Tiny heroes for immense challenges: *The path for antimicrobial peptides*



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Please note these details!

Slides will be shared!

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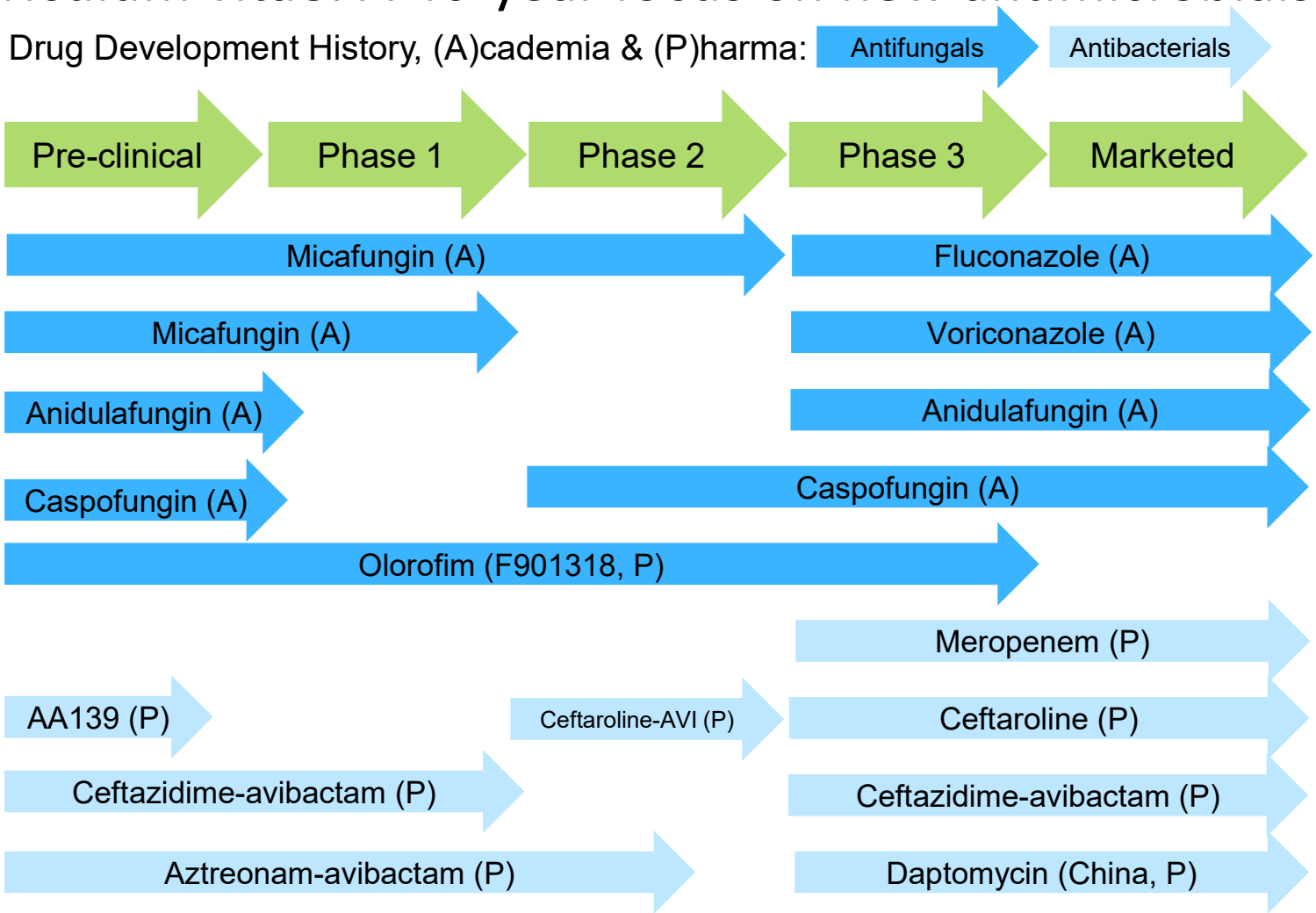
18 Nov 2026 – International Symposium on Antimicrobial Peptides

Disclosures (2022-2026)



- During the period 2022-2025, I am / have been
  - Chief Medical Officer & Director, F2G, Ltd.
  - Editor-in-Chief, AMR.Solutions: *Please subscribe to https://amr.solutions/ – it's a free resource for all!*
  - Chair, AMR Action Fund SAB
  - Operating Partner & Consultant, Advent Life Sciences
  - Adjunct Professor of Medicine, McGovern Medical School, Houston, TX.
- I have received grant support from Wellcome Trust.
- I sit on the scientific advisory board of the AMR Action Fund (AMRAF).
- 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



Agenda



- **The rising tide of antimicrobial resistance**
- The exciting promise of peptide-based antibiotics
- The big question: Is it a drug?
  - Rules of the road: Essential trial designs and their limitations
  - Traditional vs. non-traditional antibiotics
  - The narrow-spectrum drug challenge
- The economics of antibiotics
- A worthy challenge!

AMR is a global threat! #AMRSOS!



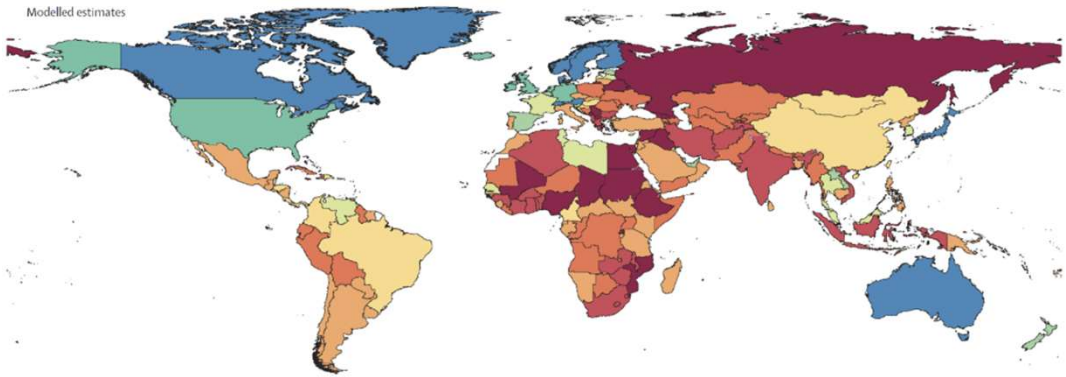
Antimicrobial-Resistant (AMR) bacteria are emerging steadily[1,2]

Landmark modeling project using 2019 data from 204 countries[3]

