CARB-X

Combating Antibiotic-Resistant Bacteria

BOSTON UNIVERSITY

Antibacterial R&D: Past, Present, & Future

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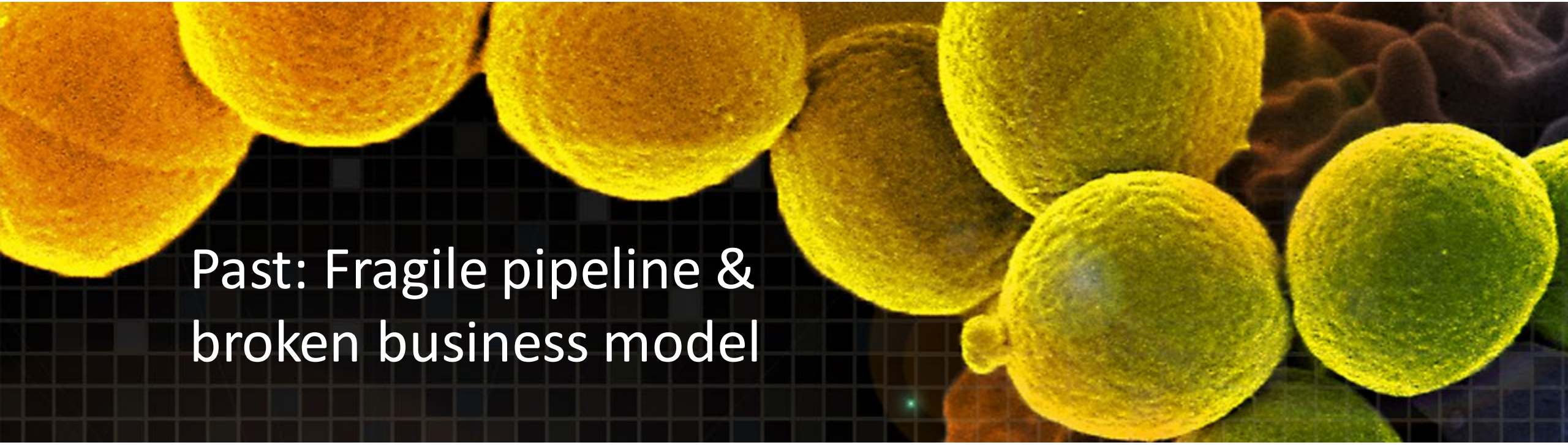
Kevin Outterson
Boston University & CARB-X

Disclaimer

Today's presentation is based on my academic work and does not necessarily represent the positions of CARB-X or any CARB-X funder, including the US Government.

