



The importance of (new) antibacterial and antifungal drugs: *And why don't we have the drugs we need?*

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Action Fund SAB; Operating Partner, Advent Life Sciences

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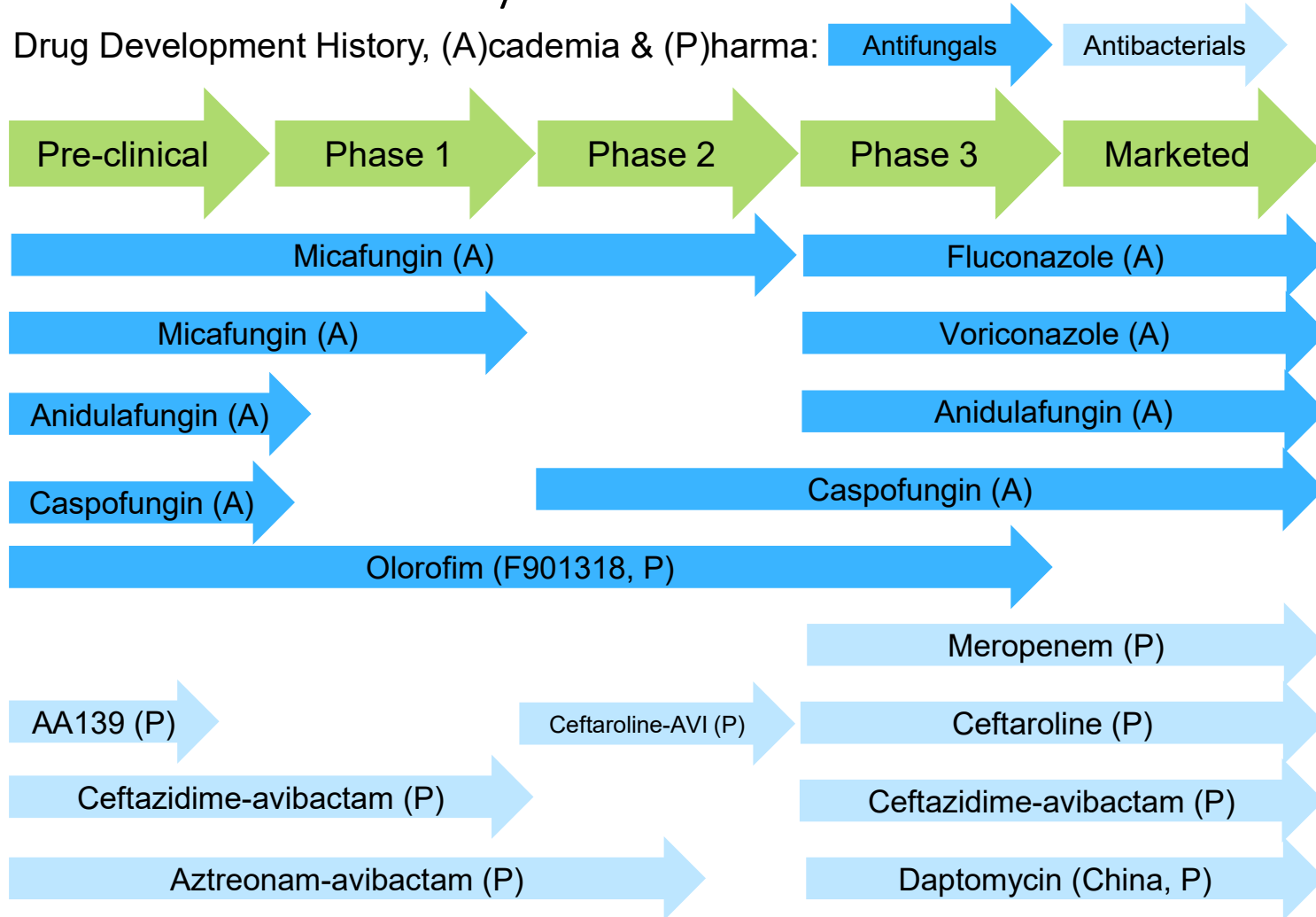
Slides happily shared



