



The future of AMR reimbursement: What types of products will succeed?

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Slides happily shared



Executive Summary

- Key messages:
 - Reimbursements that reflect the societal value of new antibiotics are coming
 - Not all new antibiotics will earn a strong reward
 - Judging the value of a given project (e.g., the project you are working on right now!) requires a deep understanding of how to work around/with the constraints on antibiotic R&D
- To that end, this talk covers
 - Rules of road / Laws of gravity
 - Know what is possible, Know how to explain to others
 - Emerging metrics for value



Agenda

Laws of Gravity

- **Non-inferiority vs. Superiority**
- The standard pathway
- Agents that augment (virulence modifiers, etc.)

Value

- #FireExtinguishersOfMedicine and reimbursement
- Summary



Trial Design 101: Two study designs everything reduces to one of these

- Superiority studies
 - X vs. Y, with an aim to show X beats Y
 - TEST vs. placebo or TEST vs. Standard of Care
 - Preferred design – result is unambiguous
 - Everybody likes the idea of Better
- Non-inferiority (NI) studies
 - X vs. Y, with an aim to show $X \approx Y$
 - Messy, harder to do accurately, confusing
- But, we (almost) always use NI for new antibiotics
 - **Why?**



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 data leads to a problem
 - Trials must (usually) be designed to avoid superiority
 - Instead, we must use non-inferiority designs showing similar activity relative to another active agent
- Example: Limb-threatening infection due to MRSA*
 - It is not ethical to randomize to methicillin vs. NEW
 - Must instead do something like vancomycin vs. NEW
 - Must NOT enroll if resistant to NEW or comparator!

*MRSA = Methicillin-resistant
Staphylococcus aureus

This idea is very, very hard



NI vs. Superiority

- Non-life-threatening illness (e.g., migraine)
 - Delayed effective therapy is not dangerous
- Cancer: Placebo is (usually) not possible, but there is always room to improve on 5- or 10-year survival
- **Infections: We routinely produce Cure of potentially fatal illness**
 - And, it's hard to improve on Cured
- But, the idea of non-inferiority is confusing
 - “We want a *better* drug.”
 - I get it, but insisting on clinical superiority before approving new agents means progress only when/if the pipeline (again) becomes inadequate
 - NI allows us to develop drugs before we need them



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Solution: The (emerging) 2-study path for new traditional antibiotics



- 1x NI RCT¹ vs. a good comparator
 - UDR (Usual Drug Resistance²) setting: **both agents are predicted to be active**
 - Done in one of the major indications (cUTI, cIAI, etc.)
- 1x study for highly Resistant pathogens
 - Randomized vs. Best-Alternative Therapy (BAT) if possible, Open-Label if N too small for this
- Example: Plazomicin initial registration program
 - Highly R: 1x study in CRE vs. colistin (prior slide)
 - NI RCT: 1x complicated UTI NI RCT vs. meropenem

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. UDR is what you have when its not MDR or XDR ... it's the usual state of play. For more, see <https://amr.solutions/2020/02/20/language-matters-cre-vs-cpe-sdd-vs-i-and-mdr-xdr-pdr-udr-vs-dtr/>



About narrow-spectrum agents...

- This is the concept of “Tier C” pathways¹
 - Rare pathogens, (only) MDR pathogens, rare diseases
 - Small trial programs, just barely (or not) powered
- Can this be done? Yes, but it’s not an easy out
 - Do not think of this as simpler, faster, or cheaper
 - It’s not (just) a regulatory hurdle – the strength of evidence will become frustrating
- See recent IDSA whitepaper and FDA workshops
 - Boucher et al. "Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs." J Infect Dis 216: 228-36, 2017
 - My blog notes: 13 Apr 2017 + 5 May 2017 workshops

¹Rex JH, Eisenstein BI, Alder J, Goldberger M, Meyer R, Dane A, et al. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. Lancet Infect Dis. 2013;13(3):269-75.