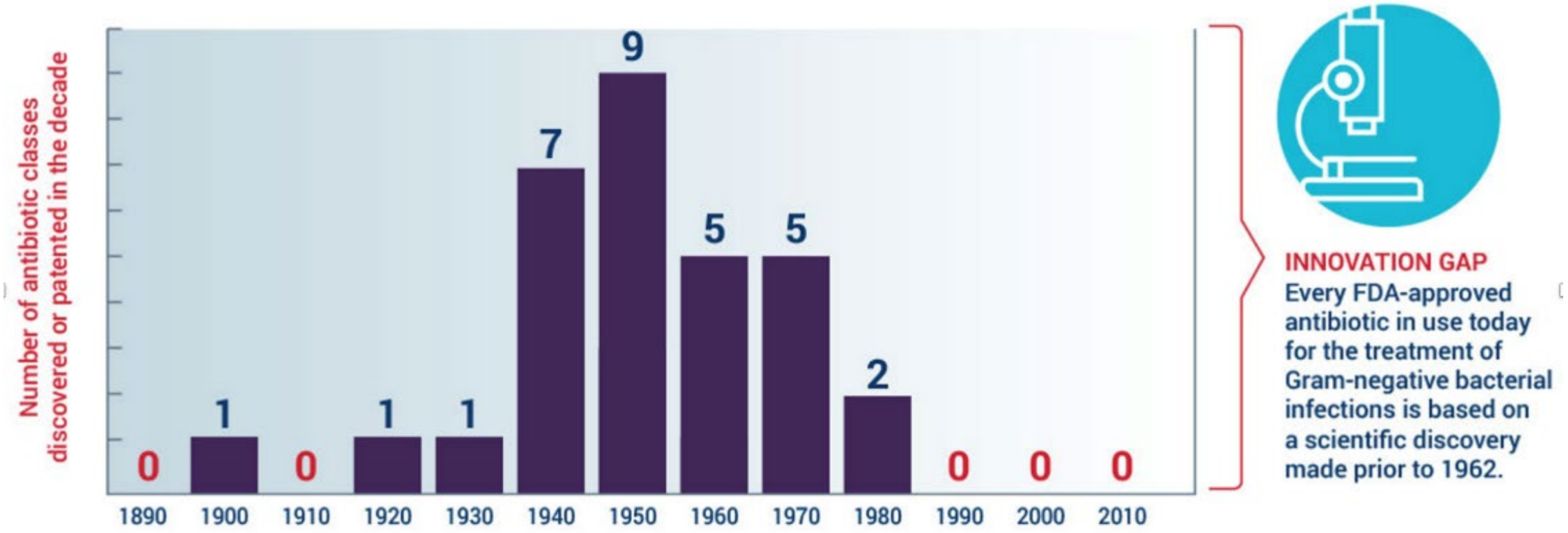
Today's presentation

- **Past:** broken economics, including new data on lack of commercial launches in Canada, Japan, and Europe
- **Present:** brief update on push incentives from CARB-X and BARDA
- **Future:** pull incentives are the strategic gap in the US National Action Plan, + new data supporting the incentives in the PASTEUR Act



Past: Fragile pipeline & broken business model

Approval of new classes has fallen behind



* Cefiderocol was approved by FDA in 2019 and EMA in 2020. The FDA-approved label for cefiderocol classifies the drug as a cephalosporin, and therefore not a new class but certainly a new mechanism of action. Some experts consider cefiderocol to be a first-in-class sideromycin. The predecessors to cefiderocol were discovered at Shionogi in the early 1990s. CID 2019;69(7):S538-S543

* 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 Resistant Bacteria?: A Review of FDA Approved Antibiotics 2010-2015. ANNALS OF INTERNAL MED. 2016 MAY 31. DOI: 10.7326/M16-0291.

Clinical pipeline “insufficient” and “increasingly fragile”

WHO 2021:

- “Overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.”
- 36/43 traditional antibiotics in clinical development achieve no innovation criteria
- Only 2/43 active against multi-drug resistant Gram-negative bacteria

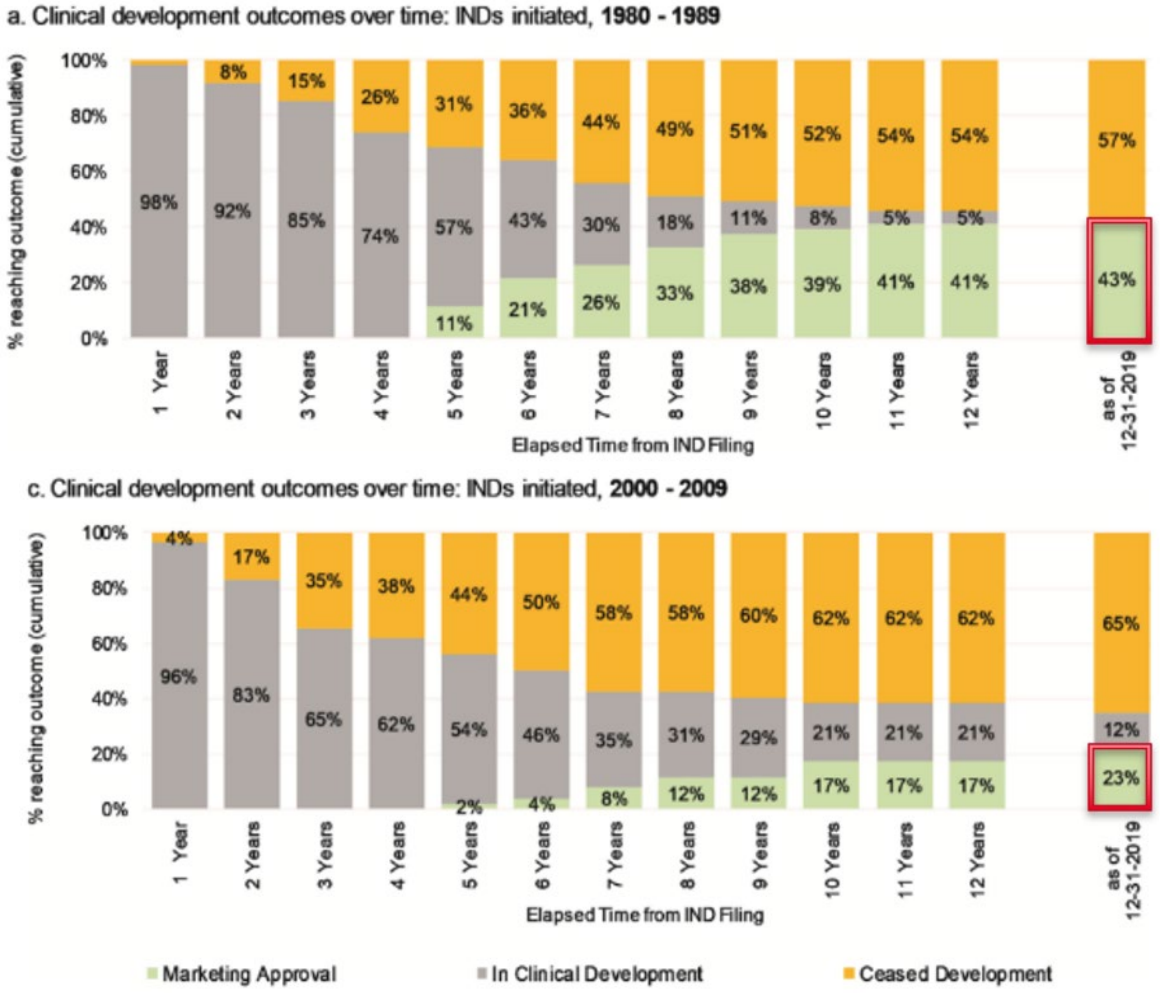
WHO, Antibacterial Agents in Clinical and Preclinical Development (2021).

