Antifungal Drug R&D: Challenges and (the need for) Incentives

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NASEM: Plant Agriculture and Antifungal Resistance workshop

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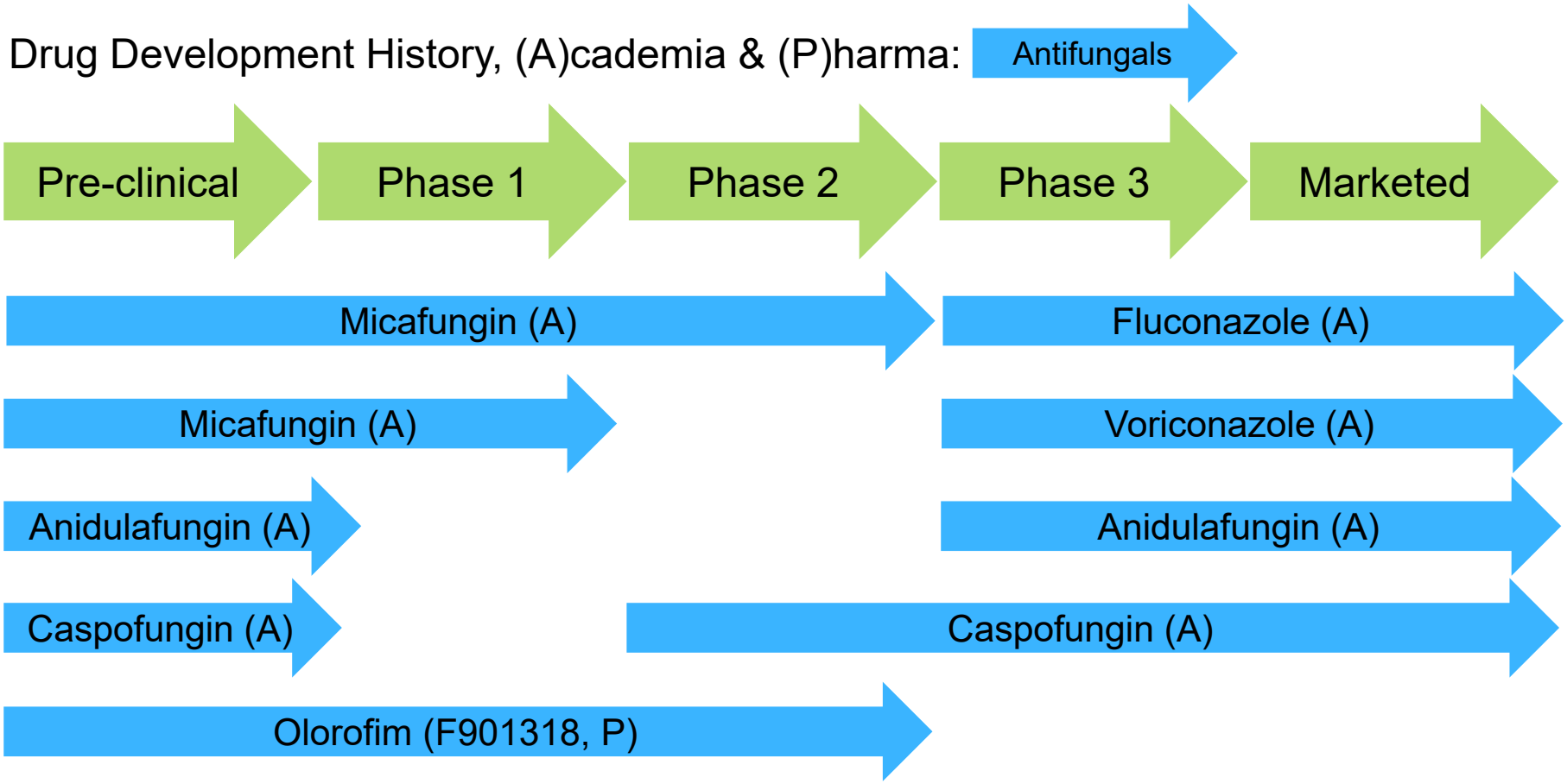
Slides happily shared … just drop me a note

