Filling the 'Discovery Void'

Policy Incentives and Antimicrobial Stewardship to Encourage Antibiotic Innovation

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BACKGROUND

Antimicrobial resistance (AMR) is one of the most important concerns that faces the global community; it threatens to undermine modern medicine and plunge the world into a dark age of untreatable bacterial infections (Davies 2010). AMR is the process in which bacteria, fungi, viruses, and parasites adapt over time to subvert the effectiveness of the treatments used to combat them (World Health Organization 2023a). The dangers of AMR are accentuated by the fact that new antibiotics are seldom produced, and novel classes of these drugs have not been introduced since 1987 in what is being referred to as “the discovery void” (Uddin 2021).

Today, AMR is quite deadly. A 2019 study estimated that the global AMR burden corresponded to about 4.9 million deaths, making it a leading cause of death after ischemic heart disease and stroke. Over three quarters of these deaths were linked to six pathogens, with *Escherichia coli* and *Staphylococcus aureus* being the most common (Antimicrobial Resistance Collaborators 2022). Novel classes of antibiotics are needed if we are to adequately fight AMR. In addition to these novel classes, policies aimed at both incentivizing development and proper stewardship will also be

necessary if we are to preserve the modern medical landscape as we know it (Wellcome 2023; World Health Organization 2023b).

The pre-antibiotic era was a harsh time for humanity because of ineffective treatments, uneducated efforts to prevent infections, and near-epidemic levels of disease being commonplace. The first antibiotic was discovered in the late 19th century by Italian microbiologist Bartolomeo Gosio, and, from there, various antibiotics were discovered that lacked broad effectiveness and safety. It was not until the 1920s that penicillin was discovered, and not until the 1930s and 1940s that its full potential was harnessed as a treatment for infections (Antimicrobial Resistance Collaborators 2022).

Today there are hundreds of different types of antibiotics, but they can be primarily classified into six groups: penicillins, cephalosporins, aminoglycosides, tetracyclines, macrolides, and fluoroquinolones (National Health Service 2022). While each of these antibiotics may still be effective against susceptible pathogens, the broad effectiveness of these drugs has waned. Poor stewardship practices such as unnecessary pharmaceutical prescription, agricultural misuse of antimicrobials, and inadequate waste disposal practices have, over time, led to the overexposure of bacteria to non-lethal doses of these drugs and encouraged the adaptation of defense mechanisms (Al Sulayyim 2022; Davies 2010; Fuhrmeister 2023; Hassoun-Kheir 2020; Martin 2015; Mulchandani 2023; Reardon 2023; US Centers for Disease Control and Prevention 2021; Vaughn 2021). The deteriorating effectiveness of these drugs further emphasizes that the development of novel classes is necessary to combat AMR.

INCENTIVES FOR ANTIBIOTIC DEVELOPMENT

Developing novel classes of antibiotics is not an easy task, especially with how convoluted the pharmaceutical industry can be. Lack of proper infrastructure to support novel antibiotic development and stewardship is one of the main roadblocks to effectively combating AMR (Wellcome 2023; World Health Organization 2023b). In the past, developmental success was driven by profits and sales (Global AMR R&D Hub 2023; Global Coalition on Aging 2023). Today, innovating how we incentivize drug development is thought to be the solution.

Two types of incentives are commonly referenced as ideal: “push” incentives and “pull” incentives; “push” meaning that development is financially supported to push the new drug through to the finish line, and “pull” meaning that the development of a novel antibiotic will be rewarded monetarily without the developer relying on sales of its new product.

PUSH

A push incentive “aims to support innovation, research, and development of new antibiotics from the early stages of basic science to clinical trials, regardless of successful access to the market. It does so by lowering developers’ costs and risks through financial, tax and technical incentives” (Global Antibiotic Research and Development Partnership REVIVE).

For instance, push incentives such as the REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund aim to reward companies that are involved in researching and developing therapies that will target antimicrobial-resistant microbes through investment into said companies (REPAIR Impact Fund 2023).

PULL

A pull incentive “aims to reward new antibiotics that have successfully proven scientific viability and relevancy to the market. It does so by reducing the risk of insufficient future revenues by utilizing mechanisms to ensure developers’ financial viability” (Global Antibiotic Research and Development Partnership REVIVE 2023).