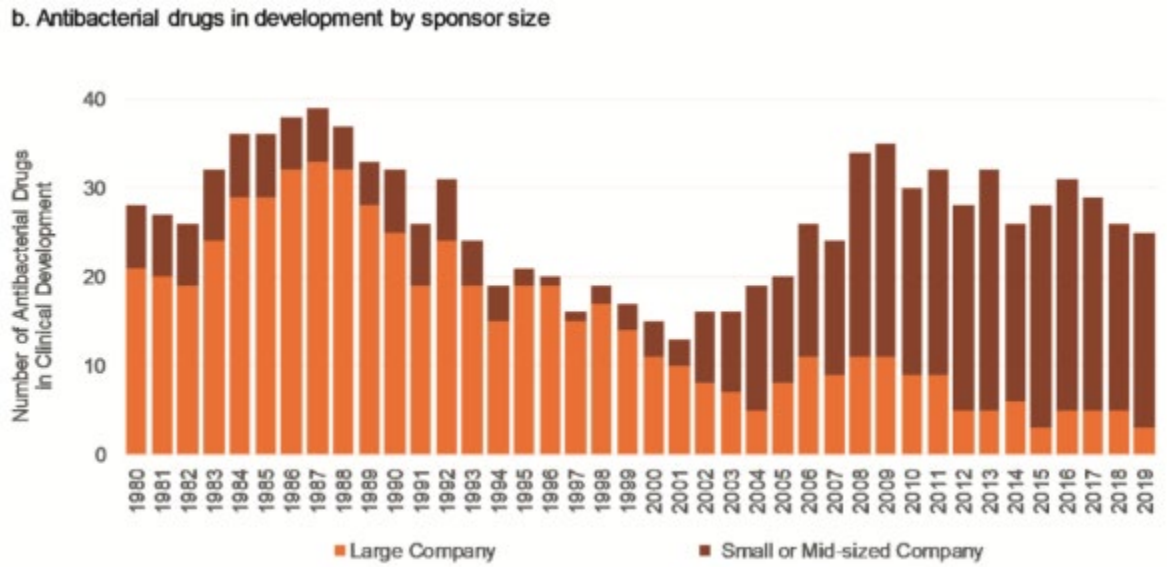
CDC 2019:

- “The drug, diagnostic, and vaccine discovery pipeline are also complex and increasingly fragile.”
- 2.8M+ antibiotic-resistant infections each year in US
- 35k+ deaths from antibiotic resistance each year in US

CDC, Antibiotic Resistance Threats in the United States, 2019.