- 1.27m deaths/year attributable to AMR
- 2026 report[4] suggests that the actual rate may be 2x higher

Global spread,[5] deadly impact

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



Percentage of isolates with resistance

<5%	40 to <50%
5 to <10%	50 to <60%
10 to <20%	60 to <70%
20 to <30%	70 to <80%
30 to <40%	≥80%

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
4. Shown is rate of K. pneumoniae resistant to 3rd-generation cephalosporins (Figure G from Murray et al.)
5. Mo Y, Hao X, Ding Y et al. Severe health-care-associated infections and antimicrobial resistance in an Asian Surveillance Network (ACORN-HAI): a multicentre, prospective cohort study. The Lancet Infectious Diseases, 2026; 0
6. Abdul Ghafur quoted in https://podcasts.apple.com/mn/podcast/superbugs-force-a-deadly-choice-for-cancer-patients/id1440051086?i=1000448639105

The WHO Priority Pathogen List shows us the targets



The 2024 critical group

Pathogen	Resistance profile
Acinetobacter baumannii	Carbapenem-resistant
Enterobacterales	Third-generation cephalosporin-resistant
Enterobacterales	Carbapenem-resistant
Mycobacterium tuberculosis	Rifampicin-resistant

But this is just a list of bacteria

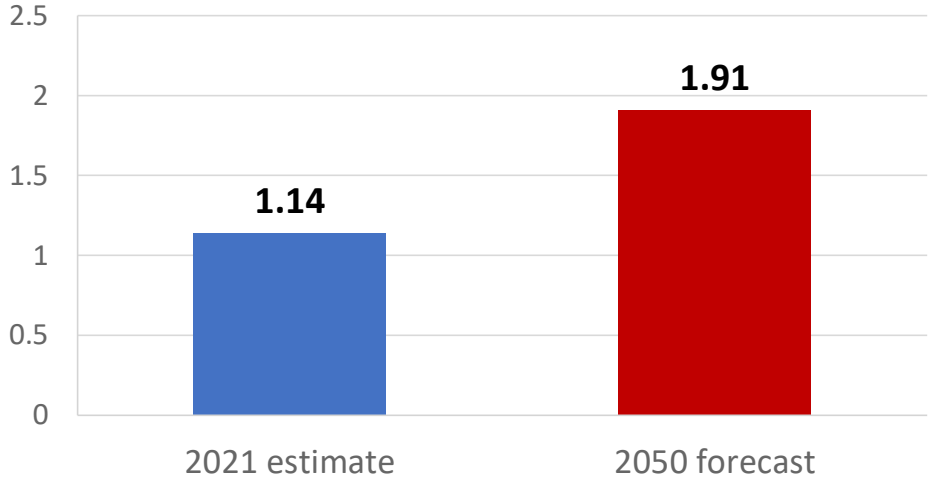
Developers must focus on the treatment gap for specific infections in specific patients

WHO Bacterial Priority Pathogens List 2024. Critical group shown, not the full list. See https://amr.solutions/pathogens-and-pipelines/ for summaries of all the current priority pathogen lists.

Future outcomes depend on action today



Deaths attributable to bacterial AMR
Millions per year



39.1 million

cumulative attributable deaths forecast for 2025–2050

UNGA 2024 target

10% fewer associated deaths by 2030 versus 2019

GBD AMR Collaborators, Lancet 2024. UN A/RES/79/2, 2024. Forecasts are modelled scenarios. See https://amr.solutions/home/unga-2024-and-the-amr-hlm-major-reports-before-and-after/ for the extensive collection of reports on the global impact of AMR that were developed for the High-Level meeting on AMR held during the 2024 UN General Assembly.

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Magainins caught my eye as a first-year ID fellow



1987

Frog skin offered a fascinating clue to natural defense[1]

The difficulties I came to appreciate

Membrane disruption can also injure the host

Useful exposure can be hard to sustain

Route and infusion tolerability can limit use

Progress includes selective targets and better peptide engineering

Most recent big review: Torrent M. Antimicrobial Peptides Beyond the Petri Dish: Translational Barriers to Therapeutic Development. ACS Bio & Med Chem Au. 2026 **and then you can dig more deeply[2]**

1. Zasloff M. Magainins from Xenopus skin. PNAS. **1987**;84:5449–5453 (https://doi.org/10.1073/pnas.84.15.5449).
2. Mookherjee N et al. Antimicrobial host defence peptides: functions and clinical potential. Nat Rev Drug Discov. **2020**;19(5):311–32. Orsi M et al. Chemical Space for Peptide-based Antimicrobials. CHIMIA. **2024**;78:648–653 (https://doi.org/10.2533/chimia.2024.648). Lewis K et al. Sophisticated natural products as antibiotics. Nature. **2024**;632(8023):39–49. Yang R et al. Advances in antimicrobial peptides: From mechanistic insights to chemical modifications. Biotechnol Adv. **2025**;81:108570. Oliveira Júnior NG, Souza CM, Buccini DF, Cardoso MH, Franco OL. Antimicrobial peptides: structure, functions and translational applications. Nature Reviews Microbiology. **2025**;23(11):687–700.

Peptides: Setbacks and progress



Example	What happened	Development lesson
Pexiganan cream	Phase III efficacy endpoints missed	Local delivery still needs clinical benefit
Murepavadin IV	Phase III programme closed after kidney injury	Selective action still needs a safety margin
Zaloganan IV	Phase I half-life 7.4–20 h Infusion reactions manageable	Engineering can improve exposure and delivery
Peceleganan spray	China approval for selected burn infections Mixed clinical and microbiology results	A defined local use can succeed

A useful product depends on the molecule, route, indication and evidence

Pexiganan and murepavadin: sponsor reports. Zaloganan (formerly, PLG0206): phase I publication. Peceleganan: trial and China approval report.

For today: A personal perspective on how to develop useful medicines



- **No one (but you) really cares how it works!***
  - Patients and caregivers only want to know that it does work
- **Patients need a visible, meaningful benefit**
  - Who benefits, and what improves compared with current care?
- **The molecule must become a routinely usable product**
  - Dose, route, safety, and manufacturing must fit the intended use
- **Approval is the goal: Nothing else will move the needle**
  - Access also requires reliable supply and sustainable financing

*We'll later come to the economic section of this talk and learn that a little bit of credit is given for novelty.

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The big question: Is it a drug?



