CARB-X

Combating Antibiotic-Resistant Bacteria

BOSTON UNIVERSITY

We have a solution to the antibacterial innovation and access crisis: PUSH + PULL

Kevin Outterson, Executive Director, CARB-X

15 October 2023

The toll of the broken AMR Market

Cumulative loss for investors and US Government grants: $3.6 billion

ACHAOGEN	melinta	TETRAPHASE	SPERO	ENTASIS	Nabriva	PARATEK
Started 2002	**Started** 2002 (as Rib-X)	**Founded** 2006	**Founded** 2013	**Founded** 2015 (spinout from AstraZenca) **Peak Market Cap** $XX	**Founded** 2001	**Founded** 1996
FDA Approval June 2018	**FDA Approval** June 2017	**FDA Approval** Aug 2018	**Peak Market Cap** $628M	**FDA Approval** May 2023	**FDA Approval** Aug 2019	**FDA Approval** Oct 2018
Bankruptcy April 2019	**Peak Market Cap** $423M	**Peak Market Cap** $1.8B	**Layoffs** May 2022	**Distressed Sale** July 2022	**Peak Market Cap** $282M	**Peak Market Cap** $797M
Investor Loss $504M	**Bankruptcy** Dec 2019	**Distressed Sale** Dec 2019	**Current Market Cap** $76M – Drug in P3	**Investor Loss** $134M	**Liquidation** Nov 2022	**Distressed Sale** June 2023
USG Grants $133M	**Investor Loss** $593M	**Investor Loss** $550M	**Investment to date** $439M	**USG Grants** $0	**Investor Loss** $507M	**Investor Loss** $162M
	USG Grants $132M	**USG Grants** $107M	**USG Grants** $60M		**USG Grants** $0	**USG Grants** $285M

Data as of 3Q 2023 and subject to updating as market conditions evolve

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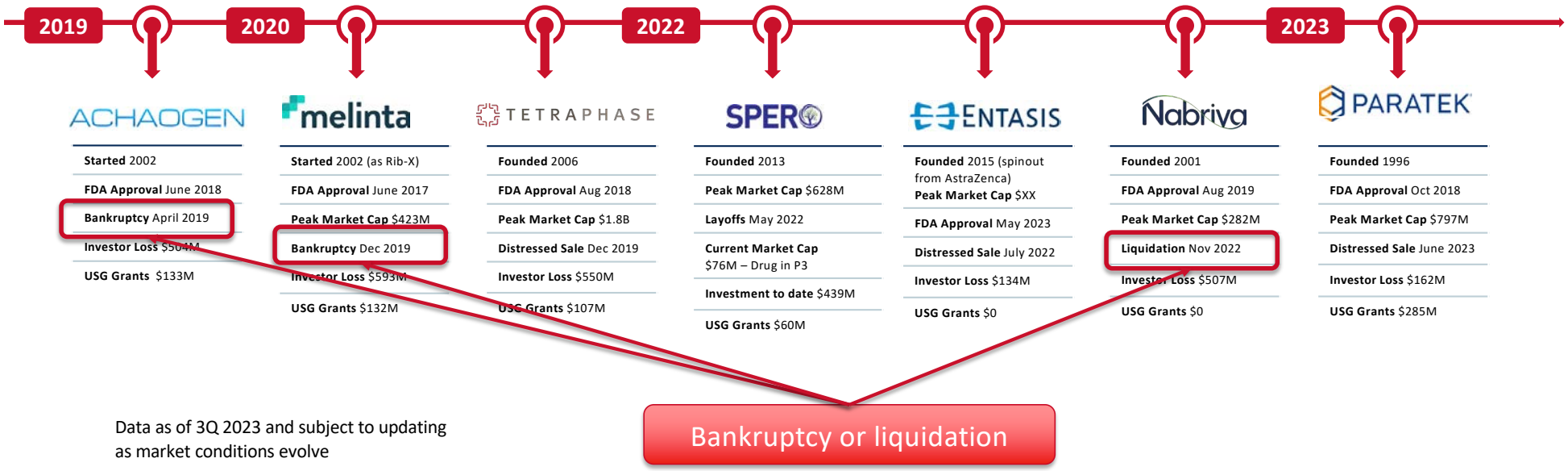