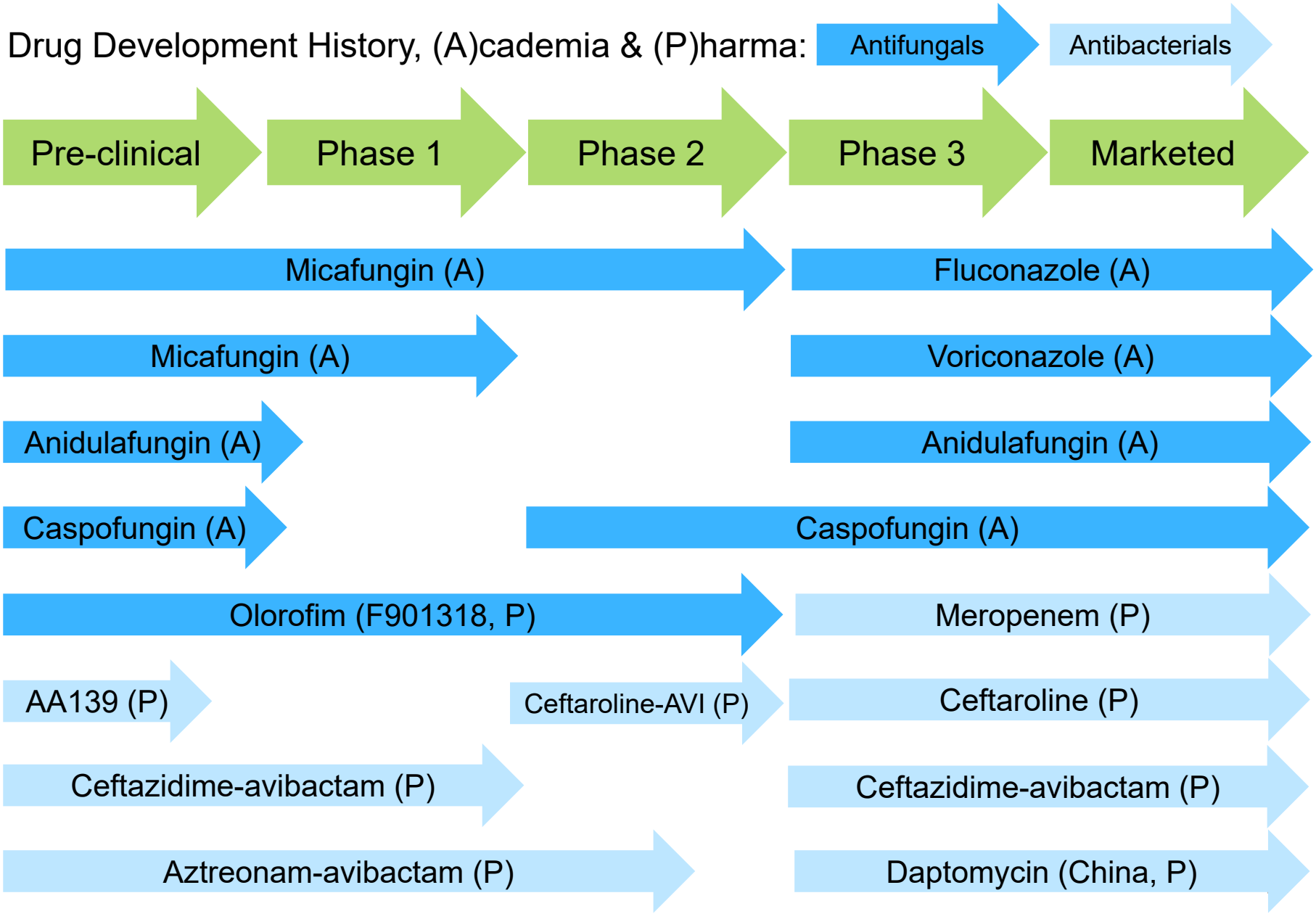
Agenda

- Introduction: A focus on drugs for use in humans
- What does it take to invent & deliver a new drug?
- Evolving payor paradigms
- Summary

Qualifications: A continuous focus on drug development!



Qualifications: A continuous focus on drug development!