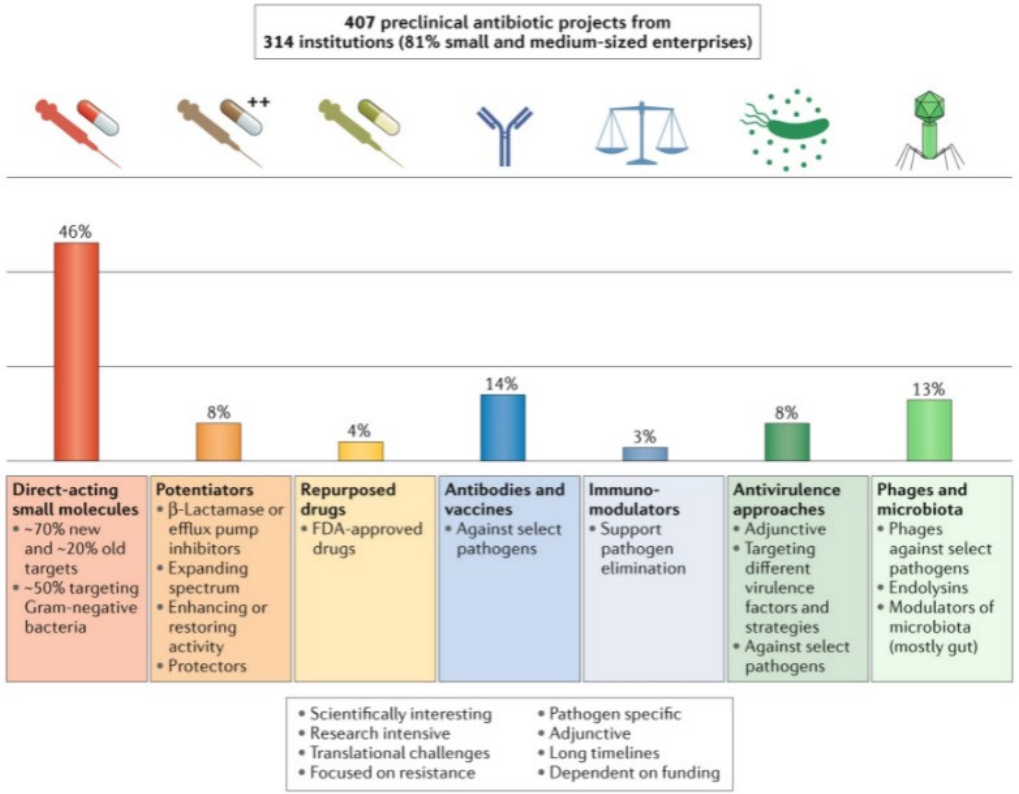
FDA: Clinical development slower, riskier, smaller





- Median clinical development times grew from 6 years (INDs from 1980-89) to 8.2 years (2000-09), projected at 9 years when still-ongoing programs conclude
- Clinical success rate now only 23% IND→FDA approval, significantly reduced from 43% in 1980s
- Clinical pipeline mainly from small or mid-sized companies

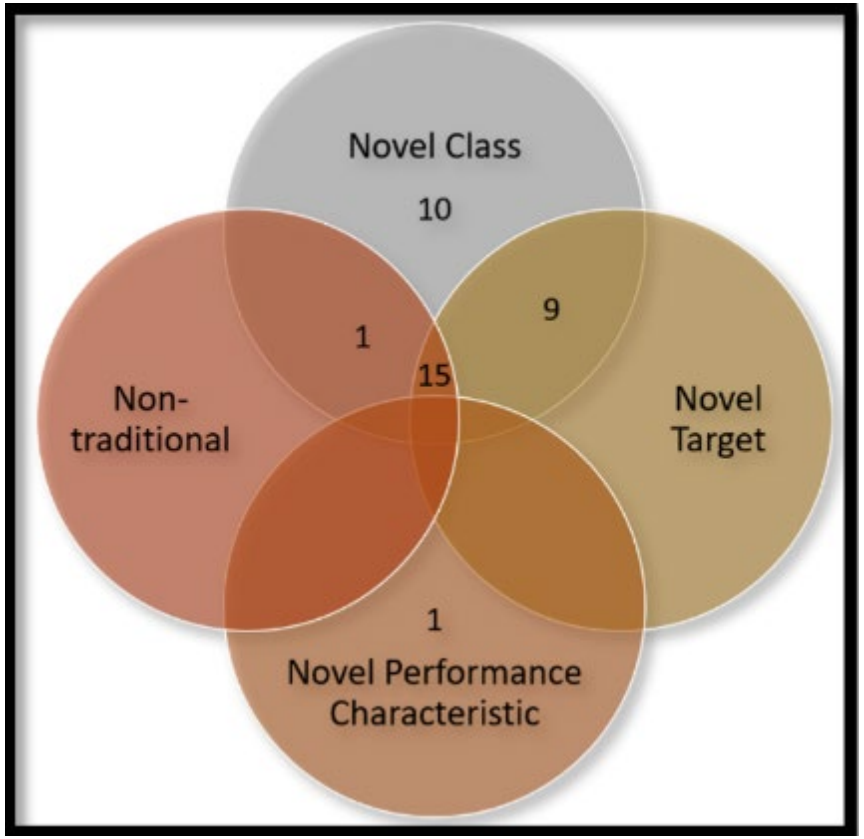
CARB-X: Preclinical pipeline is stronger, diverse



Overview of the preclinical and antibacterial pipeline. We identified 314 research and development institutions and 407 preclinical projects. The projects were categorized according to their main effect on bacteria into the following groups: direct-acting agents, antibodies and vaccines, phages and phage-related products, microbiota-modulating therapies, antivirulence approaches, potentiators of direct-acting drugs, repurposed drugs, immunomodulators or others. The high diversity of approaches provided is innovative but carries high translational risks.