Disclosures (2020-2023)

- During the period 2021-2023, I am / have been Chief Medical Officer & Director, F2G, Ltd., Editor-in-Chief, AMR.Solutions, Operating Partner & Consultant, Advent Life Sciences, and Adjunct Professor of Medicine, McGovern Medical School, Houston, TX.
- I have received grant support from Wellcome Trust.
- I sit (or have sat) on the scientific advisory boards of Basilea Pharmaceutica, Novo Holdings, Bugworks Research, Inc., Forge Therapeutics, Inc., Sumitovant, and the AMR Action Fund (AMRAF).
- I have received consulting fees from Forge Therapeutics, Inc., GlaxoSmithKline, and Bugworks Research, Inc.
- I am currently a shareholder in AstraZeneca Pharmaceuticals, F2G, Ltd, and Advent Life Sciences.
- The opinions expressed are my own and do not necessarily reflect the opinion of any of the groups with which I work.

Curriculum vitae: A 40-year focus on new antimicrobials



Have you used a fire extinguisher today?



Have you used a fire extinguisher today?



*Let's be very concrete.
Are you using a fire extinguisher **right now?***

Have you used a fire extinguisher today?



*Let's be very concrete.
Are you using a fire extinguisher right now?
You are using everything except the part that gets you wet.*



What does this have to do
with antibiotics?



Fundamental starting point

Antibiotics enable all of modern civilization!

- Safety net for surgery, cancer therapy, and essentially everything else
- Infrastructure for civilization: Healthy citizens make the economy go!

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Stated differently...

**Antibiotics are the
fire extinguishers
of medicine!**



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- Move rapidly

Fires



Infections



amr.solutions

- Move rapidly

- Fatal

Fires



Infections



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- Move rapidly
- Fatal
- Adequate tools?

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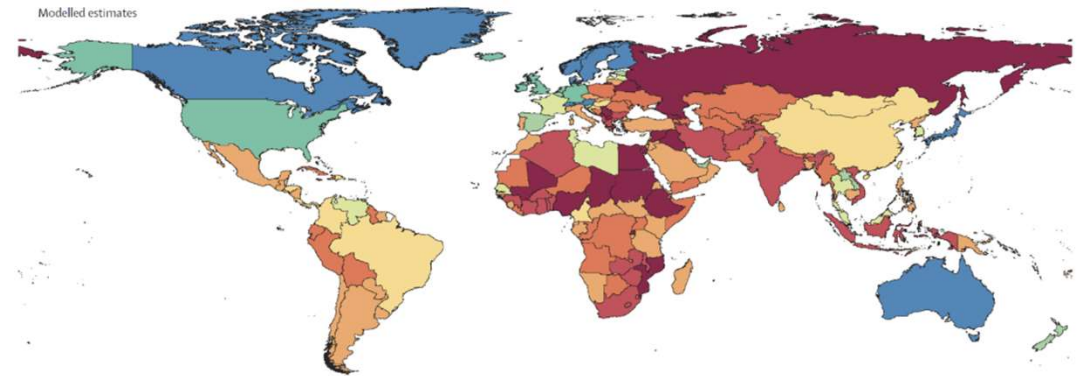


AMR is a global threat! #AMRSOS!

