Viewfinder

ESG issues in critical focus

DISCERN sustainability

# Novel Antibiotics

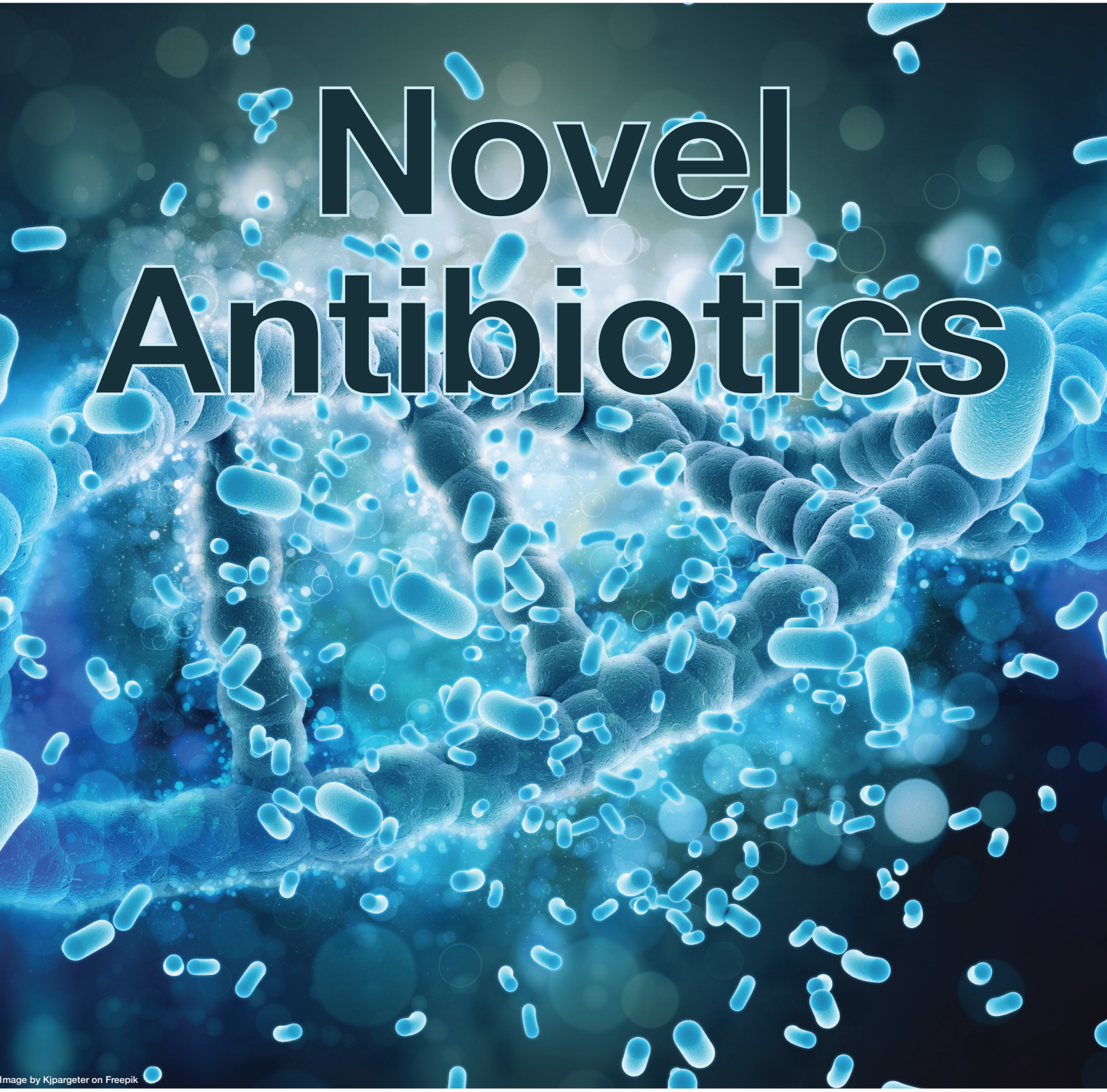


Image by Kjpargeter on Freepik

## Fixing Incentives

September 2022

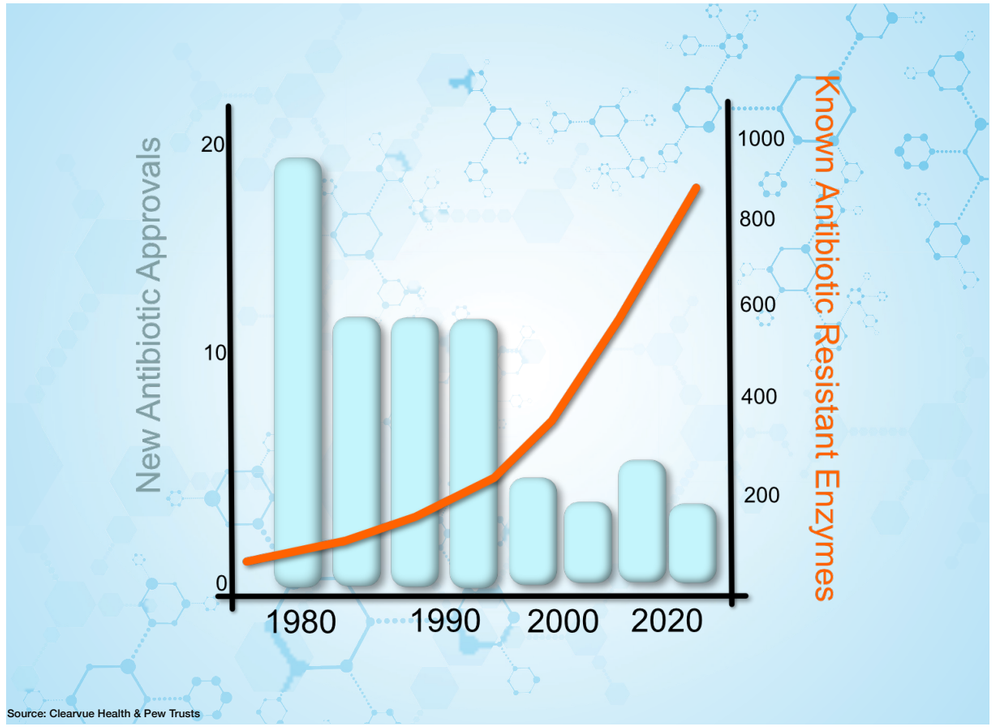
## KEY TAKEAWAYS

If the world were starting with a blank sheet, new antibiotics would be created and controlled entirely via public entities. Antibiotics are inherently unprofitable and utterly essential, a utility whose value is protected through prudent use. Nothing else better explains this market failure: the incentives are broken.

For as long as reliance on the private sector to co-develop new drugs is a reality, Jim O'Neill's proposal of a Market Entry Reward to compensate developers upfront is the most promising, but has failed to attract the financial fire power needed.

Sufficient dry powder to blow a hole in the wall of antibiotic apathy is something that might only be supplied through connecting to capital markets. This requires creative ways of de-risking pools of available finance by making it technology-agnostic and behaving like index-linked bonds, with very long or indefinite duration

We suggest a multi-lateral-backed escrow fund growing to c. $USD 40Bn. It would be wrapped within a system of fiscal carrots and sticks for pharma companies via a 'play or pay in' scheme. The result would be equitable, efficient, and stand a fighting chance of producing the 15 or so novel drugs estimated needed to push back the tide of antimicrobial resistance.



Source: Clearvue Health & Pew Trusts

## Why don't we have new antibiotics?

You may have read about running out of effective antibiotics. Scary, super-resistant bugs, "anti-microbial resistance" or AMR could mean a trip to the hospital for a routine operation could more frequently result in death. Something else you may know is that we've been prescribing antibiotics like skittles for decades. This is true not only for humans but animals. They are used with abandon as a prophylactic in factory farming to prevent infection.