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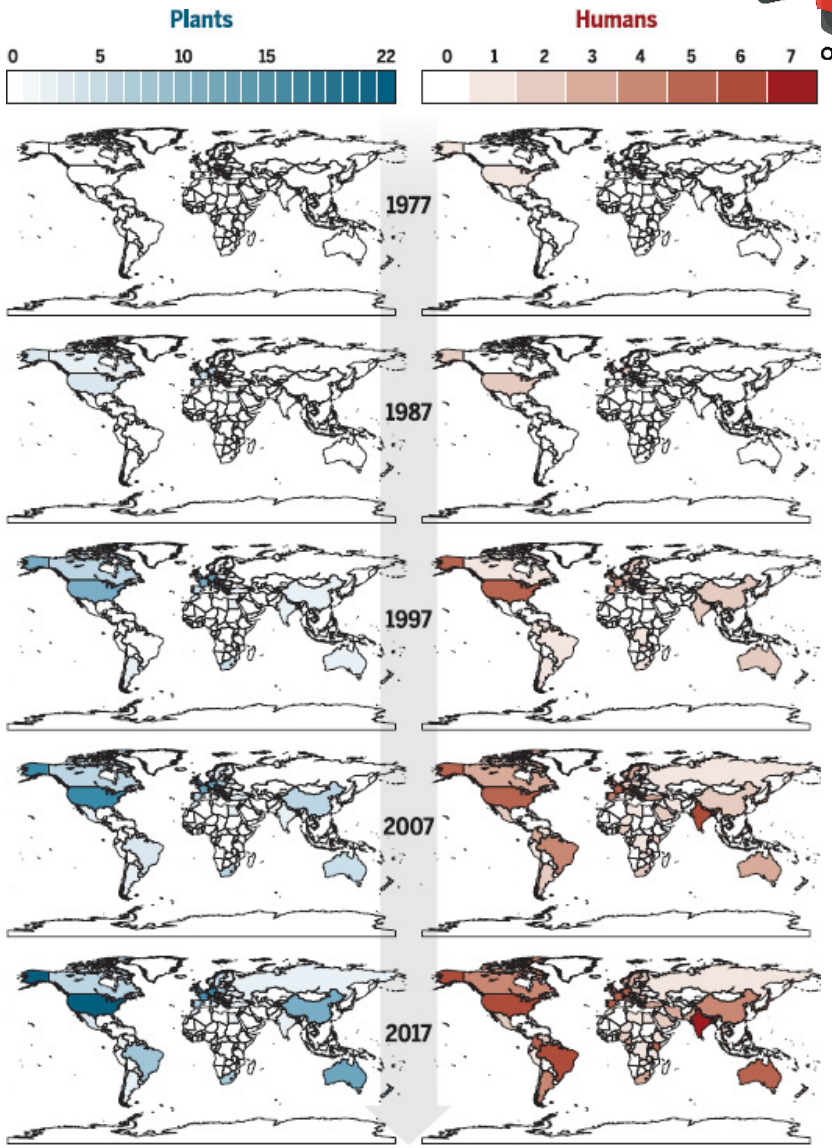
- Introduction: A focus on drugs for use in humans
- What does it take to invent & deliver a new drug?
  - It’s hard, slow, and costly
- Evolving payor paradigms
- Summary

Unmet Need in Mycology: Abundant!

- Novel mechanisms: *We have so few on the market*
  - Amphotericins, azoles, candins, terbinafine, 5-FC
  - Exciting: Several novel mechanisms are in the clinic now
- Oral: *As yet, only the azoles, terbinafine, and 5-FC*
- Spectrum: *Resistance is seemingly everywhere!*
  - *Candida*, esp. *C. auris*: Azoles & candins
  - *Aspergillus*: Azoles & amphotericins (the cryptic species have turned out to be very interesting)
- And then there are the places where current agents struggle in one way or another
  - E.g., we still can't always cure coccidioidomycosis!
- I could go on, but a picture tells a thousand words…

Fisher, 2018[1]

- Shown at right is the rate of antifungal resistance over time for plant and human products.
- Darker = more resistance
- Resistance advances!