- **It's easy to kill bacteria, fungi, and viruses**
  - Steam, fire, and bleach are very effective
- **Selective killing is a subtle art**
  - Good checklist: AAC Instructions to Authors
    - https://journals.asm.org/journal/aac/scope
  - This 3-part newsletter series on halicin:
    - Search for "halicin" and start here:
    - https://amr.solutions/2020/02/21/chemicals-vs-drugs-the-end-of-bacitracin-the-buzz-around-halicin/
- **Let's take a brief tour of 3 key points**
  - *Invisible from the outside, Pharma has a lot of important plumbing!*



Image reproduced with permission from https://xkcd.com/1217/.

Can you make it? CMC[1]



- **How does a molecule become a physical medicine (e.g., a tablet)?**
- **You must plan for**
  - Early materials for preclinical studies
  - GMP (Good Manufacturing Practice) materials for human studies
  - Sufficient quantity at scale & on stability for Ph3 and registration
- **This is a science unto itself**
  - As part of the NDA/MAA (you've heard of those), you file a dossier on the manufacturing process that is of equal length to the clinical data
- **Advice: Start early! Have a CMC guru on your team**
  - Great CARB-X + GARDP workshop from 2017 on this
  - Search the web for "amr.solutions 2017 bootcamp"

[1]Chemistry, Manufacturing, & Controls

What dose? PK, ADME, and PD



- **PK: Where does it go? What happens to it?**
  - ADME: Absorption, Distribution, Metabolism, and Excretion
  - Does it go to the right body compartments?
  - Will it be easy to use? How many doses/day? Is it (can it be) oral?
  - Does it have (is it likely to have) drug-drug interactions?
- **PD (Pharmacodynamics): What concentration do you need?**
  - Strong PK-PD supports a smaller trial program as proof of drug utility
  - Deciding on a target exposure is a subtle art. As a start see Hope 2016.[1] It's focused on antifungals, but the ideas generalize

1. Hope W, Drusano GL, Rex JH. Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality. JAC 71:3008-19, 2016

Is it safe? Toxicology (1 of 2)



- You need to study supratherapeutic exposures of new agent *and its metabolites* in 2 animal species
- Serious infections may require prolonged therapy
  - **Your studies must span relevant periods**
  - 0-90 days of exposure: day-for-day coverage in man
  - 180-270 days: enough for indefinite exposure
- Metabolites can be tricky. You can try to predict human metabolites but you don't *know* until Phase 1
  - Sometimes you have to do additional studies
  - Forewarned is forearmed. Be sure your investors know!

Is it safe? Toxicology (2 of 2)



- **Don't panic! *Everything* has toxicity**
  - But, take it seriously – toxicity is the main cause of failure
  - **See Prasad AAC 2022 "Leaks in the Pipeline"** and this newsletter
    - https://amr.solutions/2022/06/14/leaky-pipelines-when-is-a-molecule-a-drug/
- **Your job is to triangulate three things**
  - Exposure that you think is required (PK-PD is your guide)
  - The nature of the toxicity (monitorable? reversible?)
  - The Unmet Need you are addressing
- **This is your first look at benefit-risk (B-R)!**
  - B-R needs be B >>>>>> R for uncomplicated UTI
  - B-R can (perhaps) be B ≥ R for cure of endocarditis
    - It depends on the nature of the Risk
- **Advice: Have a PK-PD expert & a medic on your tox team**



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Trial Design 101: Controlled studies

Whether prospective or retrospective, ***there are only 2 designs…***

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- **Superiority studies of NEW vs. OLD**
  - Goal: Show NEW beats OLD
  - Unambiguous: Everybody likes “Better”
- **Non-inferiority (NI) studies of NEW vs. OLD**
  - Goal: Show NEW ≈ OLD
  - Messy, harder to do accurately, confusing
- **But, we (almost) always use NI for antibiotic trials**
  - Why?



Explainer:
https://youtu.be/dx9mrQfSNT4

See also:
https://amr.solutions/2020/09/19/in-praise-of-non-inferiority/

Why not superiority (1 of 3)?

The paradox of antibiotics



- **We want new drugs for bad bugs**
  - The superiority of NEW is easily shown in the lab on the basis of MIC testing or in animal models of infection
- **But, asking for clinical superiority leads to a problem**
  - **Trials must (usually) be designed to avoid superiority**
  - Instead, we **must use non-inferiority (NI) designs** showing similar activity relative to another active agent[1]
- **Example: Limb-threatening infection due to MRSA[2]**
  - It is not ethical to randomize to methicillin vs. NEW
  - Must instead do something like vancomycin (or linezolid) vs. NEW
  - Must NOT enroll if resistant to NEW or comparator

(1) See also https://amr.solutions/2020/09/19/in-praise-of-non-inferiority/. (2) MRSA = Methicillin-resistant *Staphylococcus aureus*

(Reliable) Pathways to Approval & Access



- **By using NI, we can develop NEW before OLD fails completely**
  - If superiority is easily done, something has gone very wrong!
- **NI trials are well-defined and used in most recent approvals[1]**
- **FDA[2] and EMA[3] have clear guidance documents**
- **NI trials give the sponsor a predictable route to initial approval**
- **You might do other studies after that the initial pivotal NI trial**
  - But getting to initial approval is critical

1. Rex, J. H., et al. (2017). "Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance." Clinical Infectious Diseases 65: 141-146.
2. FDA: “Substantial evidence of efficacy based on adequate and well-controlled clinical investigations” with efficacy based on an endpoint based on how a patient feels, functions, or survives.
3. EMA: https://www.ema.europa.eu/en/about-us/what-we-do/regulatory-science-research/benefit-risk-methodology: “The Agency can recommend the authorisation of a medicine whose benefits are judged to be greater than its risks”

Center of gravity: An NI-based Phase 3 path



- **1x NI RCT[1,2] vs. a reliable comparator**
  - **UDR setting (Usual Drug Resistance) where both agents are reliably active[3]**
  - Done in one of the major indications (cUTI, cIAI, etc.)
- **1x salvage study for highly Resistant pathogens**
  - Randomized vs. Best-Alternative Therapy (BAT) if possible
  - Single-arm (no comparator) if N is very small
- **Example: Plazomicin's initial registration program**
  - NI RCT: 1x complicated UTI NI RCT vs. meropenem
  - Salvage: 1x study in CRE vs. colistin
- **Feasible & deliverable in non-geologic time at a predictable cost**

1. NI RCT: Non-Inferiority design Randomized Controlled Trial. See extended discussion of these trials in Rex JH et al.: Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. Clinical Infectious Diseases 65: 141-146, 2017.
2. Note that this pathway also depends on the concept of "a single pivotal trial is sufficient.". This is usually true for antibiotics, but not always. For more, see https://amr.solutions/2026/03/01/fda-one-pivotal-trial-confirmatory-evidence-is-default-expectation-for-approval/
3. UDR is discussed in detail later.. See https://amr.solutions/2019/01/13/categories-of-resistance-mdr-xdr-pdr-udr-and-new-dtr/ and https://doi.org/10.1093/cid/ciw244.