This pervasion of our eco-system with antibiotics creates abundant target practice for bugs to become resistant to the drugs. Clamping down on over-prescribing and restricting its use in the food system (part of 'antibiotic stewardship') is beginning to take place in some jurisdictions and should help slow the growth of resistance. But people in need of antibiotics cannot be just left to their fate. To achieve a re-set, we urgently need a generation of novel antibiotics against the ingenious bugs. That upper hand must then be sustained through the correct prescribing behaviours and regulations.

Given that there are potentially tens of millions of lives threatened, why don't we have the new school of antibiotics, already? The short answer is that they lose money for pharmaceutical companies. It is very hard to find new ones because the low-hanging fruit are picked. They cost upwards of USD$1Bn to develop, before any ongoing expenses. Once you make them, their use is going to be restricted anyway, and what you can charge for them is rightly limited by contracting health authorities.

As of 2018, "Nine of the twelve US antibiotics launched since 2009 are being sold at a loss, even if the R&D had been free; none are in a position to recover R&D investment", notes the Global Antibiotic Research & Development Partnership.

**Despite the higher long-term mortal threat and losses to productivity antibiotics have failed to attract a fraction of the investment in COVID-19 vaccines. Humans are better at putting out fires than avoiding slow-motion car crashes.**

Furthermore, antibiotics treat acute, not chronic illnesses. Pharmaceutical companies see more opportunity in focusing on medicines with healthy profit margins that you'll need your whole life, or at least for which there's no alternative (see the price of Hepatitis C drugs).

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*"The experience of Ebola is an unfortunate example of what can happen when investment is needed urgently due to an outbreak. Alarmed at the global health emergency that Ebola represented, the US Congress agreed an appropriation of 5.4 billion USD…It demonstrates the scale of funding that governments are willing to allocate when faced with an acute public health emergency.*

*This is because untreatable infectious diseases are both scary and expensive to deal with once there is an outbreak. When it comes to dealing with AMR (Anti-Microbial Resistance), countries have three options in how they pay. First, they could wait until there is a problem and then try to get on top of it. As MRSA, Swine Flu, Ebola and other outbreaks have taught us, this is expensive both in lives and money. Second, they could recognise that prevention is better than cure and individually invest in the tools needed to stop resistance, in a patchwork or uncoordinated fashion.*

*This has not succeeded so far, we think mainly because of the worry of 'free-riders' benefiting unfairly. Or third, by working together and paying for global public goods in a pooled way, countries could most efficiently and effectively work to avoid the type of large-scale outbreak of an untreatable infection that nobody wants to see."*

The O'Neill Report: Tackling Drug Resistant Infections Globally: final report and recommendations, May 2016

## If not now, then when? AMR is primed for a major boost in the arm

A decade ago, an economist, Jim O'Neill, was tasked with diagnosing this market failure and proposing remedies spanning the gamut of obstacles. By most accounts, he got things right. His principal recommendation on how to stimulate greater investment in novel antimicrobial agents was the idea of a Market Entry Reward.

A Market Entry Reward is when a pharma company comes up with a successful drug that meets the Reward's rules. The company would be paid a fee up front on delivery of an approved drug that targets the bacterial strains prioritized by public health experts, namely the WHO. In this scenario, a command-and-control system for dispensing antibiotics would more stringently regulate use, to avoid propagating further resistance. The company's activities, especially in manufacturing and sales, consequently, would be curtailed ever more than at present.

O'Neill's idea for  a fund has resulted in…not very much substantial in terms of money committed. The reasons why not are rarely discussed, but aside from the daunting economic model for antibiotic development, his proposal of a USD 2Bn fund is less than half that approved by the U.S. Senate to combat Ebola, alone. Sufficient dry powder to blow a hole in the wall of antibiotic apathy is something that might only be fixed through connecting to capital markets.

## Fixing incentives, lowering risks

So how might we design a fund that is sufficiently large, attractive and affordable for all the stakeholders needed to make it happen? Let's split these stakeholders into groups. What are the triggers for their involvement?

