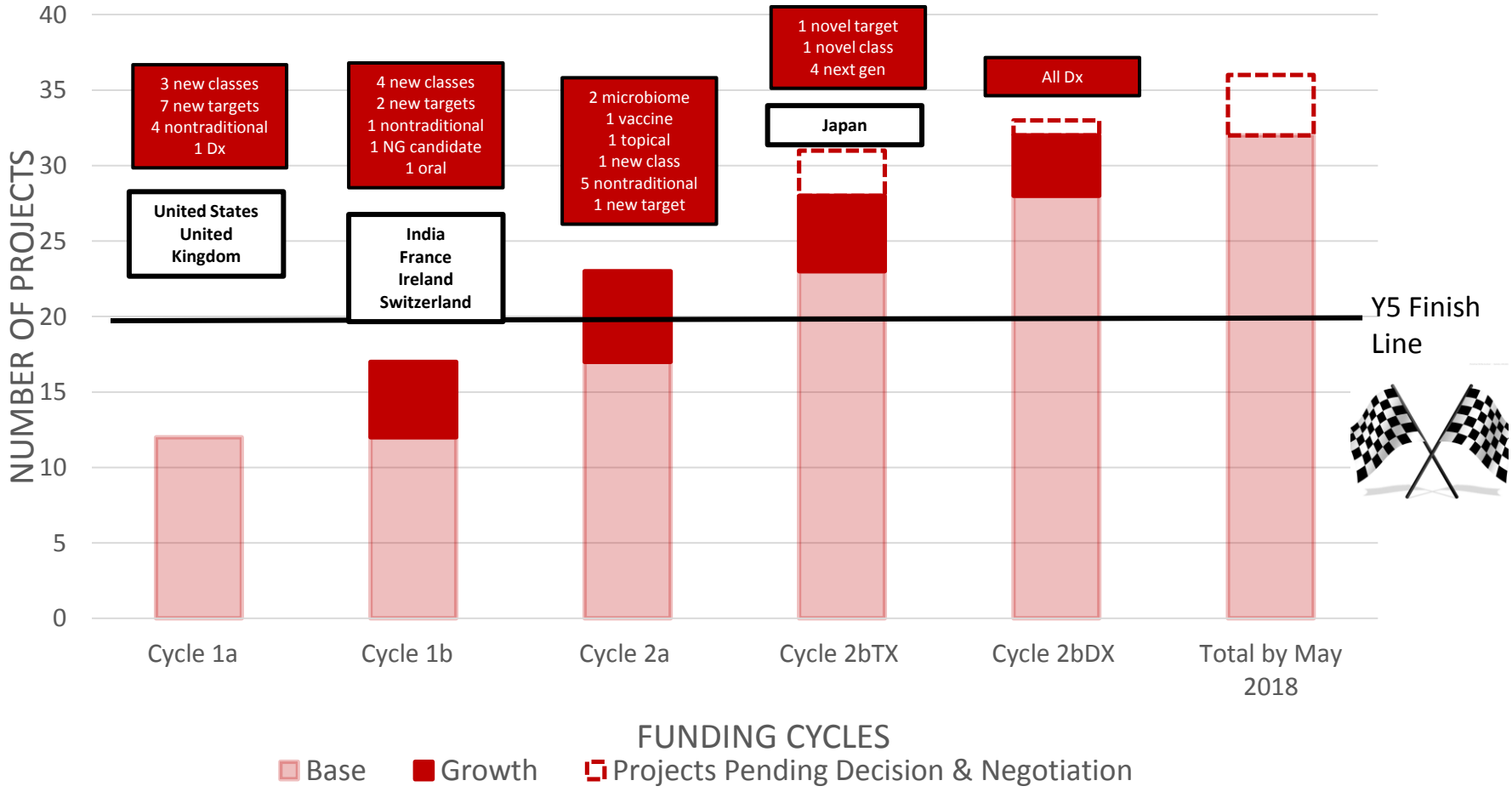
- CARB-X welcomes applications from around the world
- Expressions of Interest applications must be submitted on-line at https://carb-x.org/apply/
- To qualify for funding and support, projects must be in scope and organizations must meet certain criteria
- The *Powered by CARB-X* portfolio is the world's largest and most scientifically diverse portfolio of early development antibacterial products to respond to the threat of the most serious drug-resistant bacteria and we intend to continue to build the portfolio