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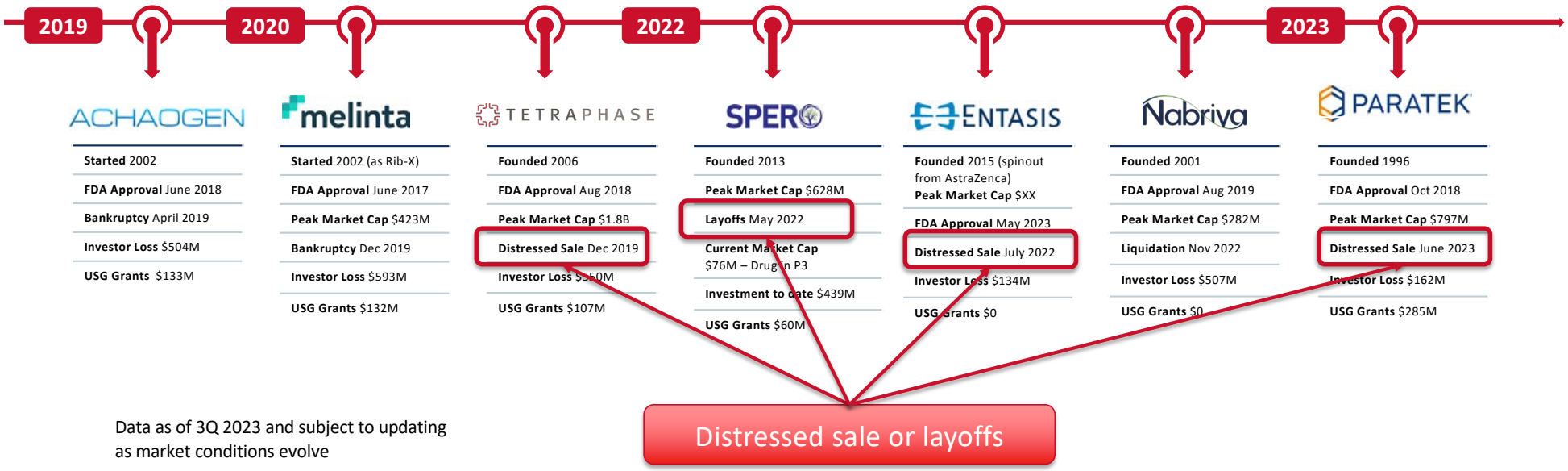

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Where have the antibiotic scientists gone?