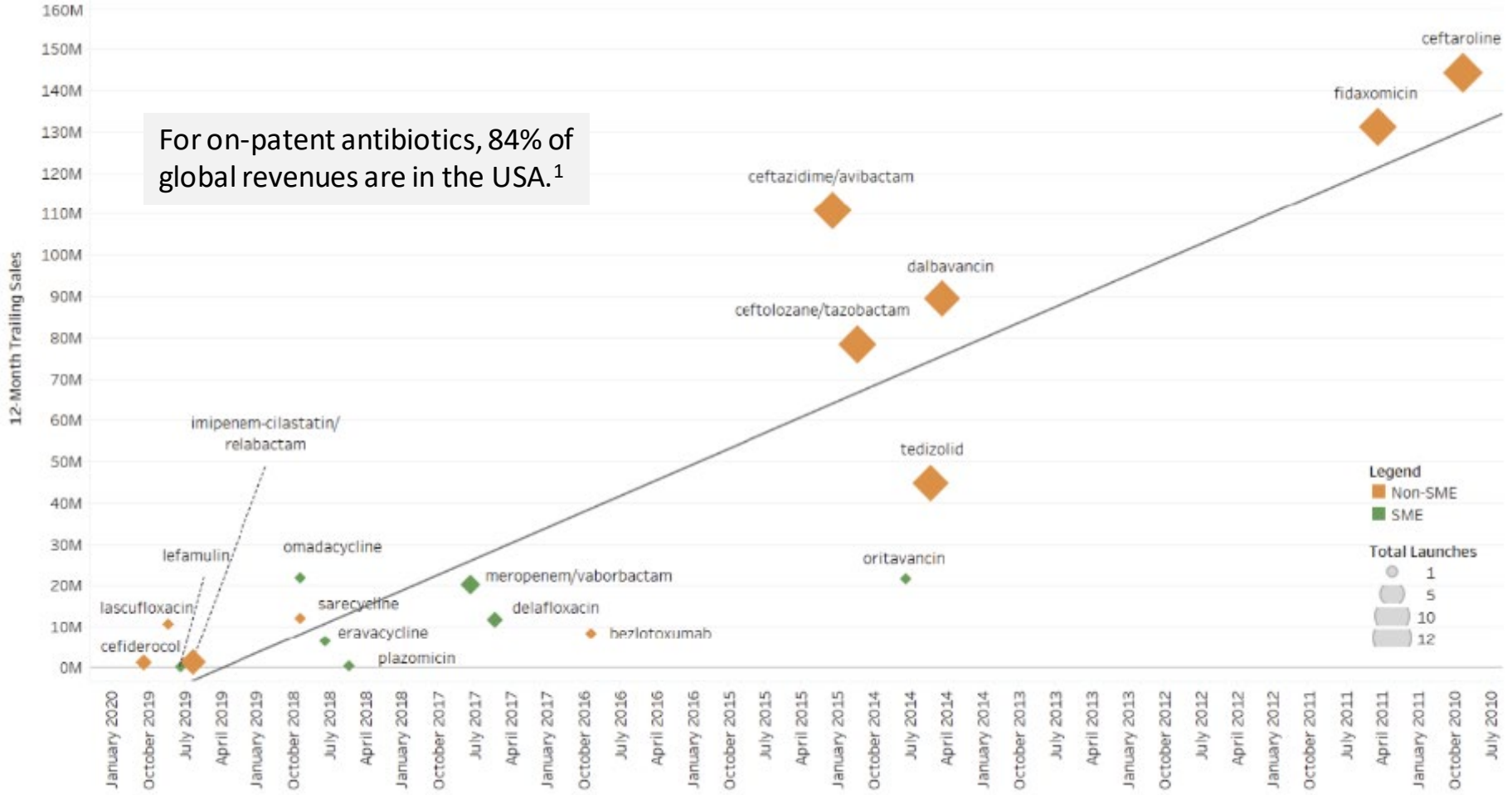
Theuretzbacher U, et al. NatRevMicro 2019; see also WHO 2020 for the public preclinical pipeline

Active CARB-X Therapeutic Projects (June 2021): indicia of novelty & innovation



Limited market impact of recent antibacterials

US revenues & national launches of NME antibacterials first approved by FDA, EMA, PMDA, or Health Canada, 2010-2019, by SME status



- Median US sales (2020) = $16.2M
- Entire class sales = $714.3M
- Sponsors of 7/18 bankrupt or in economic distress since April 2019

Source: Outterson K, Orubu ESF, Rex J, Årdal C, Zaman MH. (pending) 2021.