Why not superiority (2 of 3)?

Is it really out of reach? Really?



- **Non-life-threatening illness (e.g., migraine)**
  - Delayed effective therapy is not dangerous
- **Cancer: Placebo is (usually) also not possible but…**
  - … there is always room to improve on 5- or 10-year survival
- **Infections: Current agents are effective!**
  - **We routinely produce Cure of potentially fatal infections**
  - **It's hard to improve on Cured!**
- **It is improbable that the response to (say) imipenem can be beaten**
  - In the UDR setting of susceptible bacteria, response rates are 80-85% ...
  - … any improvement is numerically limited to just a few % and hard to show



YouTube Explainer:
https://www.youtube.com/watch?v=dx9mrQfSNT4

See also
https://amr.solutions/2020/09/19/in-praise-of-non-inferiority/

Why not superiority (3 of 3)?

Really out of reach for all types of infection?



- **Minor infections can be studied vs. placebo (or delayed therapy)**
  - Impetigo, for example
- **Add-on to (not very good) Standard of Care (SOC)**
  - Inhaled amikacin for poorly controlled NTM[1] was studied in this way
- **Vs. poor-quality (but best available!) SOC**
  - *Acinetobacter*: sulbactam-durlobactam was studied vs. colistin-based SOC[2]
- **Other than the minor infections, these designs are one-offs**
  - Once we have a compelling alternative for a particular bad bug, it becomes important to start using that as the comparator for the next new drug
  - And with that, we're back to NI in the UDR[2] (usual drug resistance) setting

[1]NTM: Non-tuberculous mycobacteria. [2]Technically, this was not a superiority study but the key to its utility was the possibility of seeing superiority emerge from a an NI design. Kaye KS et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii-calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet ID 23:1072-1084, 2023. doi: 10.1016/S1473-3099(23)00184-6. [3]UDR is discussed in detail later – see also https://amr.solutions/2019/01/13/categories-of-resistance-mdr-xdr-pdr-udr-and-new-dtr/ and https://doi.org/10.1093/cid/ciw244.

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What is a non-traditional?[1]



- **Two possible lenses: Structure vs. Purpose**

	Traditional (T)	Non-Traditional (NT)
Structure	Typical small molecule	Bacteriophage, lysins, (monoclonal) antibodies, charcoal, and oligonucleotide
Purpose	Treatment or prevention of a standard infection	Other goals: prevention of development/acquisition of resistance, improving/restoring microbiome status, and slowing spread of resistance

- **In fact, no one (but you) really cares about structure or mechanism**
  - You are doubtless excited by science (and so am I)!
  - You get a bit of credit for novelty in value scoring schemes (see later), but the only thing that (ultimately) matters is what it does for patients

[1]Rex, J. H., H. Fernandez Lynch, I. G. Cohen, J. J. Darrow and K. Outterson (2019). "Designing development programs for non-traditional antibacterial agents." Nature Communications 10(1): 3416.

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- **Non-traditional purposes are tricky: you must show value to individuals**

[1]Rex, J. H., H. Fernandez Lynch, I. G. Cohen, J. J. Darrow and K. Outterson (2019). "Designing development programs for non-traditional antibacterial agents." Nature Communications 10(1): 3416.

Other language to note

(… and then mostly bypass)

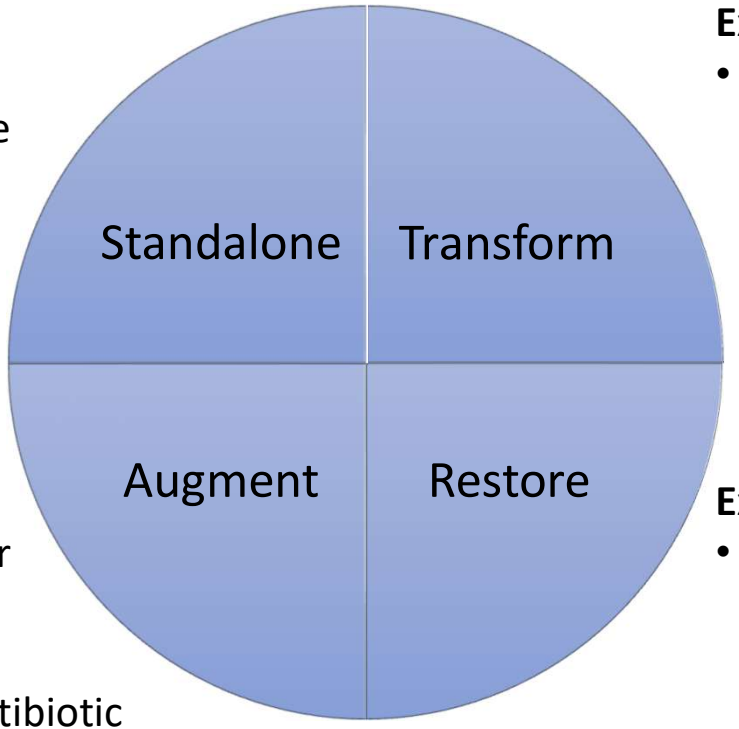


- **Alternatives to antibiotics**
  - A very broadly used term, sometimes taken to be the same as non-traditional and sometimes taken as a superset that includes non-medicinal tools (e.g., a super smooth catheter to which nothing sticks)
  - I mostly just treat as equivalent to non-traditional
- **Potentiator or Enhancer**
  - These terms are applied to many types of combinations
  - I find them too ambiguous to be helpful
- **Instead, the 4 categories of STAR are helpful…**

STAR: Four treatment archetypes[1]



Examples
- Traditional small molecule
- Phage
- Peptide
- Antisense



Example
- Gram-negative activity from colistin + approved Gram-positive antibiotic

Example
- Virulence factor inhibitor or anti-toxin antibody + approved antibiotic