### Pharmas

Antibiotics are not where profits are at, but for social license-to-operate motives, the larger companies would be willing to do more if their investment was made less risky. For small, specialist biotech companies, the effects of success could be similar to that of BioNTech and COVID vaccines: a way of making its mark. For companies that could participate but won't, being under threat of some form of sanction might be what drags them over the line. At a personal level, microbiologists are the most poorly paid group in medical research and citations among the lowest. Their prestige must be improved through financial and other rewards. They should receive better career paths in the business and more profile.

### Financial markets

The motives here are quite similar. To get money flowing in the tens of billions, you need mass participation by investors who do not want to be in the business of 'backing winners' on antibiotics. Generalist investors often allocate a sizable wedge of their portfolio to solid, government-backed investments that pay them an acceptable interest rate. If that helps create new antibiotics, they will be happy to bask in the reflected glory. They will not tie up their capital in something exotic and illiquid that they can't ascertain the value of and sell on.

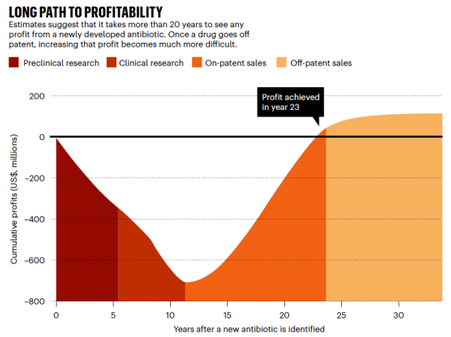
### Governments

A crude but useful way to think about them is what they don't want; to conspicuously raise taxes (and less so for a specific long-term cause); nor suffer a virtue penalty by funding what others do not; nor hand out corporate welfare, especially for failure. Multi-lateral institutions like the World Bank, that are funded by governments anyway, and whose job it is to funnel finance into such trans-boundary problems, offer an acceptable bridge at which to meet.

## Some gotchas

### Fund size

At a cost of upwards of USD$1.5Bn to develop per drug, for up to 15 approved drugs focused on the most vexing pathogens, plus superior diagnostics and vaccines, and factoring in inevitable failures of many to get to market, a fund might need to accumulate and disburse at least USD 40Bn of dry powder between now and 2035. This would allow companies to re-coup their development costs and a modest profit upfront, via the Market Entry Reward. In 2020, a voluntary industry fund to bring forward two to four new antibiotics had only mustered USD$1Bn from participating companies. If the drugs see the light of day, they are guaranteed to be loss-making. This is corporate philanthropy by another name, and while welcome is simply not up to the scale or urgency of the task.




Source: Securing New Drugs For Future Generations, 2015

### Debt duration

Under a system where much larger flows of capital are accessed, creditors should expect to wait a very, very long time to get their capital back - if ever. Say what? No, it's not that we mean charity. It's just that the *capital* of the loan should either be long-duration: say 40 years or only to re-paid if ever, at a time of the debtor's choosing (a call option). This is logical when you consider that a pharma successful in creating a qualifying drug is just going to keep the up-front, one-off Reward. They are not allowed, even currently, to generate an exclusive, sell-all-you-can revenue stream from it.

### Hybrid forms

Creditors normally lend in large part on the strength of the debtor's balance sheet. The debtor's ability to re-pay is based strongly on the expectation of adequate future revenue streams to more than meet its liabilities. All that is irrelevant, here. The motive to sell as much of the stuff as possible needs to remain excluded from the equation. That's how we got into this mess! So, how can creditors still make money? We will suggest a hybridisation of instruments that already exist for a long time in financial markets, but let's get back to the gotchas.

### Protecting innovation

As Big Pharma has quietly withdrawn from the antibiotic scene it has been left to smaller, more financially vulnerable companies to take on the daunting challenge of developing novel categories of antimicrobials. Should they not make it through the antimicrobial valley of death, the promising research or drugs they had die with them.