[1] Rahman S, Lindahl O, Morel CM, Hollis A. Market concentration of new antibiotic sales. The Journal of Antibiotics. 2021.

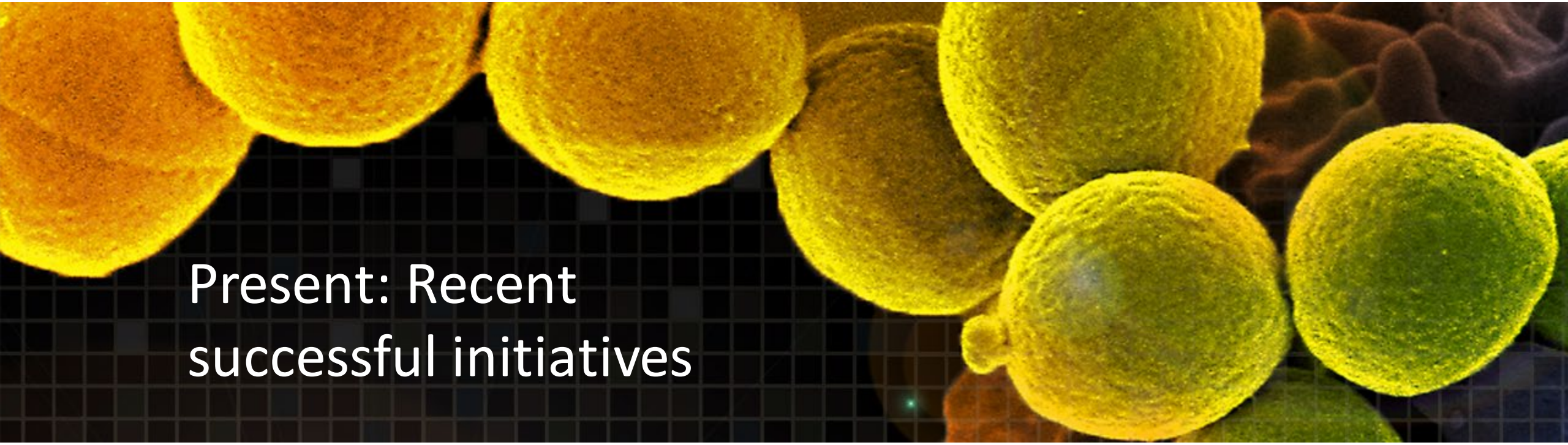
Limited availability in high-income countries, outside US

Approval and commercial launch in fourteen high-income countries of NME antibacterials first approved by FDA, EMA, PMDA, or Health Canada, 2010-2019

INN	1st Approval	US	EMA*	UK	Sweden	France	Germany	Italy	Norway	Spain	Greece	Romania	Croatia	Denmark	Japan	Canada	Launches
cefiderocol	14-Nov-19	102	161	306	413												3
lascufloxacin	20-Sep-19														103		1
lefamulin	19-Aug-19	21	343														1
imipenem-cilastatin/ relabactam	16-Jul-19	321	212	382	382				290								4
omadacycline	2-Oct-18	122															1
sarecycline	1-Oct-18	92															1
eravacycline	27-Aug-18	35	24														1
plazomicin	25-Jun-18	6															1
meropenem/ vaborbactam	29-Aug-17	33	448	815	1037	1064											4
delafloxacin	19-Jun-17	196	910	1121													2
bezlotoxumab	21-Oct-16	115	89	174	131	1045	527	618	206	557					413		9
ceftazidime/ avibactam	25-Feb-15	35	484	748	827	1967	720	1049	310	999	980	933	1184	841			12
ceftolozane/ tazobactam	14-Dec-14	49	278	352	383	598	322	657	383	443	383	808	657	352	1630	291	14
oritavancin	6-Aug-14	56	224														1
tedizolid	20-Jun-14	10	276	315	438	577	276	1046	390	294	681	742		276	1432		12
dalbavancin	23-May-14	39	272	914	1279	1097	918	740		619	954	862	923				10
fidaxomicin	27-May-11	35	192	371	371	542	585	889	385	554	432	797	1711	371	2651	1648	14
ceftaroline	29-Oct-10	64	663	726	764	844	717	1007	755	1162	1315	795	2764	734			12
N approved or launched	18	17	14	11	10	8	7	7	7	7	6	6	5	5	5	2	0