- More information: www.carb-x.org

Portfolio



CARB-X Portfolio Growth



Does not include awards in process

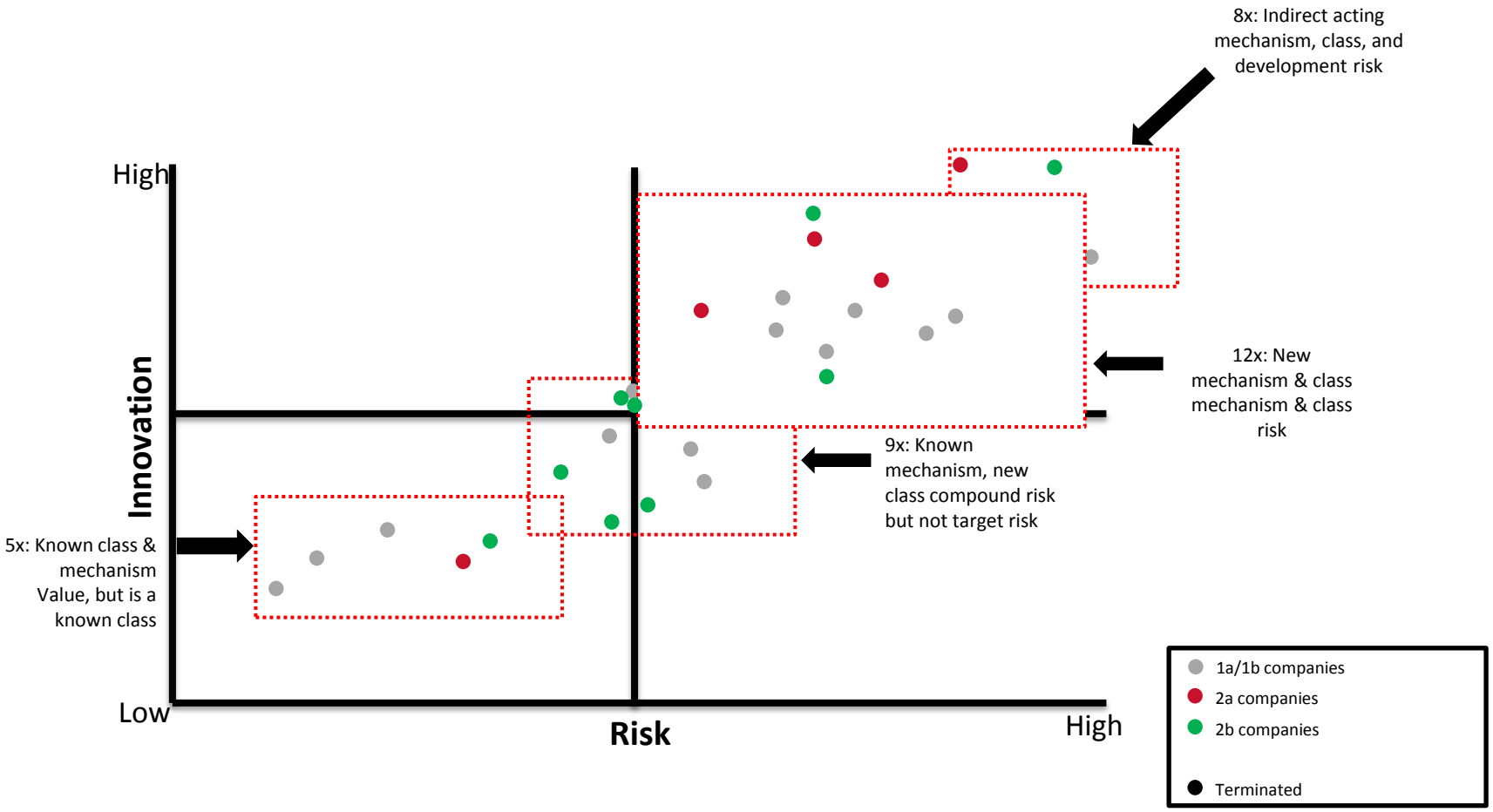
CARB-X Goals re Type/TRL – April 2018

Categories	Year # 1 Projected	Current Status
Antibacterials		
Direct acting- Gram-negative	16	20 (+2)
Direct acting- Gram-positive	0	1 (+1)
Indirect therapeutic	2	5
Preventatives	1	1
Diagnostics	1	5 (+1)
Σ	**=20**	**=32 (+4)**
TRL	**Projected**	**Current Status**
TRL #3 HTL	8	4
TRL #4 LO	6	15 (+4)
TRL #5 PC	4	6
TRL #6 P1	2	7