Example
- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

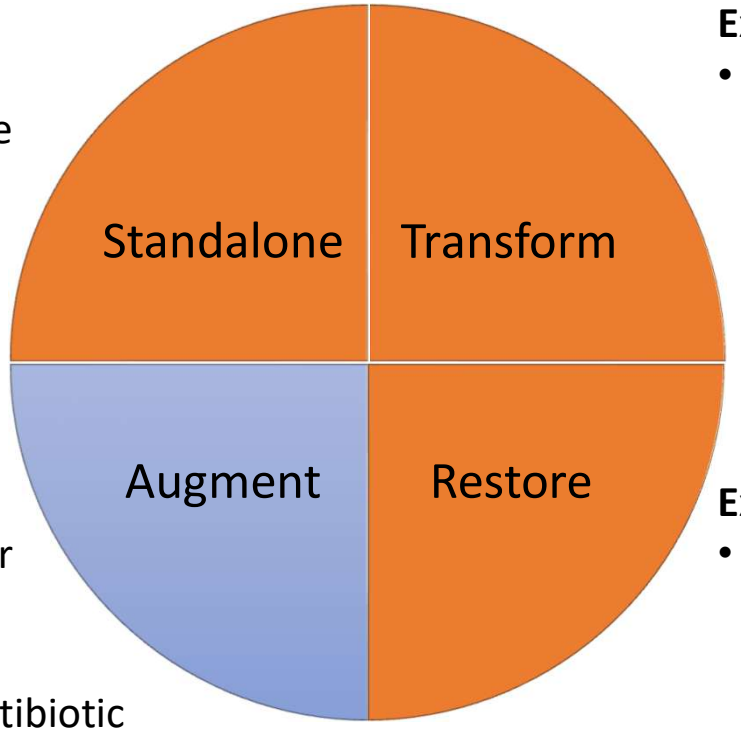
1. Note that these archetypes could also be used for traditional antibiotics. Examples of Standalone and Restore are pretty common. Transform and Augment are possible in theory but are rare in practice.
2. The terms “Potentiator” or “Enhancer” have been used for products in all 3 of these categories

STAR: Four treatment archetypes[1]

Three of them have something in common…



Examples
- Traditional small molecule
- Phage
- Antisense



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Standalone, Transform, and Restore:
The common feature? ***Potential as sole therapy***



- **Speed and spectrum to be the sole therapy for a syndrome (SSSS)**
- **Examples:**
  - Standalone (NEW on its own):* Phage, peptides, lysins, antisense
  - Transform: NEW added to otherwise inactive 2nd agent (e.g., polymyxin + known Gram-positive agent where combo has Gram-negative activity)
  - Restore: Beta-Lactam with a Beta-Lactamase inhibitor (BL-BLI)
- **In either case, an entity complete in itself**
  - Even if it has more than one component
  - Usually has an MIC
- **Advantages: Standard NI designs may be suitable**

*This would also describe ANY new mechanism standalone molecule, small or large.

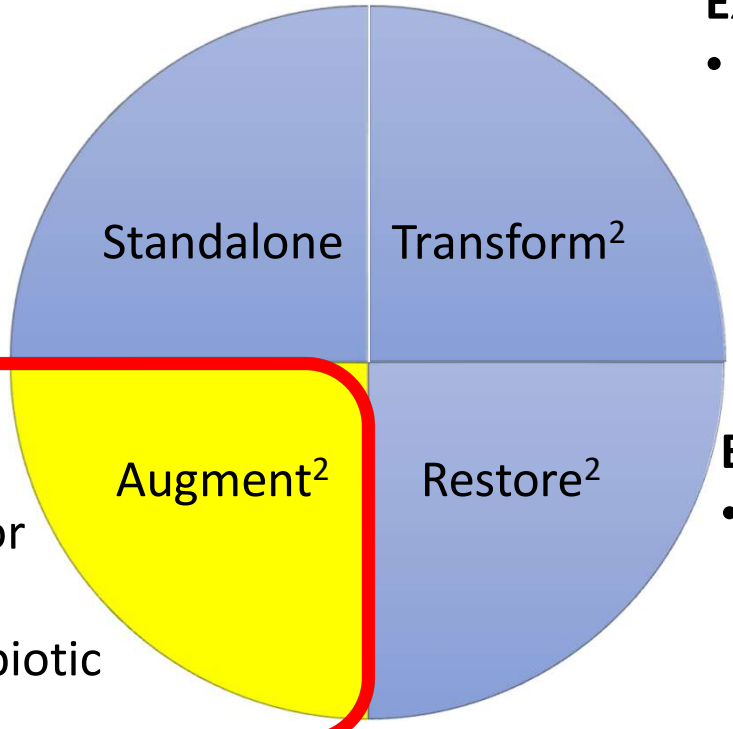
STAR: A way to think about the options[1]



Examples

- Covalent combinations
- Phage

A special issue here!



Example

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1. Rex et al. "Designing development programs for non-traditional antibacterial agents." Nature Communications 10(1): 3416, 2019.
2. The terms “Potentiator” or “Enhancer” have been used for products in all 3 of these categories

The challenge of *Augment*



- **NEW alone is not sufficiently active to be monotherapy in a trial**
  - Lack of speed, limited potency
  - Thus, equipoise cannot be achieved for NEW vs. OLD in clinical trials
- **Instead, NEW + OLD must be compared with OLD (+ placebo)**
  - In this case, NEW + OLD must show superiority to OLD based on a clinical endpoint grounded in how a patient feels, functions, or survives
- **This creates a steep hurdle**
  - Clinical trials must be designed to avoid superiority!
  - No one wants to be randomized to a potentially suboptimal therapy arm!

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Narrow-spectrum problem (1 of 2)



- **Infections are initially diagnosed and treated as syndromes**
  - "Pneumonia" rather then "pneumonia due to X"
- **Narrow-spectrum antibiotics** require a syndrome where activity for a specific pathogen can be seen in isolation. There are 3 possible patterns:
- **Pattern A:** Organism = Syndrome (*N. gonorrhoeae*)
  - Other examples: TB, *Salmonella*, etc. Never normal to carry these!
  - Diagnostic can select; Straightforward study design
- **Pattern B:** Organism appears within a syndrome and symmetrical gaps in the spectrum of existing agents make it possible to show activity of NEW:
  - Ertapenem[1] does not cover P*. aeruginosa*.
  - So, NEW + ertapenem vs. imipenem shows activity of NEW vs. *Pseudomonas*
  - A diagnostic could support selective enrollment of patients infected with *Pseudomonas*

Ertapenem is a carbapenem that lacks activity against *Pseudomonas aeruginosa*. Imipenem is a carbapenem that DOES cover P. aeruginosa. So, you could say that ertapenem has a *Pseudomonas*-sized hole in its spectrum relative to imipenem.