Notes: INN = international nonproprietary name; Empty cell = not commercially launched, except in the EMA column where empty cell = not approved by EMA; Number = lag from first approval to commercial launch, in days, except in the EMA column where number = lag from first approval to EMA approval, in days. The US was the country for all first approvals and first commercial launches, with the exception of lascufloxacin, approved and launched only in Japan. Color key: green = lowest lag in days; red = highest lag in days; yellow = 50th percentile lag in days.

Source: Outterson K, Orubu ESF, Rex J, Årdal C, Zaman MH. (pending) 2021.



Present: Recent successful initiatives

CARB-X accelerates innovative products against drug-resistant bacteria

Therapeutics, preventatives and diagnostics

Global partnership funds and advances high-risk projects with big-impact potential for patients

- Investing $480 million in 2016-22 to accelerate innovation addressing the global rise of antibiotic resistance
- Targeting the most serious antibiotic-resistant bacteria (CDC, WHO)
- Non-dilutive funding to product developers to drive innovation. Companies assume 10%-20% cost-share
- New rounds possible only after new funding received

62 active PROJECTS*

$343M to date

92 PROJECTS since 2016

12 COUNTRIES

20 on new classes

8 project GRADUATES

2 graduates win contracts with BARDA

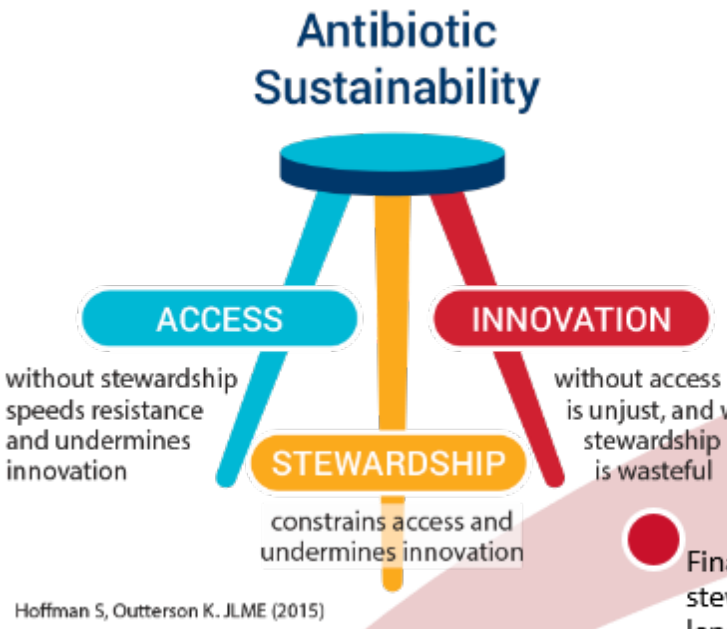
World's largest and most scientifically diverse early development portfolio … more to come

- 37 Therapeutics (new classes, novel targets, non-traditional)
- 13 Preventatives (vaccines, antibodies, microbiome, phage)
- 12 Rapid Diagnostics

*As of June 8, 2021

ASPR Assistant Secretary for Preparedness and Response · BARDA · wellcome · NIH National Institute of Allergy and Infectious Diseases · UKaid from the British people · Federal Ministry of Education and Research · Bill & Melinda Gates foundation

Development guide for global stewardship & access



Contractual stewardship & access language proposed (March 2017)

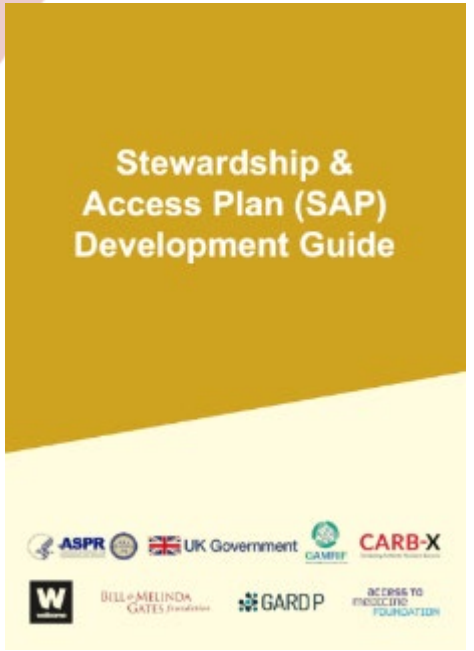
Final consensus on stewardship & access language (March 2018)