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Agents that Augment

- Example: Virulence inhibitor or such
 - Not sufficient alone: Must also give an active agent (e.g., toxin inhibitor + active 2nd agent)
- Distinctive hurdles
 - **Base therapy needs to work**
 - Might protect a base therapy from emergence of resistance but doesn't solve existing resistance problems
 - Dose: Lack of an MIC → harder to apply PK-PD
 - If the PK-PD rationale has gaps, it may become harder to validate dose/exposure logic
 - Superiority problem: Must show $NEW + OLD > OLD$
 - May need a novel endpoint to show value

Superiority & Endpoints



- Ultimately, must study NEW + SOC vs. SOC
 - We will want to see that NEW + SOC is **superior to SOC**
 - And this superiority must be grounded in how the patient feels, functions, or survives
- Are there settings where this might be possible?
 - Endocarditis is a good candidate: more rapid bloodstream clearance might have a measurable clinical effect
 - Chronic infections (**many fungal infections!**) may also offer scope for showing improvement
- **Endpoints:** Would different endpoints help?
 - How would you show a clinical benefit for reduced rate of onset of resistance? Can you show this at a community level?
 - A challenging question! Whatever is proposed must be compelling.
- **Finally, know that this is not a regulatory problem per se**
 - The agencies are simply the first to point out the issue
 - Why should I use this? Why should I pay for this?



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Pop Quiz: Have you used a fire extinguisher today?



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



Fundamental starting points

- Antibiotics enable all of health care:
 - Safety net for surgery, cancer therapy, and essentially everything else
 - Fire extinguishers (or fire departments) of medicine
 - Infrastructure for civilization

- Stated differently...

STEDI: Antibiotic value beyond mere use

But, we don't (yet) have an agreed way to capture these values



Antibiotics are the fire extinguishers of medicine!

The "STEDI" values of antibiotics

Value	Description of benefit
Spectrum	Replacing broad spectrum agents with narrow spectrum agents and thereby reducing collateral damage to the microbiome
Transmission	Avoiding pathogen spread to the wider population by effectively treating patients
Enablement	Availability of effective treatment enables other types of medical interventions (eg, surgery, oncology)
Diversity	Having a range of treatment options reduces selection pressure
Insurance	Having an agent available in case of a sudden or significant increase in the prevalence of pathogens resistant to existing agents

Table from Outterson K, Rex JH. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research*, 2020. The STEDI concept was adapted from Rothery et al. Framework for Value Assessment of New Antimicrobials. <http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf>, 2018.

Fire extinguisher value: \$0 vs. ∞

COVID as an example



- Thought experiment. *Let's hop in a time machine...*
 - You own a company that has developed a novel small molecule with broad activity vs. all Coronaviridae
 - You've shown that it shortens the duration of URI symptoms for the coronaviridae strains that cause URI
 - There is in vitro activity for SARS and MERS but no clinical data as no cases. So, you use human challenge models to develop the drug
- You receive FDA & EMA approval in 1 Jan 2018
 - What are your sales during 2018-19?
 - Could you have stayed in business?
 - What's the fix?



Fire extinguisher value: \$0 vs. ∞

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 - What's the fix? *Delinked Pull rewards that are independent of use*

Fire extinguisher value: \$0 vs. ∞ *COVID as an example*



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 - Value of the molecule in 2021? *If it had been used early on to contain the outbreak in Wuhan, total sales might be low ... but the value to the global community would nonetheless be enormous*



It's expensive!

- Average all-in cost to approval¹ = \$1.3b
- Running costs of a drug in its first 10 years: \$350m²
 - \$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}
 - New antibiotics often have \leq \$25m/year in sales
- Can it be done for substantially less?^{5,6}
 - 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 lean⁵

¹Wouters 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/>. ³AMR.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/>. ⁴AMR.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/>. ⁵Drakeman DL. Benchmarking biotech and pharmaceutical product development. *Nat Biotechnol*, 32(7): 621-5, 2014. ⁶AMR.Solutions: “All-In Cost Of A New Antibiotic From Discovery To 10 Years On Market”, available at <https://amr.solutions/2021/01/09/all-in-cost-of-a-new-antibiotic-from-discovery-to-10-years-on-market/>



Push and Pull are both needed

- 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
 - Lots of (mostly small) companies have engaged
 - Pull incentives paid **on successful approval**
- Many papers on this, see amr.solutions for more
 - In particular, the 1 Sep 2020 newsletter is a good start
 - <https://amr.solutions/2020/09/01/reimbursing-for-innovative-antibiotics-encouraging-updates-from-the-amr-conference/>