1. Fisher et al., Science 360:739–742, 2018

Finding new therapeutic antimicrobials is very hard

- Easy to find: Targets
  - Multiple fungal/bacterial genomes are fully sequenced
- Easy to find: Things that kill fungi/bacteria
  - Bleach works quite well, as do steam and fire
- Hard to find: Kills fungi/bacteria & is well tolerated*
  - Failures: physical properties, pharmacology, **tolerability**
  - Need high levels to penetrate bug → high doses
    - Typical lipid-lowering agent: 5-20 mg/day
    - Typical antibiotic: 100-2000 mg/day

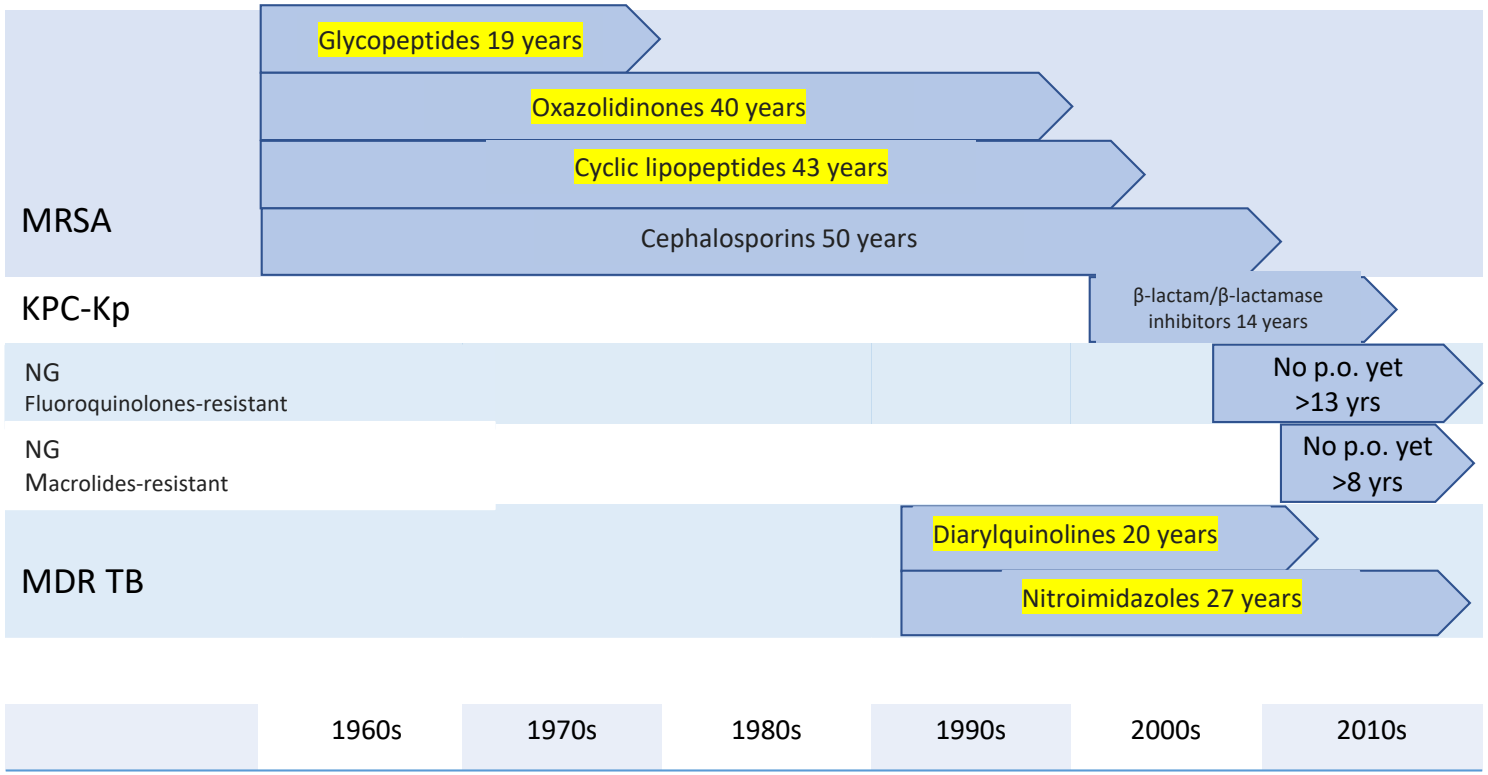
*Prasad 2022 AAC (doi:10.1128/aac.00054-22) provides a good discussion of this from a bacterial R&D standpoint – the same issues apply for antifungals. See also https://amr.solutions/2022/06/14/leaky-pipelines-when-is-a-molecule-a-drug/

True novelty requires years of effort

Completely new classes are higher risk and even slower

Time from discovery to FDA approval

Antibacterial examples are shown here – antifungals are just as slow



Sources: CDC AR Threats 2019, at 35; MRSA 1960 (Jevons MP 1961. BMJ); KPC-Kp 2001 (Yigit H, et al. AAC 2001); NG-CR 2007 (CDC, MMWR 2007); NG-AR 2012 (Soge OO, et al, STD 2012); MDR-TB 1992 (Vallarino ME, et al., Pub H Rep 1992). Drug approvals: Vancomycin approved 1958, but US usage did not grow until 1979 (Kirst HA 1998. AAC). Other approvals from Drugs@FDA.gov. For emergence of MRSA resistant to ceftaroline prior to its FDA approval, see Kelley WL et al., AAC 2015.