Narrow-spectrum problem (2 of 2)



- **Pattern C:** Organism is one of several causes of a syndrome and existing agents often cover it
  - Ex: *Klebsiella* as a component of cIAI & pneumonia
  - Therapy in these conditions is syndromic
  - There is a strong desire for therapy that covers all likely pathogens
- **Danger, Danger, Will Robinson!**
  - **ALERT: This is a HARD problem ... Be careful!**
  - It will likely be hard to arrange things so that your product can be seen to be active
  - Perhaps you could do this for *E. coli* in UTI
  - A diagnostic is NOT a reliable fix for this … it is very hard to know which bug is doing what
  - This difficulty surfaces both during development (hard to run a trial) and in routine care (hard to know when to use the selective agent)
  - And a focus on just MDR *K. pneumoniae* will not fix it (next slide)…

Narrow (and/or Rare): Summary



- **Unless the pathogen is distinct to the infection, pursuit of individual pathogens or (just) rare pathogens (MDR or otherwise) is very hard**
  - A rapid diagnostic does not create the patients!
  - If the target organism has a frequency of 1%, then you must screen 100 to find that 1 patient … or even more if the diagnostic is imperfect
- **Net of all this advice:**
  - Products that can be used as sole therapy for an entire syndrome are much more easily developed
- **Everything else is harder**
  - Get help early – make plans to solve this problem!!

Agenda



- The rising tide of antimicrobial resistance
- The exciting promise of peptide-based antibiotics
- The big question: Is it a drug?
  - Rules of the road: Essential trial designs and their limitations
  - Traditional vs. non-traditional antibiotics
  - The narrow-spectrum drug challenge
- **The economics of antibiotics**
- A worthy challenge!

The (other) 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!

Aside: NI trials are not the *only* cause of this paradox, but they are a substantial contributor

For more on this issue, start with Rex JH and Outterson K (2021): "Antibacterial R&D at a crossroads: We've pushed as hard as we can … now we need to start pulling!" Clin Infect Dis 73:e4451–e4453 and Miller LG (2019): "Another New Antibiotic for Skin Infections and Why Infectious Disease Specialists Are Hypocrites." Clin Infect Dis 68: 1223-4.

The toll of the broken AMR Market



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

2019

ACHAOGEN

- **Started** 2002
- **FDA Approval** June 2018
- **Bankruptcy** April 2019
- **Investor Loss** $504M
- **USG Grants** $133M

2020

melinta

- **Started** 2002 (as Rib-X)
- **FDA Approval** June 2017
- **Peak Market Cap** $423M
- **Bankruptcy** Dec 2019
- **Investor Loss** $593M
- **USG Grants** $132M

TETRAPHASE

- **Founded** 2006
- **FDA Approval** Aug 2018
- **Peak Market Cap** $1.8B
- **Distressed Sale** Dec 2019
- **Investor Loss** $550M
- **USG Grants** $107M

2022

SPERO

- **Founded** 2013
- **Peak Market Cap** $628M
- **Layoffs** May 2022
- **Current Market Cap** $76M – Drug in P3
- **Investment to date** $439M
- **USG Grants** $60M

ENTASIS

- **Founded** 2015 (spinout from AstraZenca)
- **Peak Market Cap** $XX
- **FDA Approval** May 2023
- **Distressed Sale** July 2022
- **Investor Loss** $134M
- **USG Grants** $0

Nabriva

- **Founded** 2001
- **FDA Approval** Aug 2019
- **Peak Market Cap** $282M
- **Liquidation** Nov 2022
- **Investor Loss** $507M
- **USG Grants** $0

2023

PARATEK

- **Founded** 1996
- **FDA Approval** Oct 2018
- **Peak Market Cap** $797M
- **Distressed Sale** June 2023
- **Investor Loss** $162M
- **USG Grants** $285M

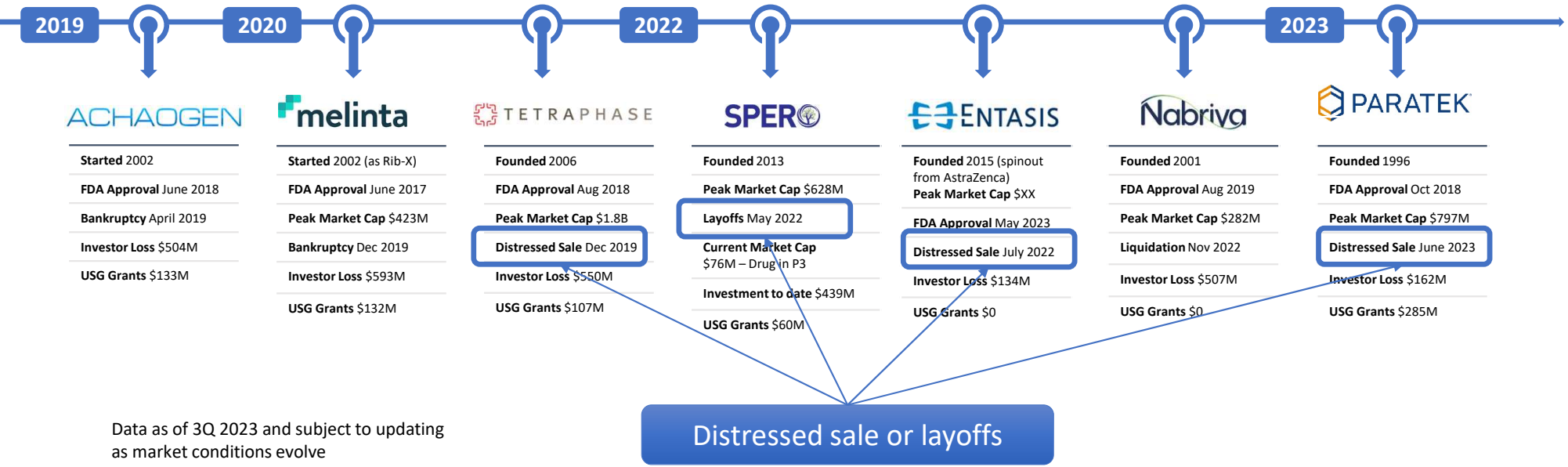
Data as of 3Q 2023 and subject to updating as market conditions evolve