Source: Welcome - It's time to fix the antibiotic market

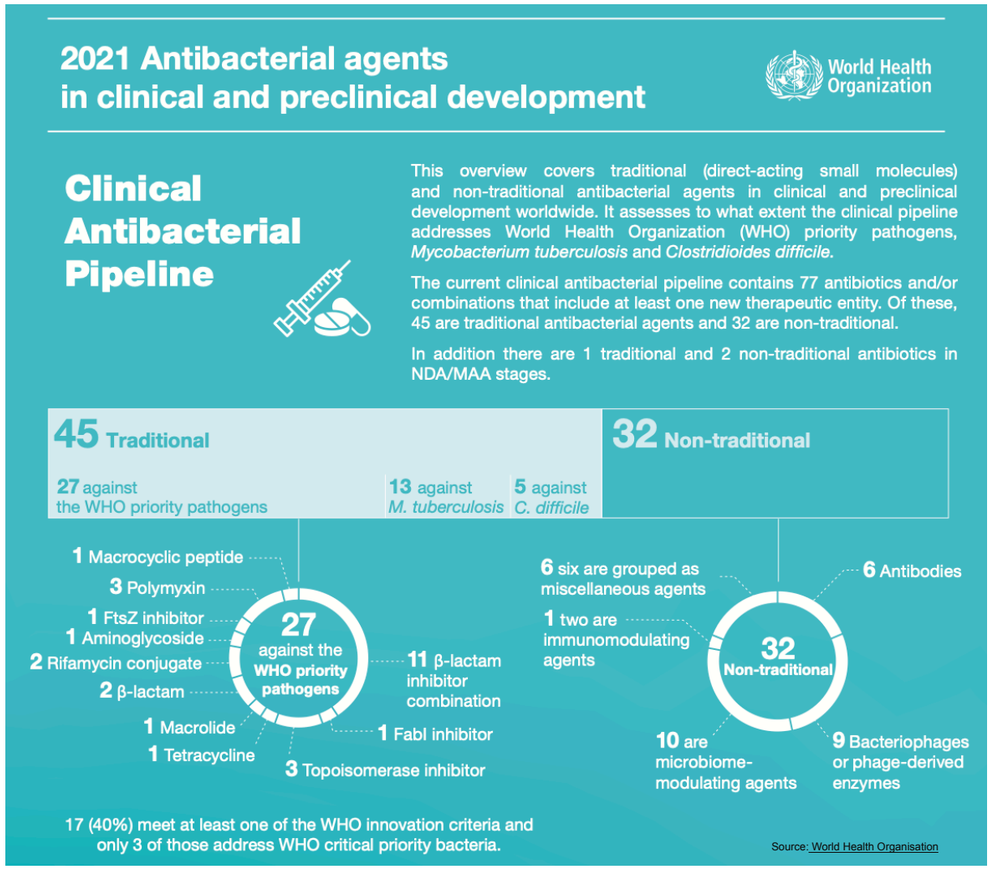
### Trust
Following on from the above, if creditors cannot rely on balance sheet analysis for the necessary trust, what, or more accurately, who is it that they must trust?

### Re-charging
What happens when a pharma comes up with a qualifying drug and cashes out? It will take more than one drug to push back the tide of resistance. You can't have the treasury of the fund suddenly emptied. Indeed, a granting of a Reward will not in every case result in a new penicillin. The road from laboratory to doctors' surgeries is strewn with once-promising casualties. Everyone would have reasons to want to see an AMR fund infused with fresh cash. A re-charging mechanism is needed.

### Free riders
The free-rider problem: we can assume that some companies that have relevant expertise to contribute will choose not to contribute, and let others do the heavy lifting. The Market Reward is just not interesting for them. "Not only do investors lack incentives to intervene, but the economic literature suggests firms perform better when exploiting such a market failure." (Herron, 2019, p.101). Short of nationalising their assets, how do we mitigate the refuseniks?