Antimicrobial-Resistant (AMR) bacteria are emerging steadily^{1,2}

Landmark modeling project using 2019 data from 204 countries³

- 1.27m deaths/year attributable to AMR



Percentage of isolates with resistance



1. <https://www.cdc.gov/drugresistance/biggest-threats.html>
2. <https://amr-review.org/>
3. Murray, C. J. L., et al. (2022). "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis." The Lancet. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
4. Shown is rate of *K. pneumoniae* resistant to 3rd-generation cephalosporins (Figure G from Murray et al.)
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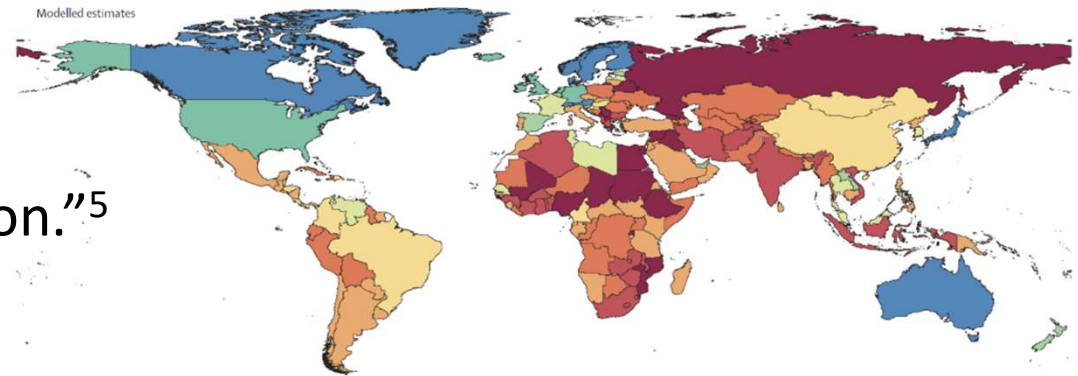
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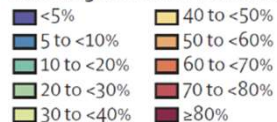
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Global spread,⁴ deadly impact

- “Your cancer will be controlled, but then you may die of infection.”⁵



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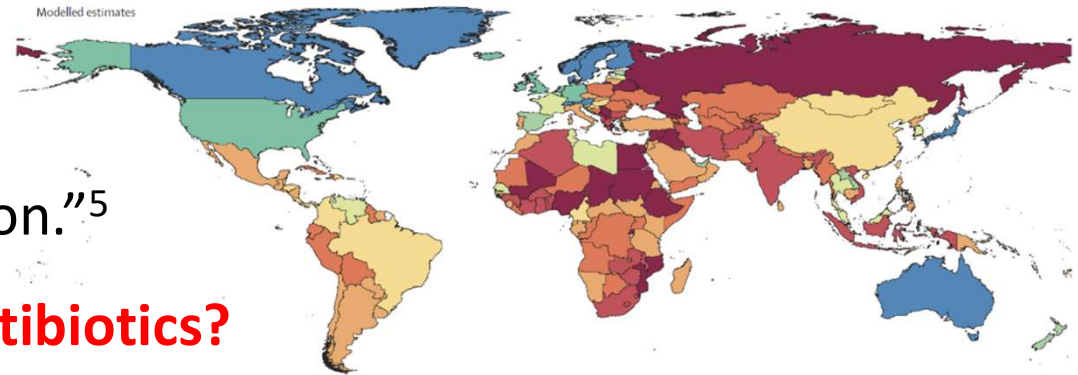
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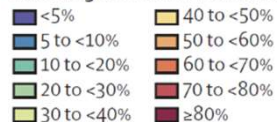
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So, why do we lack adequate antibiotics?

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Fires

- Move rapidly
- Fatal
- Adequate tools?
- Build/Invent



Years: Fire Station,
Water supply

Infections



Decades: New
antibiotic



Build a fire Station? *100% success rate*

Discover an antibiotic? *Very hard, very slow*

Easy to find: Genetic targets

- Multiple bacterial genomes are fully sequenced

Easy to find: Things that kill bacteria

- Bleach, steam, and fire

Hard to find: Kills bacteria & is generally well tolerated

- Failure due to safety issues is common: High doses usually needed

From initial discovery to approved new antibiotic class?