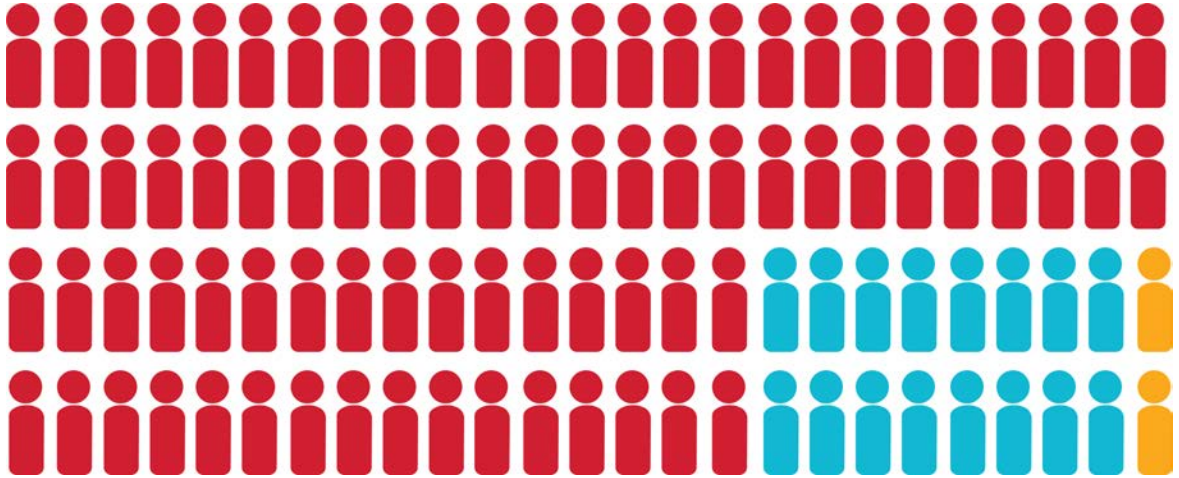
Confidential until published

June 2018[1] – June 2023[2]

82% out of antibiotics

16% in antibiotics (for profit)

2% in antibiotics (non-profit)



15-Oct-23

1. As of June 2018, number of M.S., M.D., or Ph.D. employees working at least 50% in antibiotic R&D at Achaogen, Entasis, Melinta, Macrolide, Nabriva, Novartis, Paratek, Spero, and Tetraphase (n= 314)
2. As of June 2023, whether these 314 scientists were working in antibiotics (for-profit & non-profit) or had left antibiotic R&D. 6 were unable to be located and were presumed lost to antibiotic R&D.

Source: CARB-X data from personal communications & surveys.

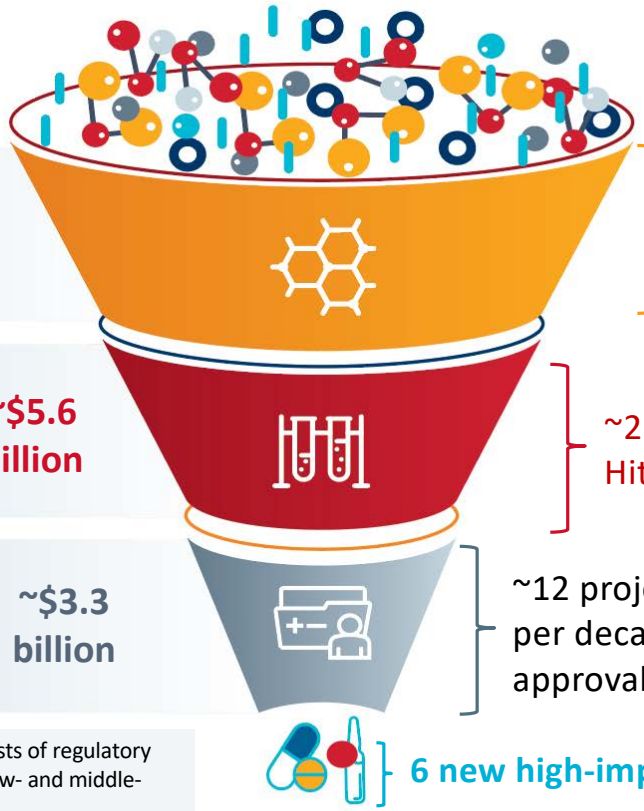
The urgency to close the funding gap in the early stages of AMR product development

Funding early-stage R&D is indispensable AND urgent

- **Early-stage R&D is where the most promising projects, but also the most vulnerable product developers are**
  - The AMR Action Fund has struggled to find investment opportunities, with its CEO acknowledging publicly that the clinical pipeline is "much thinner" than he had originally realized (Jan 2023)
  - The World Health Organization found found that "the ***clinical*** pipeline and recently approved antibiotics are insufficient to tackle the challenge of AMR." In contrast, "[t]he ***preclinical*** pipeline is innovative and includes a large number of non-traditional approaches" (May 2022)
  - Yet, "[t]he ***preclinical*** antibacterial pipeline continues to rely on micro (< 10 employees) and small (< 50 employees) companies and academic institutions," and the "analysis of groups with programmes in the ***preclinical*** antibacterial pipeline clearly indicates significant volatility and turnover" (May 2022)