Slide courtesy of Kevin Outterson

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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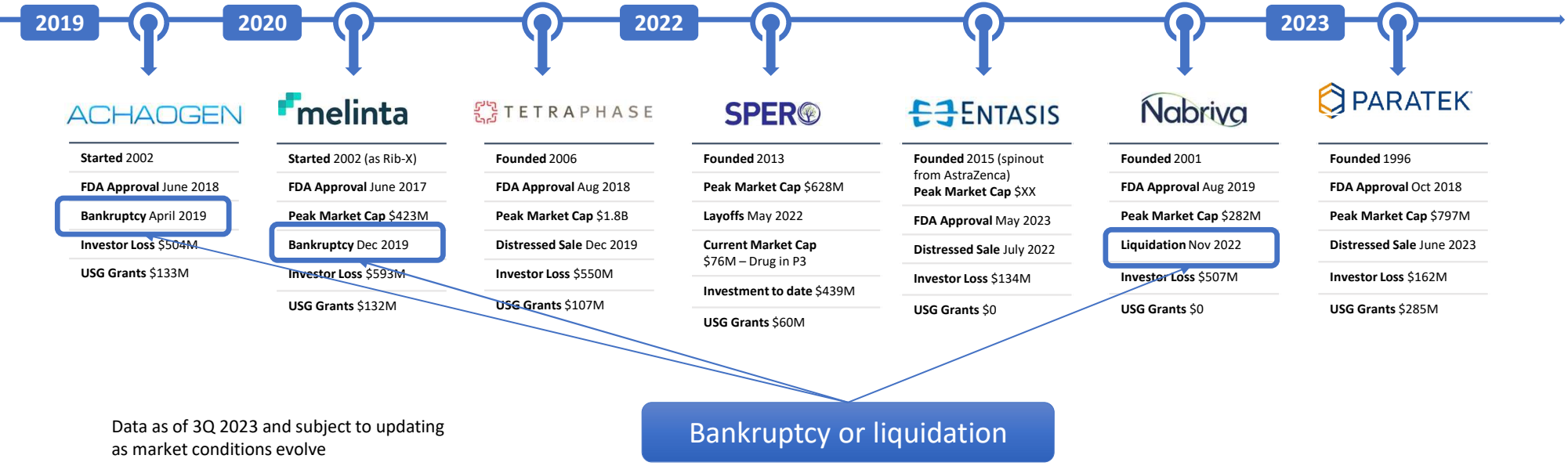
The toll of the broken AMR Market



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



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

Slide courtesy of Kevin Outterson

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!
- Antibiotics (like fire extinguishers) have value by existing

For more on this issue, start with Rex JH and Outterson K (2021): "Antibacterial R&D at a crossroads: We've pushed as hard as we can … now we need to start pulling!" Clin Infect Dis 73:e4451–e4453 and Miller LG (2019): "Another New Antibiotic for Skin Infections and Why Infectious Disease Specialists Are Hypocrites." Clin Infect Dis 68: 1223-4.

Pop Quiz: Have you used a fire extinguisher today?



Pop Quiz: Have you used a fire extinguisher today?

amr.solutions



Let's be more concrete.
Are you using a fire extinguisher <u>right now?</u>

Fundamental starting points



- **Antibiotics enable all of health care:**
  - Safety net for surgery, cancer therapy, and everything else
  - Infrastructure for civilization

Fundamental starting points



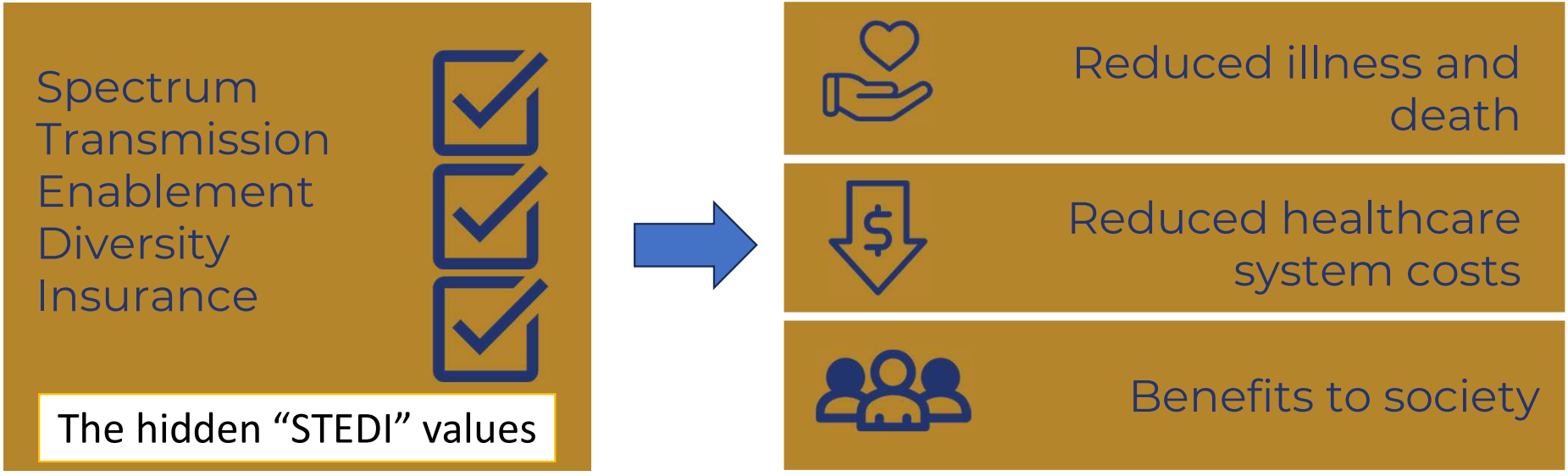
- **Antibiotics enable all of health care:**
  - Safety net for surgery, cancer therapy, and everything else
  - Infrastructure for civilization

- **Stated differently…**

Antibiotics are the fire extinguishers of medicine

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. See also see Miller, L. G. "Another New Antibiotic for Skin Infections and Why Infectious Disease Specialists Are Hypocrites." Clin Infect Dis 68: 1223-4, 2019 for a thoughtful perspective. 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/.

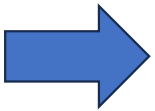
Hidden fire extinguisher *"STEDI values"*

Subtle but real[1,2]



Example STEDI value:
Transmission

After treatment,
Infection in Person A
cannot spread
to Person B





Reduced illness and death



Reduced healthcare system costs



Benefits to society

(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. See also see Miller, L. G. "Another New Antibiotic for Skin Infections and Why Infectious Disease Specialists Are Hypocrites." Clin Infect Dis 68: 1223-4, 2019 for a thoughtful perspective. 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/.

So, antibiotic benefits go beyond simple use

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



Antibiotics are the fire extinguishers of medicine!