- **Antibiotic R&D is slow: expect 20-40 years**



Not just slow ... also expensive

Many failures along the way: Average cost to approval = \$1.3b¹

Running costs of a drug in its first 10 years: \$350m^{2,3}

- \$100m in post-approval commitments: pediatrics, etc.
- \$25m/year to run the plant that makes your drug, surveillance, pharmacovigilance

All together: ~\$1.7b per (ultimately successful) molecule⁴

- Usage-based income will not recover those costs⁴
- New antibiotics often have \leq \$25m/year in sales⁵

Can it be done for substantially less?³

- On average, no. There are no discounts or regulatory shortcuts for being small or large, for-profit or non-profit, degree of novelty, etc.
- Small company models are already very, very lean⁶

1. Wouters OJ, et al. JAMA 2020;323:844–53. 2. AMR.Solutions: Melinta, Part 2 / Bankruptcy Is Not The End / Post-Approval Costs For An Antibiotic. Available at <https://amr.solutions/2020/01/07/melinta-part-2-bankruptcy-is-not-the-end-post-approval-costs-for-an-antibiotic/> Accessed March 2022; 3. Based on speaker expert opinion; 4. AMR.Solutions: What Does An Antibiotic Cost To Develop? What Is It Worth? How To Afford It?. Available at: <https://amr.solutions/2020/03/06/what-does-an-antibiotic-cost-to-develop-what-is-it-worth-how-to-afford-it/> Accessed March 2022; 5. AMR.Solutions: Mandatory Reading: Alan Carr's Jan 2020 Antibacterial And Antifungal Market Review. Available at: <https://amr.solutions/2020/01/28/mandatory-reading-alan-carrs-jan-2020-antibacterial-and-antifungal-market-review/> Accessed March 2022; 6. Drakeman DL. Nat Biotechnol. 2014;32(7):621-5.



The clinical pipeline is thin

Pew's Analysis of Antibiotics in Clinical Development

42

antibiotics in development

2

new drug applications submitted

19

could treat infections caused by certain Gram-negative bacteria

10

could address urgent threats *N. gonorrhoea* or *C. difficile*

1 in 4

is a novel drug class or novel MOA

As of December 2020

“...resistance will eventually develop to those [antibiotics] that are approved, it is clear that there are too few drugs in development to meet current and anticipated patient needs.”

– Pew Charitable Trusts, 2020

The Pew Charitable Trusts 2021. Tracking the Global Pipeline of Antibiotics in Development. Available at: <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development>. Accessed March 2022. For additional reviews, see <https://amr.solutions/pathogens-and-pipelines/>. All subsequent reviews (e.g., WHO 2020) have similar findings. MOA, mechanism of action.



Fires

- Move rapidly
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- Adequate tools?
- Build/Invent
- Maintain



Years: Fire Station,
Water supply

**Purchased as a
common resource**

Infections



Decades: New
antibiotic

**Paradoxical
economics**



Root cause: The antibiotic paradox

The better the new antibiotic (e.g., spectrum)...

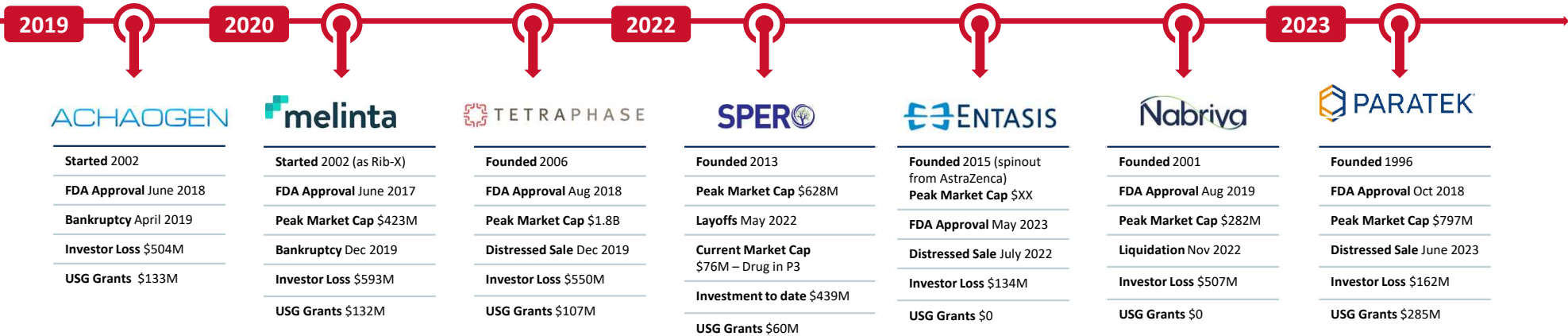
- The lower the use will be!
 - *We must be good stewards of each new antibiotic*
-