- **Without a healthy early-stage pipeline, there will be no R&D projects to develop clinically and no treatments for pull incentives to make accessible**

6+ innovative high-impact treatments require a pipeline



Basic Research ~$3 billion

>6000 basic research projects per decade

Early-stage product development ~$5.6 billion

~215 projects per decade, from Hit-to-Lead to First-in-Human studies

Advanced development and post-approval ~$3.3 billion

~12 projects beginning clinical efficacy studies per decade, including regulatory and post-approval costs

3+ years

6 years

6.5 years

Approved

6 new high-impact treatments per decade

IMPORTANT: These estimates do not account for the costs of regulatory submissions, post approval and access in high-burden low- and middle-income countries. Also, TB is not included.

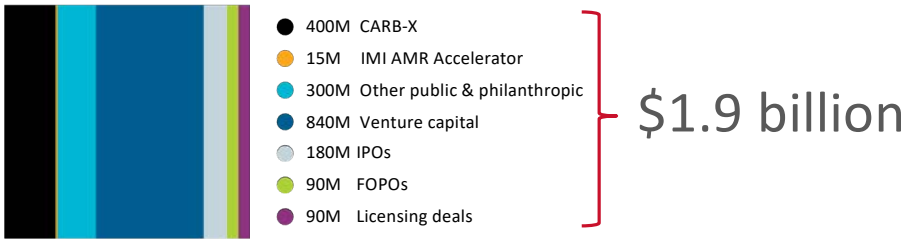
Preliminary results based on probabilities of success and phase costs from best available data. Validation is underway with upstream and downstream partners, including AMRAF and GARDP.

Funding gap for early-stage R&D: USD 370M a year

Total investment needs

$5.6 billion

Expected investments at current levels



$1.9 billion

Funding gap

$3.7 billion

US$370M per year

Preliminary results based on data from the Global R&D Hub and BIO, plus expert views.

Same conclusion: all major reports from past 10 years

- AMR Review (2015): “a global AMR Innovation Fund of around $2B over 5 years” = **additional USD $400 M annually**
- GUARD (2017): a Global Research Fund with $87.5M for preclinical development and $85M for Phase 1 studies = **additional USD $172.5 M annually**
- Drive-AB (2018): “additional annual global push funding in the range of $200M to $500M would particularly benefit early-stage research” = **additional USD $200-500 M annually**
- WHO/Global AMR R&D Hub (2023): “**need additional push funding** to replenish a weak clinical pipeline”
- LSE Policy Brief for Swedish EC Presidency (2023): “There remains **a very significant funding gap for early-stage product development** …”
- PwC for DG HERA (2023): “There is relative consensus on the need to provide additional push funding, in a range between **$250M and $400M on an annual basis**, and at a global level …” = **additional USD $250-400 M annually**

Summary: additional USD $172.5-500 M annually

The unique role of CARB-X

CARB-X

Combating Antibiotic-Resistant Bacteria

The global non-profit partnership replenishing the clinical pipeline of innovative products to prevent, diagnose and treat the most dangerous drug-resistant infections