YouTube explainer
<https://youtu.be/6gd8iXLBZak>



Pull equalizes the economics

- 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 Pull¹, it is starting to emerge
 - The UK subscription pilot as a benchmark: The “Netflix” model
 - GBP 10m/yr x 10 yrs for good antibiotic **whether used or not**
 - The UK is 3% of the G20: 100m x 33 = GBP 3.3b ≈ \$4b
- This is on target: Economic research says ~\$2-4b is large enough to drive R&D (the full value is even higher²)
- So, how do we engage and extend?
 - Wealthy countries need to contribute their fair share
 - Targets must be fair and consistently available
 - So far, the only sizeable further effort is in the US (PASTEUR Act)



YouTube explainer
<https://youtu.be/fpgvnrnaliek>

¹US: 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/> ²See 2014 ERG report to DHHS: <https://aspe.hhs.gov/report/analytical-framework-examining-value-antibacterial-products>



Why \$2-\$4b as the reward?

- What does a new antibiotic *really* cost?
 - As noted above, \$1.7b all-in would be a good guess
- A reward in the range of ~\$2-4b balances the risk
 - Substantial modeling has been done on this
 - A reward of this size makes antibiotics \cong cancer drugs
 - DRIVE-AB¹, ERG review², UK AMR Review³, PACCARB⁴
- Investment will occur if reward is predictable
 - Pharma & VCs will take on the technical risk
 - Reward should be triggered by approval

¹DRIVE-AB: <http://drive-ab.eu/drive-ab-outputs/drive-ab-reports/>. ²Sertkaya et al. <https://aspe.hhs.gov/report/analytical-framework-examining-value-antibacterial-products>. ³UK AMR Review: <https://amr-review.org/>. ⁴PACCARB incentives: <https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf>



Pull awards can/will guide R&D

- Think of R&D as a big ship ... *a 10- to 15-year-long ship*
 - Big ships turn slowly, but they do turn
- Pull awards tied to desired features will turn the ship
 - **Novelty, Indications, and Spectrum can all be measured¹**
 - **The UK Pilot has published a point scoring system²**
- Key: Targets must be held constant
 - Products coming to approval at any given time are the result of decisions made a decade or more previously
- Some additional detail on next slide. *For an extended discussion...*
 - AMR.Solutions:³ “Assessing Antibiotic Value: DTR, Fire Extinguishers, And A View From Australia”
 - The idea of Difficult-to-Treat-Resistance (DTR) is a noteworthy build on features such as novelty and spectrum
- Hint, hint: What does this tell you about choosing a project?

Example on
next slide

¹Rex JH, Outterson K. Antibiotic Reimbursement in a Sales-Delinked Model: Context and a Benchmark-Based Global Approach. The Lancet Infectious Disease, 16: 500-5, 2016. ²Search for “slide 25” on <https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/>. ³<https://amr.solutions/2020/06/07/assessing-antibiotic-value-dtr-fire-extinguishers-and-a-view-from-australia/>



UK Pilot: Point Score Scheme

- Up to 11,250 points for priority pathogen coverage
- Unmet need: Up to 6000 points across High, Medium, and Low unmet need
- Coverage of key resistance determinants: Up to 6000 points based on extent of coverage of pathogens expressing various resistance determinants.
- Utility in various disease settings: Up to 6000 points for the spectrum of primary care (lowest) to ICU (highest)
- Novelty: New class (2000 points), New target (1500 points), New Mechanism of Action (1500 points), low rate of development of resistance (1500 points), lack of cross-resistance (1000 points), and Other benefits (up to 500 points)
- Certainty of supply, Stewardship, and arrangements for Surveillance are each worth up to 5000 points

The PASTEUR Act in the US is likely to have a similar feel!



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Summary



- The AMR problem is now well-defined
 - After 10 years of effort, we really understand the issues
 - Antibiotics are the Fire Extinguishers of Medicine
 - Like other infrastructure, we must buy them in advance
- The possible solutions are now well studied
 - Push funding is familiar and is having an effect
 - The big mental shift is in Pull
- It takes years of effort to find novel new agents
 - Reward must match required risk
 - Delinked Pull ties together creativity and stewardship
 - Chose your research project wisely!

#FireExtinguishersOfMedicine