**Sufficient dry powder to blow a hole in the wall of antibiotic apathy is something that might only be supplied through connecting to capital markets.**

### WHO's dissection of the pipeline includes alternatives to established antibiotics, but the scale of research remains out of step with the urgency






## An AMR Escrow Fund: How it would work

### G20 governments agree to seed a fund of size (perhaps $20Bn)

This could be achieved by the conventional means of donations from governments, agencies and existing unallocated capital in multi-lateral banks. It begins to address size and scale but now we must determine how additional funding can be raised.

### On the never-never or the never-sometime? Multi-lateral banks issue this finance by means of long-duration or perpetual bonds

The point here is to postpone repayment until two events are more likely: a) governments are in better fiscal shape, post the current cost-of-living/energy crisis and b) that the efficacy of rounds of AMR development financing can be assessed by donor governments and institutions, so the system is seen to be working as intended.Long-duration bonds are normally issued by utilities and sometimes multi-laterals like the World Bank, for up to 40 years. They are of special interest to pension and insurance investors for long-term liability matching purposes. Perpetual bonds ("perps") have no fixed date for repayment of the original loan, the capital, and are only repaid, if ever, at the choosing of the debtor (in cases where there is a call option).

Perps historically have been used by cash-strapped governments in times of macro-economic turbulence. Alas, the global market is very small, indeed, standing at USD 37.2 Bn in 2020. So, reaching even $20Bn of new issuance would be challenging. A risk to their putative creditors is that we are in a highly inflationary environment. A fixed coupon set too low might either not attract capital or go on to lose money for creditors if it fails to keep pace with inflation. In theory, perp bonds could even be hybridised with index-linked bonds, which are guaranteed to pay above inflation. This could be for a set number of years to see us through the crisis, before a 'step down' in the bond would reduce the coupon to more normal-and affordable-levels. Indeed, the vastly bigger 'linker' market is making a comeback, as investors seek to beat inflation. For a creditor/investor, the value in owning a tiny slice of an inflation-linked perp bond would have little to do with the expectation of repayment of your slice of the capital, which may or may not happen while they own it. The attraction lies in it being a relatively solid source of regular income above inflation, that therefore other investors will also be happy to own, if they decide to trade it on.

What 'gotcha' do inflation-linked perpetual bonds fix in this fund? They don't necessarily have to be repaid, so the fund does not have an immovable future liability problem, once the proceeds of the loan are used to make a Reward to company. The multi-laterals (and indirectly their donor governments) will pay a higher interest rate, initially. Depending on the terms, this may be a more palatable and equitable solution than having to fund the entire treasury of an AMR fund directly through up-front cash from donor countries. Multi-laterals, at the behest of countries, could include a call option to re-pay at an opportune time.

In the end, it may be that long-duration bonds may be the simpler solution: to be paid back in the 2060s. The World Bank raised USD3.6Bn last year for a Sustainable Development Goal bond issuance dated for 2061 and the issuance was over-subscribed. It might take a brace of such issuances over a period of a few years to give the fund the dry powder it needs, but Green Bond markets have shown that this is eminently do-able.

### Awards to pharmas from this 'escrow' fund are made contingent on multi-laterals first raising matching debt finance i.e. another $20Bn

In short, governments and other non-profit agencies with an interest in the health outcomes kick in half the money but no money gets released until the multi-laterals, with this seed funding raise an equal amount from private markets. You can think of this like an escrow account: the money is held there securely and only released when the party that wants to draw down the funds delivers their end of the bargain.

On whose financial strength and reputation are the private markets backing? It's not really the pharmas, though their chances of success are relevant. It's really banking on the solidity of the multi-nationals to pay the interest they owe, new drugs or no new drugs. Those multi-laterals are backed by governments. This requires no change at all in how markets view this kind of debt. Multi-lateral debt is regarded as one of the safer asset classes because governments very rarely default.