ASPR
Administration for Strategic Preparedness and Response

BARDA
Biomedical Advanced Research and Development Authority

UKaid
from the British people

Federal Ministry of Education and Research

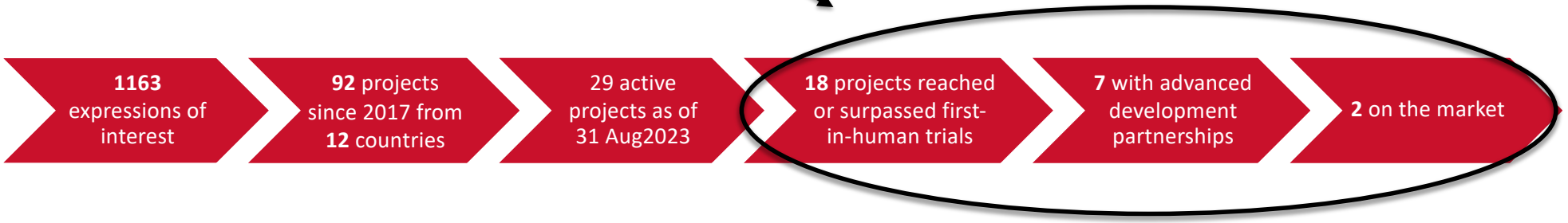
Canada

wellcome

Bill & Melinda Gates foundation

18 R&D projects reached or surpassed first-in-human trials

- Three pillars: therapeutics, preventatives and diagnostics
- Accelerates R&D projects from Hit-to-Lead to First-in-Human studies
- Provides non-dilutive funding **and** business, technical and scientific support
- Product developers are responsible for 30-40% cost-share
- Invested more than $400M since 2017
- Created the world's most promising discovery & early-development portfolio to address AMR, **with significant progress already**