Graphic borrowed and adapted from Kevin Outterson, July 2020

That time & effort comes at a cost

- Average cost to approval[1] = $1.3b
- Running costs of a drug in its first 10 years: $350m[2]
  - $100m in post-approval commitments: pediatrics, etc.
  - $25m/year to run the plant that makes your drug, surveillance, pharmacovigilance
- All together: ~$1.7b per molecule
  - **Usage-based income will not recover those costs**[3,4]
- Can it be done for substantially less?
  - 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 lean[5]

[1]Wouters J, et al. *JAMA* 2020;323:844–53. 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/. [2]Based on expert opinion – see 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/. [3]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/. [4]Drakeman DL. Benchmarking biotech and pharmaceutical product development. Nat Biotechnol, 32(7): 621-5, 2014.

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  - Have you used a fire extinguisher today?
- Summary
- Resources

Current economic model is broken

- Current approach to antibiotics
  - Everyone is delighted to have a new antibiotic
  - But, use is delayed and deferred in effort to preserve new antibiotic
- Stewardship perspective: Entirely rational
- Economic perspective: A financial loss
  - Many analyses show same thing
  - It is not financially rational to do antibiotic R&D
  - Bankruptcies! Achaogen, Melinta
    - http://amr.solutions/blog/scary-scarier-scariest-achaogen-ft-editorial-cbs-60-minutes-on-amr
    - https://amr.solutions/2020/01/05/melinta-goes-bankrupt-never-let-a-good-crisis-go-to-waste/
- Problem: Current pay-per-use model reimburses for only a piece of the value

Pop Quiz: Have you used a fire extinguisher today?

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Actually, we can get more concrete. Are you using a fire extinguisher <u>right now?</u>

Antibiotic benefits go beyond simple use

But, we don't (yet) have an agreed way to capture that value

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The STEDI values of antibiotics

- (S)pectrum
- (T)ransmission
- (E)nablement
- (D)iversity
- (I)nsurance

Antibiotics & Fire Extinguishers

STEDI values of antibiotics

Antibiotics are the fire extinguishers of medicine!

Easy example: An infection treated does not spread!

- See also https://amr.solutions/2021/01/18/new-youtube-videos-cost-of-rd-antibiotic-value-and-lessons-from-covid/

The Fix: New Incentive Models

- Multiple major reports and analyses[1]
  - DRIVE-AB, UK AMR Review, and more
  - Links below
- Recommendation: Two types of incentives
  - Push: More grants and coordination of grants
    - We're doing this: CARB-X, Novo's REPAIR, NIAID, etc.
  - Pull: Market entry rewards & Long-term continuity
- **The idea of *Pull*** requires a bit of explanation

[1]http://drive-ab.eu/; https://amr-review.org/; https://amr.solutions/incentives/

Pull: Market Entry Reward (MER)

- How do we separate usage from payment?
- Essence of the solution:
  - A defined sum of money (a MER) is paid (over time) to the creator of a new antibiotic
  - **The MER is independent of volume of use**
  - **The MER provides (most of) the financial reward**
- There will be stewardship / access requirements
  - The company does not (need not) actively market!
  - **Pull incentives create alignment of all parties on stewardship!**
- Multiple global calls for Pull; Models now being tested
  - UK NHS pilot, US PASTEUR Act

For more, see https://amr.solutions/2022/05/21/g7-health-ministers-pull-incentives-to-support-stewardship-access-and-innovation/ , https://amr.solutions/2022/06/04/notable-reports-incentives-who-amr-hub-strategy-barda-capacity-building-fleming-fund/, and this video on Push/Pull:

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New antifungals for human use…

- … will be few and far between
- … will be expensive to find and develop
- … will need to be preserved via careful stewardship
- … can be encouraged via a different payor model

Thanks for listening!

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