That's a good thing for the community...

- **But it causes companies to go bankrupt!**

The toll of the broken AMR Market

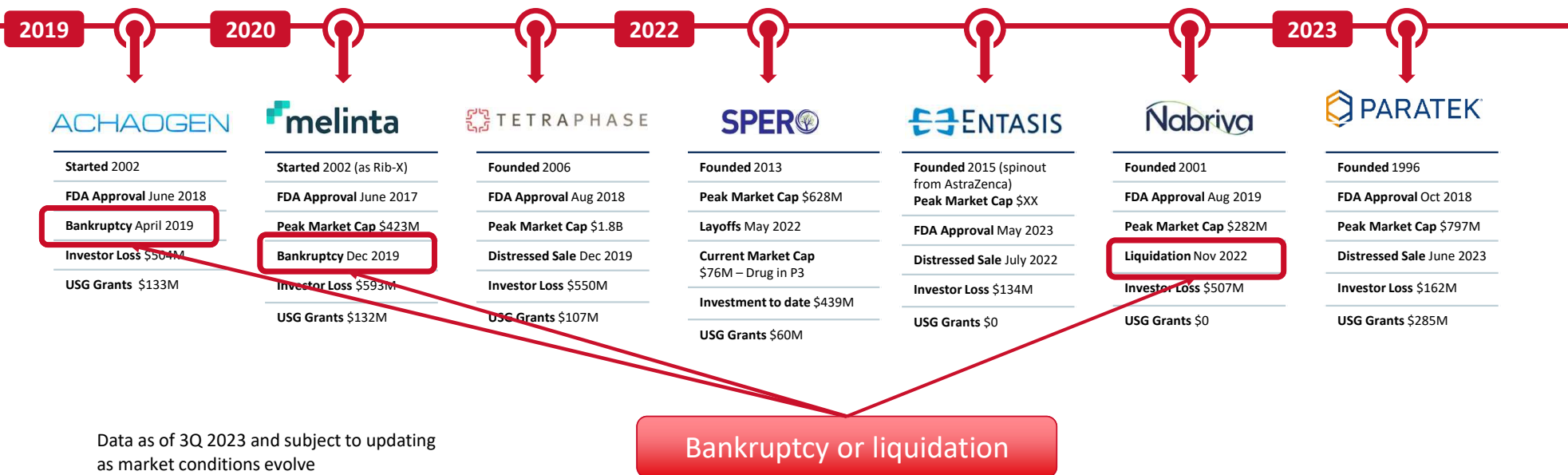
Cumulative loss for investors and US Government grants:
\$3.6 billion