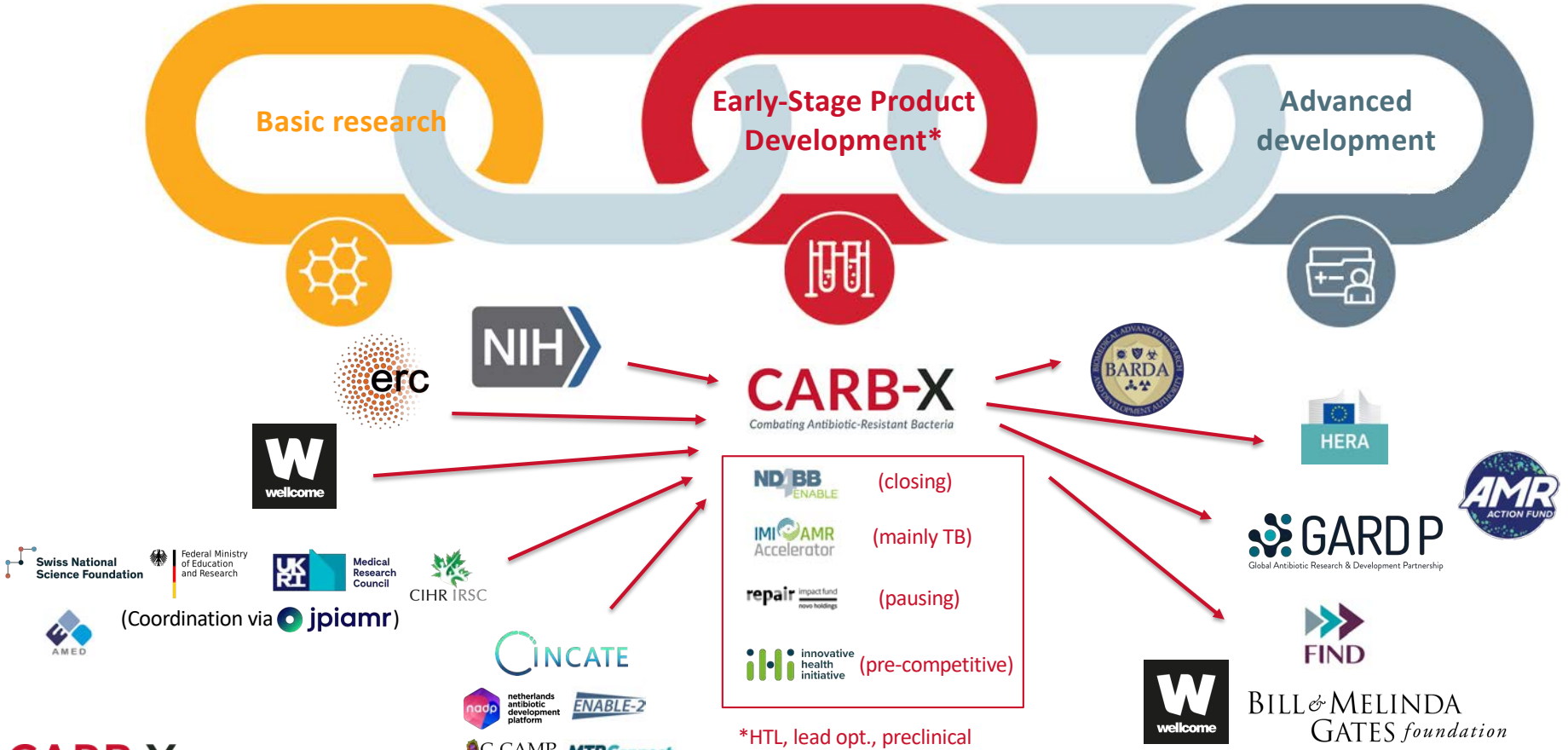


CARB-X targets the most burdensome infections globally

Global deaths attributable to (dark grey) and associated with (light grey) drug-resistant bacterial infections, by syndrome, 2019*

Source: Antimicrobial Resistance Collaborators, The Lancet, published online January 20, 2022
*: mostly targeted secondary indication

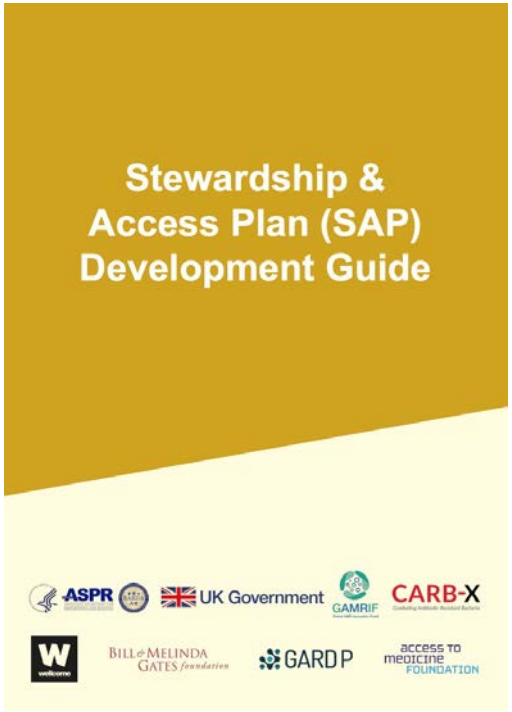
CARB-X is a crucial link in the AMR innovation chain



*HTL, lead opt., preclinical development, FIH

Contractual obligations related to stewardship and access

- Product developers prepare a non-confidential Stewardship and Access Plan (SAP) when product enters pivotal clinical trials
  - Every CARB-X PD has agreed to the same terms
- SAP updated and published on CARB-X website when product is first approved by any of the FDA, EMA (or national authorities), MHRA, or PMDA
  - Updated following any significant market or product changes
- Obligations survive termination/expiration of CARB-X funding; follows the product to the expiration of Project IP Rights
- Wellcome Trust succeeds to CARB-X's rights, if need be



Pull incentives complete the solution

PHARMACEUTICALS & MEDICAL TECHNOLOGY

DOI: 10.1377/hlthaff.2021.00688
HEALTH AFFAIRS 40,
NO. 11 (2021): 1758–1765

By Kevin Outterson

Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines

- Best estimate for a global antibacterial subscription = **$310M** (**range: $220M-$480M**) per drug annually over 10 years
  - The PASTEUR Act is within this range, as is the global pull incentive implied by the UK program
- Both push and pull incentives are necessary for sustainable and robust antibacterial drug development