Public presentation of CARB-X S&A contractual provisions (Ghana Call to Action workshop, Nov. 2018)

Wellcome Trust collaborative process to develop Development Guide for Product Developers (March 2019)

Completion (Jan. 2021)

Public rollout (March 2021)



The Guide is useful as a benchmark to the broader antibacterial R&D community

Future: Pull incentives required

Antibacterial pull incentives

- Must be willing to pay for antibiotics NOT used in patients today
- Difficult to reimburse for population-level benefits in a patient-level market
  - How do you contract for a payment from the person who didn't get sick?
  - What is the economic value of less dangerous bacterial evolution?
  - Easy to free ride (cancer treatments are not paying for antibiotic R&D)
  - One Health (agriculture & environmental) externalities underexplored
  - **Any skimping means antibiotic R&D < what we need**
- Medicare bundled payment (DRG) impedes hospital patient access
  - DISARM or CMS IPPS Rule are vehicles to address this issue
- Delinkage (pay for **value, not volume**) solves the broken business model
  - See examples of subscription programs (next slides)

"Netflix" subscriptions:

Major gap in current National Action Plan

England

- 2 antibiotics selected for subscription (cefiderocol & ceftazidime+avibactam)
- Explicitly designed to pay for England's fair share of STEDI values, through Health Technology Assessment process
- Up to $130M/drug over a decade

Sweden

- Contracting for availability in Sweden
- Guaranteed revenue of SEK 4M (<$500k)/drug/year
- Not designed as an R&D incentive, but could be scaled
- 4 NME antibiotics in initial contracts (3 βL+βLIs & cefiderocol; 3 not previously launched in Sweden)

USA

- PASTEUR Act (*proposed* by Senators Bennet & Young)
- 10-year subscription for highly novel new antibiotic
- Per drug subscription of $750M to $3B per drug, based on target product profile

Active discussions in EU, Japan, & G7

How large should antibacterial pull incentives be?

5 gov't reports:

- Sertkaya 2014 (HHS/ERG)
- AMR Review 2016 (UK/O'Neill)
- GUARD 2017 (German BMG/BCG)
- DRIVE-AB 2018 (IMI)
- WHO 2020

Source: Outterson K. 2021 (in submission)

All pull incentive values > $1B (2021$), but:

- Most estimates are partially delinked market entry rewards, not subscriptions
- Most assume increased push incentives
- Some issues with input parameters on antibacterial R&D, especially R&D costs, post-approval costs, preclinical success, and estimated global peak year sales (GPYS)
- Difficult to estimate impact of different assumptions

A transparent net present value (NPV) model

Answers the question: "what size of pull incentives are required for the sponsor to achieve 10% expected internal rate of return?"

- Pull incentives examined:
  - global peak year sales (GPYS)[1]
  - market entry reward (MER)[2]
  - subscription (SUB)[3]
  - For MER & SUB, also the business case of acquisition of a Phase 2-ready asset (ACQ) (i.e., transaction with the AMR Action Fund)
- Duration, cost, probability of success, and other parameters from best published sources, plus realistic commercial estimates from the last decade
- Sensitivity testing to generate best estimates + upper and lower bounds
- Dashboard allows other researchers to test alternate parameters and assumptions, with full transparency

[1] Revenues are only from sales (not delinked);
[2] Revenues are from sales + the MER (partially delinked);
[3] Revenues only from SUB (fully delinked)

Source: Outterson K. 2021 (in submission)

eNPV model bottom line results

- Global subscription = $3.1B ($2.2B-$4.8B) per drug over 10 years
  - SUB includes pre-payment for all US federal purchases over 10 years
  - Amounts should be reduced by any clinical push incentives received
  - Subscriptions in other countries should be encouraged as well
- PASTEUR + UK will solve the commercial issues blocking R&D
  - Amounts are within "fair share" estimates within the G7/G20
- Pull incentives are required
  - Even 100% grants for all preclinical costs were not sufficient, due to the large cost of clinical and post-approval studies compared to low revenues
  - UK alone insufficient
- Push incentives are good value
  - In the absence of push incentives, the pull incentives required increase by several billions
- Even non-profit antibacterial development would require substantial pull incentives

Source: Outterson K. 2021 (in submission)

Conclusion

- The economics of antibiotic R&D are worse than we thought
- Push incentives are working, but insufficient without substantial pull incentives
- The incentives in the PASTEUR Act would solve the economic problems

PACCARB should recommend pull incentives, filling a key gap in the US National Action Plan