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

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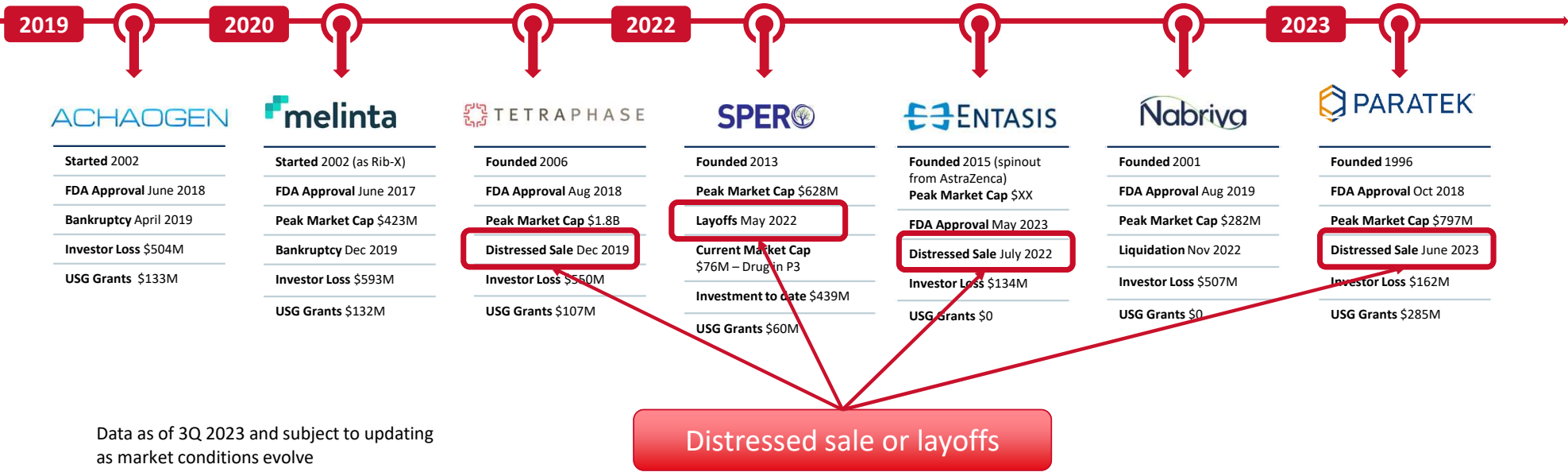
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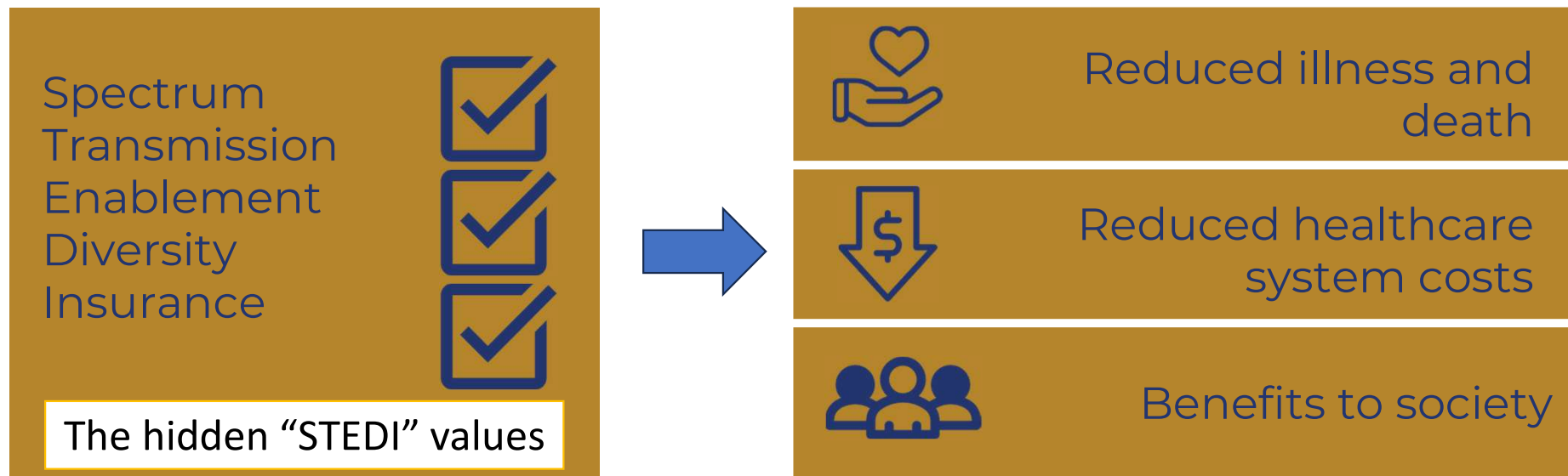
That's a good thing for the community...