**This is a nice proposition for investors if the financial hurdle for them is met. They get to say they are investing in novel antibiotics via a financial instrument with low risk. The use of proceeds for a good cause is guaranteed and said investors don't have to factor in, less be responsible for, the actual health outcomes.**

### Players and Payers: pharmas with AMR competence that decline to participate in the scheme pay a levy into the AMR Escrow Fund

A satisfactory solution to companies opting out is them being required to pay a levy into the system. This is how it works with many 'polluter pays' schemes while allowing them to carry on with their business and focus on the priorities they see fit. Pro-market types can get on board with it, and it is easy to sell to the public and participant companies because it's seen as fair. It also means that smaller, precarious companies with promising research or trial drugs can receive upfront reimbursement and crystallise some profit before all their financial lifelines dry up, something Big Pharma doesn't have to worry about. In order to avoid all Rewards being 'cliff-face' i.e. non-recurring, countries could experiment with subscription models as the United Kingdom is trialing and the U.S. PASTEUR Act going through Congress is emulating. The fund can also offer partial milestone payments to smaller companies meeting very promising clinical thresholds in the drug development process.

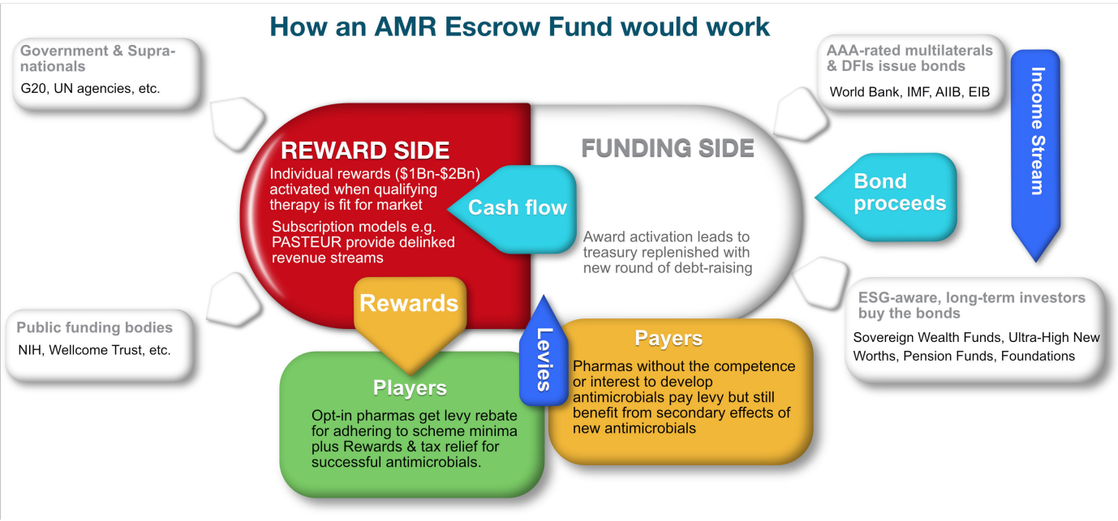
### When awards to pharmas are made following meeting minimum hurdles for a new drug, the AMR Escrow fund is refreshed by new issuances: so that begets success

This is just as it sounds. Of course, it depends on markets responding well to the initial issuances, other stakeholders being satisfied that the fund represents value for money, is generating good health outcomes and is properly governed. But similar expectations would attach to any fund launch. The multi-laterals issuing some form of perpetual bonds could, at an opportune time in some, richer future, opt to re-pay certain tranches of bonds in issuance according to their call options, when it is cheaper to do so, and the rewards of the scheme have been demonstrably reaped.

### Participating pharmas not only avoid a levy but receive improved fiscal treatment

This might be applied, for example, to qualifying R&D and costs where not already enjoyed, and other inducements. This would have to be subject to international agreements e.g. via the G20 group of countries, to ensure a level playing field.