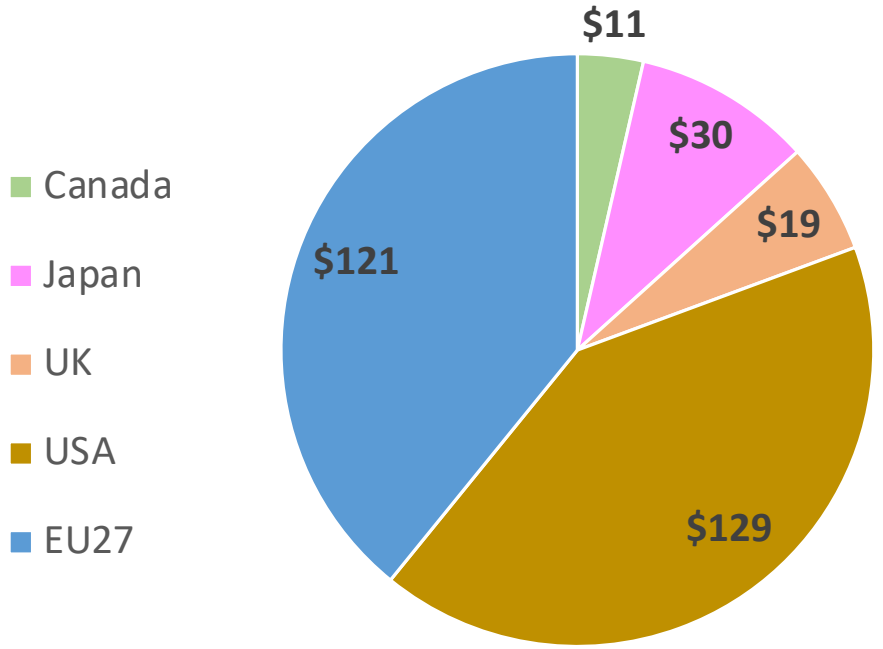
Outterson K. Estimating the appropriate size for global antibacterial pull incentives. Health Affairs 2021 https://pubmed.ncbi.nlm.nih.gov/34724432/

Advancing delinked pull incentives[1]

- **UK** (2 drugs covered; upgrade in progress: up to £20 m/drug/year)
- **Japan** (pilot announced by MHLW during its G7 Presidency)
- **EU** (European Commission included transferable exclusivity extension vouchers in its pharma revision)
- **Canada** (PHAC-commissioned pull incentive report from CCA was published last month)
- **US** (PASTEUR Act slowly gains bipartisan co-sponsors, Congressional hearings held in April & July 2023)

[1] Includes only pull incentives (subscriptions & revenue guarantees) not dependent sales volumes (i.e., delinked)

“Fair share” pull incentive targets: G7 + EU27



Outterson 2023, https://open.bu.edu/handle/2144/42568

Fair share of a $3.1B global subscription pull incentive, allocated by relative GDP within G7+EU27. Adding additional economies decreases the targets.

Figures are average per drug, per year, paid over 10 years

Payments might be lower at registration, but could increase as stronger evidence is presented

Australia ”fair share” = US$ 9M
South Korea = US$ 8M
Switzerland = US$ 4.4M

Conclusions

- Absent reform, the R&D ecosystem is collapsing → **Access for no one.**
- The AMR R&D ecosystem needs BOTH push and pull incentives
  - CARB-X demonstrates a global push incentive can replenish the clinical pipeline, but US$370M / year is needed in additional push incentives for early stage product development
  - The UK implemented an innovative subscription pull incentive, which can be adapted to other healthcare systems with modifications (Canada, Japan, EU, US)
  - Initiatives that focus on late-stage R&D and access for LMICs (e.g., GARDP, EDCTP3, ADVANCE-ID, SECURE) are crucial and should be prioritized and funded as well
- Each high-income country should contribute its “fair share”
- Conditionalities on stewardship and access have been successfully applied to push incentives; pull incentives should build on this progress