- Another useful variation on this idea is that of life insurance
- Do you have life insurance?
- If so, did it pay off today?
- How do you feel about that?

Push and Pull are both needed as fixes



- **Substantial public thinking over the past 10+ years**
  - UK AMR Review; DRIVE-AB project; US legislative efforts; Swedish pilot project, EU Pharma strategy, and more
- **Key insights: We need 2 different kinds of funding**
  - **Push incentives** that encourage work to start: Grants
    - $750m for Discovery to Phase 1: CARB-X, Novo REPAIR, etc.
    - $1b for Phase 2-3: AMR Action Fund
  - **Pull incentives** paid on successful approval



YouTube explainer
https://youtu.be/6gd8iXLbZak

- **Many papers on this, see amr.solutions for more**
  - Incentives summary webpage: https://amr.solutions/incentives/
  - 17 Sep 2026 newsletter: https://amr.solutions/2026/09/17/global-review-of-pull-incentives-pasteur-sign-on-letter/

Pull equalizes the economics



YouTube explainer
https://youtu.be/fpgvrnaliek



- **A Pull Incentive rewards creation of a valuable new therapy**
  - Key: It is paid on approval and is independent of actual use
  - Analogy: We don't pay fire fighters per fire; we pay to be ready
- **With multiple global calls for Pull[1], it is starting to emerge**
  - The UK subscription process as a benchmark: The "Netflix" model
- **Global goal: ~$2-4b (per drug over 10 years) is large enough to drive R&D**
  - The full value is even higher[2]
- **So, how do we engage and extend?**
  - Wealthy countries need to contribute their fair share
  - Targets must be fair and consistently available
  - EU soon do this via transferrable exclusivity vouchers.[3] The PASTEUR Act will do this in the US
- **Keep up via the amr.solutions newsletter – it's a topic that I follow closely!**

[1]US: PACCARB (https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf) and PASTEUR Act (https://www.congress.gov/bill/116th-congress/senate-bill/4760/text); EU: IMI DRIVE-AB: http://drive-ab.eu/drive-ab-outputs/drive-ab-reports/ and 2020-25 EU Pharmaceutical Strategy (https://ec.europa.eu/health/human-use/strategy_en), UK: AMR Review: https://amr-review.org/ and UK pilot itself: https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/ [2]See 2014 ERG report to DHHS: https://aspe.hhs.gov/report/analytical-framework-examining-value-antibacterial-products and Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. Health Affairs. 2021;40(:1758-65. [3]See https://amr.solutions/2025/12/12/pull-incentives-in-europe-tevs-to-be-included-in-legislative-update/

How will new antibiotics be valued?

The UK model makes it clear



Criteria	Weights
1A: Activity against WHO bacterial priority pathogens	12.2%
1B: Activity against resistance mechanisms	10.4%
1C: Activity against UK unmet needs	11.2%
1D: Effectiveness compared with current UK best standard care	11.2%
2A: Chemical entity novelty	4.5%
2B: Target site novelty	4.0%
2C: Drug exposure at the site of infection	4.5%
2D: Absence of cross-resistance	4.5%
2E: Absence of rapidly emerging resistance	4.0%
2F: Impact on gut microbiome	3.5%
3A: Adverse events	5.4%
3B: Drug-drug interactions	3.9%
3C: Formulation or delivery of therapy	4.5%
3D: Dose frequency	4.5%
3E: Product stability and storage	2.7%
3F: Monitoring requirements	3.6%
3G: Reduced hospital-led care	5.4%

Band 1: £23.7m/yr	**Band 2:** £17.8m/yr	**Band 3:** £11.9m/yr	**Band 4:** £5.9m/yr
Breakthrough antimicrobial	Critical new antimicrobial	Priority new antimicrobial	Important new antimicrobial
≥80% of max	70 to 79%	60 to 69%	50 to 59%

Other programs are likely to use similar rules – there are only so many ways to do this!

Values shown are the combined total for England, Scotland, Wales, and Northern Ireland. For details: https://amr.solutions/2024/08/19/uk-subscription-model-goes-live-value-bands-cover-entire-uk/

Implications for R&D



- **Substantial Pull can / should go only to impressive new products**
  - If it makes you think “Meh” … it’s not going to qualify
  - We (R&D) must take our part of the moral hazard of the risk of failure
- **So, is it “Go big or go home?”**
  - Yes, that’s pretty much the message
  - CARB-X has shown a willingness to fund high-risk ideas
- **Pay close attention to what doesn’t work / is hard**
  - Single pathogen? Harder than you’d guess
  - Inhaled products? MUCH harder than you’d guess[1]

[1]See this newsletter: https://amr.solutions/2020/10/18/fda-workshop-insights-on-inhaled-antifungals-and-antibacterials/

Agenda



- The rising tide of antimicrobial resistance
- The exciting promise of peptide-based antibiotics
- The big question: Is it a drug?
  - Rules of the road: Essential trial designs and their limitations
  - Traditional vs. non-traditional antibiotics
  - The narrow-spectrum drug challenge
- The economics of antibiotics
- **A worthy challenge!**

At heart, I'm an ID doc who went into Industry because I didn't have the drugs I wanted



My key lesson from > 20 years in pharma?

- In theory, there is no difference between theory and reality.
- In practice, there is.

… or stated differently …

- Don't let the perfect be the enemy of the good

So, accept the challenge! Peptides are intriguing and you are making progress!



- **Key points**
  - Look to the future of Pull incentive-led R&D … the scoring schemes are visible
  - Products that must show superiority for initial approval face an especially difficult road. Plan carefully!
- **Inspiration**
  - “Don't undertake a project unless it is manifestly important and nearly impossible.” *Edwin Land (inventor of instant photography)*
  - “It always seems impossible until it's done.” *Nelson Mandela*
  - “Life's most persistent and urgent question is, 'What are you doing for others?’” *Martin Luther King, Jr.*
- **Have courage! Thanks for being part of this community!**
  - Your children (and your children’s children) will thank you!

Many thanks for inviting me to be with you today! I'm delighted to see what you are doing! I'm cheering for you!



Tiny heroes for immense challenges: *The path for antimicrobial peptides*

John H. Rex, MD

Editor-in-Chief, AMR.Solutions
Chief Medical Officer, F2G Ltd
Operating Partner, Advent Life Sciences
Adjunct Professor of Medicine, McGovern Medical School

25 Mar 2026, CAN-AMR training course

Please note these details!

Slides will be shared!

Email: john.h.rex@gmail.com

Newsletter: http://amr.solutions

18 Nov 2026 – International Symposium on Antimicrobial Peptides