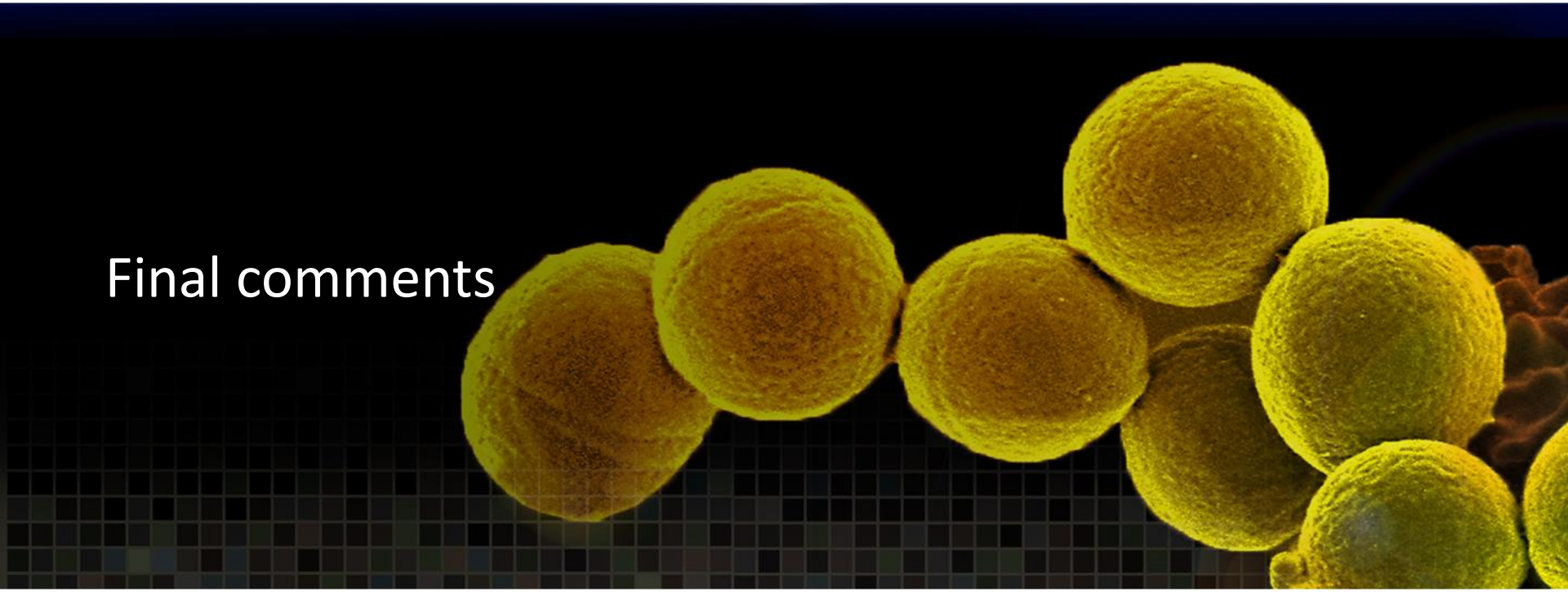
Pathogen Profile of CARB-X Portfolio

Pathogen Profile	Announced Projects	Pending Projects	Total
Pseudomonas	Antabio, Contrafect, Inhibrx, Microbiotix, Visterra		5
Acinetobacter			0
CRE	VenatoRx, Shionogi		2
Klebsiella			0
NG	Debiopharm, Talis	+1	2
Broad Spectrum Gram-negatives	Bugworks, Cidara, Eligochem, Entasis x 2, Forge, Iterum, Spero, Tetraphase, Seres, Amicrobe, Achaogen AG, Idorsia, Curza, Macrolide, MicuRx, Specific Diagnostics, Helixbind, T2, Proteus , Melinta, MicrobeDx		22
C difficile	Vedanta	+1	2
Staph aureus	Integrated Biotherapeutics		1

CARB-X Therapeutics Portfolio: Innovation and Risk Analysis



Final comments



The limits of push incentives

- Push incentives like CARB-X can only reduce costs, making the NPV less negative
- No one wants stronger antibiotic revenues through unchecked drug-resistant infection pandemics or aggressive sales tactics
- Large companies continue to exit. Down to a handful from >30 a few decades ago. In the past 3 years: Cubist, AZ and now Novartis
- **A sustainable global solution requires a significant pull incentive**

Bagley N, Outterson K. We will miss antibiotics when they are gone. NYTimes Jan 18, 2017.

Questions