### How an AMR Escrow Fund would work






## SOME INDICATORS FOR PROJECT PROGRESS

**By 2030**

- A large majority of companies with domain competence and meeting other screening criteria have opted into the fund
- The pipeline, as measured by the Pew Charitable Trusts, the WHO etc, is showing a pronounced upward trend in the number of antimicrobials across different delivery platforms with a substantially higher number making it to phase 3 trials and beyond
- The underlying index-linked perpetual bonds (or long-duration bonds) that replenish drawdowns from the fund are over-subscribed, trading with good liquidity in secondary markets and not putting undue stress on sponsoring organisations' credit ratings
- Microbiology and infectious disease are among the new areas for research prestige-as seems a little more likely, in a post-COVID world
- Pharmas can justify to shareholders that any additional antimicrobials it has brought to the table at least cover their cost of capital compared to what were guaranteed loss-making gestures in the past, though by design *not* a key driver of future revenue streams
- Employees, especially microbiologists report better satisfaction and loyalty, retention rates are improved
- Sovereigns, supra-national agencies and foundations are fulfilling their mandates via a debt-servicing model that is smoothed and affordable
- Stewardship controls are not undermined by skewed incentives or sweetheart deals on licensing and Intellectual Property Rights.

## CONCLUSION

**Responsible Investment has been good at describing the 'antibiotic apocalypse' and better at leaving it for others to develop answers on the supply side. In this paper, Discern Sustainability hopes to contribute something constructive to the debate and engage financial markets in bringing their ingenuity to bear on solutions.**

**Any fund needs to be large, re-chargeable, allow mass participation by institutional investors and favour successful participant companies while collecting from non-participants. This fund model in this paper attempts to address these challenges.**

**Our desire is to find and fix the holes in this model (for they surely exist) by consulting experts in the different fields it involved and come back with something that can withstand the white heat of scrutiny from all sides. We welcome expressions of interest from like-minded parties to help take this forward.**

**PRINCIPAL SOURCES**


Access to Medicine Foundation. Antimicrobial Resistance Benchmark 2020 https://accesstomedicinefoundation.org/publications/2020-antimicrobial-resistance-benchmark

CARB-X. Combatting Antibiotic Resistant Bacteria, https://carb-x.org/

Clearvue Health. Antibiotic Resistance Research & Statistics April 18, 2019 https://www.clearvuehealth.com/b/antibiotic-resistance-research-statistics/

Herron, A. Superbugs and Super risks: A critical assessment of antibiotic resistance as a frontier topic in responsible and sustainable investment. Unpublished Masters of Studies in Sustainability Leadership, submitted December 2019. University of Cambridge.

Nature. The antibiotic paradox: why companies can't afford to create life-saving drugs, 19 August 2020 https://www.nature.com/articles/d41586-020-02418-x

O'Neill, J. Review on Antimicrobial Resistance, 2016. Tackling drug-resistant infections globally: final report and recommendations. Review on antimicrobial resistance. https://amr-review.org/Publications.html

ReAct Europe. Ensuring sustainable access to effective antibiotics for everyone, everywhere, March 2021 https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf

REVIVE. Time to pull out all the stops in the fight against superbugs, 13 February 2019 https://revive.gardp.org/time-to-pull-out-all-the-stops-in-the-fight-against-superbugs/

The Pew Trusts. The Critical Need for New Antibiotics. Updated April 2020 https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2016/the-critical-need-for-new-antibiotics

The Pew Trusts. Continued Deficiencies in Antibiotic Development since 2014, March 9, 2021 https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2019/five-year-analysis-shows-continued-deficiencies-in-antibiotic-development

UK Government. World-first scheme underway to tackle AMR and protect UK patients, 17 June 2020 https://www.gov.uk/government/news/world-first-scheme-underway-to-tackle-amr-and-protect-uk-patients

Wellcome Trust. It's time to fix the antibiotic market, 1 November 2020 https://wellcome.org/news/its-time-fix-antibiotic-market

World Health Organisation. A financial model for an impact investment fund for the development of antibacterial treatments and diagnostics, June 2020. https://www.who.int/publications/i/item/a-financial-model-for-an-impact-investment-fund-for-the-development-of-antibacterial-treatments-and-diagnostics-a-user-guide

World Health Organisation. 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis, 27 May 2022 https://www.who.int/publications/i/item/9789240047655



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niall@discernsustainability.com
linkedin.com/in/discernsustainability
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