- But it causes companies to go bankrupt!
- **Antibiotics (like fire extinguishers) have value by existing**



Hidden fire extinguisher “STEDI values”

Subtle but real^{1,2}

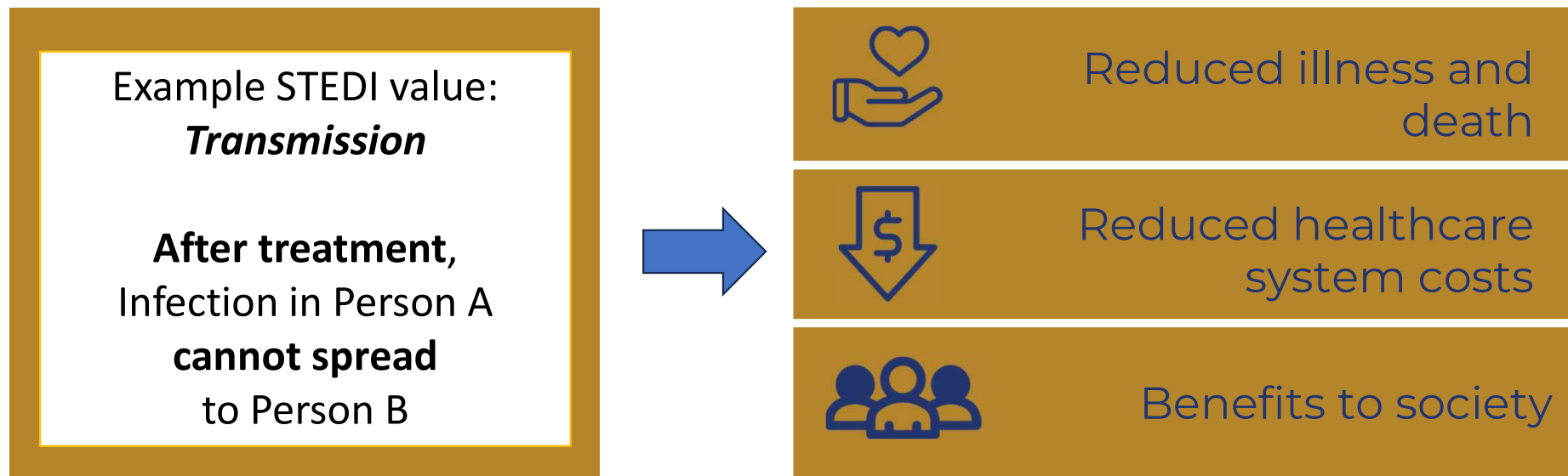


(1) <https://amr.solutions/2020/04/14/pull-incentives-for-antibiotics-how-much-and-why/> for details on STEDI. (2) Colson et al. "Antimicrobial Resistance: Is Health Technology Assessment Part of the Solution or Part of the Problem?", Value in Health 24:1828-1834, 2021, <https://doi.org/10.1016/j.jval.2021.06.002>
Graphics from the 2023 report by the Canadian Council of Academia (CCA) on Pull incentives: <https://amr.solutions/2023/09/08/canada-says-lets-pull-together-in-a-major-new-report/>



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The fix: **Push** and **Pull**

Substantial public thinking over the past 10+ years

- UK AMR Review;^{1,2} DRIVE-AB project;³ US legislative efforts;^{4,5} Swedish pilot project;⁶ etc.

Key: Two different kinds of funding

- Push incentives that encourage work to start: Grants
 - CARB-X, Novo REPAIR, etc.
 - *Japan plans to contribute to CARB-X: THANK YOU!*

Pull incentives paid on successful approval...



Video explainer:

<https://www.youtube.com/watch?v=6gd8iXLBZak>

1. NICE 2020. Developing and testing innovative models for the evaluation and purchase of antimicrobials: subscription-based payment model. Available at: <https://amr.solutions/wp-content/uploads/2020/03/2020-03-25-NHS-AMR-Market-Engagement-Briefing-Final.pdf>; 2. AMR.Solutions. NHS England antibiotic procurement pilot project 2020. Available at: <https://amr.solutions/2020/03/11/nhs-england-pilot-antibiotic-procurement-project-update-webinar-on-25-mar-2020/>; 3. Innovative Medicines Initiative. DRIVE-AB: Driving re-investment in R & D and responsible antibiotic use. Available at: <https://www.imi.europa.eu/projects-results/project-factsheets/drive-ab>; 4. USA 116th Congress 2019-2020. H.R.4100 - DISARM Act of 2019. Available at: <https://www.congress.gov/bills/116/congress-house-bill/4100/text>; 5. USA 116th Congress 2019-2020. PASTEUR Act. Available at: <https://cobioscience.com/wp-content/uploads/2020/05/PASTEUR-Act-Text-05042020.pdf>; 6. The Public Health Agency of Sweden. Availability of antibiotics. Available at: <https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics/>. All weblinks accessed April 2022; Speaker Expert opinion.

How does Pull work?



Pull = Payments made without regard for use¹⁻³

- UK pilot: The UK has identified 2 high-end new agents for Gram-negative bacterial infections
- The UK is contracting to buy them for the UK at ~GBP 10m/year x 10 years = GBP 100m
 - Note: The upper limit amount for the UK has been revised to GBP 23m/drug/year
- The purchase is independent of actual use

This is right on target as a UK-sized fair share! Strong work, Team UK!

- All estimates⁴ converge on \$2.2-4.8b as the needed total **global** reward size
- This type of Pull incentive levels the economic playing field!
- This type of Pull aligns stewardship with access and innovation

So, how do we engage and extend?

- Wealthy countries need to contribute their fair share; Targets must be fair and consistent

1. AMR.Solutions: <https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/> Accessed March 2022; 2. See also this excellent 5-minute video explainer: <https://www.ft.com/video/adada10f-5747-4976-a3e0-958b0165e0ef>; 3. NICE. Models for the evaluation and purchase of antimicrobials. Available at: <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials> Accessed March 2022; 4. Multiple estimates have been made. The best current summary is found in Outterson K, Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. Health Affairs 2021;40(11):1758-65;



Pull Awards: Key concepts

Must be earned! Only for special drugs

- Agents earning substantial Pull must obviously be special
- Expect no more than 2-4/decade

Must be earned over time! Paid over 10 years following approval

- Payments are linked to requirements for supply, stewardship, etc.

Must be earned by fire extinguisher values! STEDI attributes, not use

- Spectrum, Transmission, Enablement, Diversity, Insurance
- Some will earn less (\$1-2b), some more (\$3-4b), some nothing

CARB-X + Pull: Builds on ongoing JPN AMR initiatives



EXISTING



↑
filling a gap
↓



↑
filling a gap
↓

RECOMMENDED

CARB-X
Combating Antibiotic-Resistant Bacteria

Japan joins this global push incentive

Pull incentive created in Japan



Summary

The AMR problem is now well-defined

- Antibiotics are the Fire Extinguishers of Medicine
 - Like other infrastructure, we must buy them in advance

The possible solutions are now well studied

- The big mental shift is the idea of Pull

It takes years of effort to find novel new agents

- Reward must match required risk
- Delinked Pull ties together creativity and stewardship

#FireExtinguishersOfMedicine