With the development of a novel class of antibiotics, however, proper stewardship is also a necessity. Without proper stewardship, antibiotic effectiveness may wane further and contribute to resistance against new medications (AMR Solutions 2023).

The contradiction between incentivizing drug development and safeguarding against overuse is at the crux of the development issue. Companies cannot be incentivized to develop new medications if they are unable to receive the fruits of their labor through sales profits. Incentives funded by nations and nongovernmental organizations (NGOs) are thought to be the answer, and these incentive plans and policies have been supported by multinational groups and subject matter experts the world over (CIDRAP News 2023a; Global AMR R&D Hub 2023; Global Coalition on Aging 2023; AMR Solutions 2023).

By rewarding pharmaceutical companies to research, develop, and produce these novel classes of antibiotics, companies can forgo the fear of not being able to earn profit by not selling their products. Policies such as those that support incentives and that promote stewardship and education are the key to making any headway against AMR (Global Coalition on Aging 2023).

While work is certainly needed to improve the current antimicrobial research and development (R&D) climate, there is hope. Antibiotics such as ceftazidime and cefiderocol present first-in-class mechanisms of action that may greatly benefit those infected with bacteria that are resistant to other drugs in their class or who are experiencing life-threatening reactions to toxicity from “last-resort” antibiotics. These drugs are examples of what great work can be done by the scientific community and specifically the antimicrobial R&D community.

While neither drug is part of a novel class, their unique mechanisms for eliminating pathogenic bacteria help accentuate the idea that, with properly supported research, great antimicrobial innovations can be made (AMR Solutions 2023; National Institute for Health and Care Excellence 2022a; Wu 2020; National Institute for Health and Care Excellence 2022b; Richards 1985).

In May 2023, the World Health Organization (WHO) released a report outlining the progress in instituting a robust pipeline of antibiotics to combat AMR. The WHO also highlighted, however, that there are still many gaps in this pipeline. This progress has been largely possible due to policies and initiatives supported by the international community and multinational groups such as the Group of Seven (G7) and the European Union (EU) (World Health Organization 2023b).

One such policy worth noting is the United Kingdom's take on a subscription-based pull incentive that is commonly called a "Netflix model," for which ceftazidime and cefiderocol are the first pilot antibiotics. The subscription uses an estimated value of quality-adjusted life years (QALYs) that represents the amount of years a patient has left after receiving a treatment. The amount of QALYs per year is then extrapolated out to a subscription period, which is then multiplied by a monetary value to get a value per year to be paid out to the company (AMR Solutions 2023).

Incentives like these provide reasons for pharmaceutical companies to research and develop treatments that may be seldom sold or used. Ideally, any new class of antibiotic should be treated in this way—on an as-needed basis so as not to promote resistance to a newly minted treatment (Davies 2010; Global AMR R&D Hub 2023; US Government Accountability Office 2023).

The UK is not the only nation or multinational group developing incentive plans intended to combat AMR. Future policies have already begun to take shape in many countries, such as in the United States and its appropriately named PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act.

The bill proposes a subscription-based pull incentive model, similar to the UK program, in which an upfront sum is paid to pharmaceutical companies in return for access to their drugs. This system ensures that any novel antibiotic's profit is based not on the volume of sales but rather on efficacy and innovation.

While a past version of the PASTEUR Act was introduced before and dismissed, the PASTEUR Act was reintroduced in April 2023 with hopes that it will mitigate the failures and inefficiencies in the American antimicrobial market (CIDRAP News 2023b; Office of US House Representative Scott Peters 2023; Office of US Senator Michael Bennet 2023).

THE ROLE OF ANTIMICROBIAL STEWARDSHIP

Incentive-based policies will be necessary in encouraging antibiotic development that addresses AMR, but, on the stewardship side, policies aimed at restricting antimicrobial consumption and encouraging appropriate use have already shown benefits. A 2011 study done in a Chinese hospital used pharmacist-driven education to evaluate how stewardship may affect AMR. The researchers found that antimicrobial stewardship education and practices had a positive impact on reducing antibiotic use overall, and specifically on antibiotic prescribing and surgical prophylaxis (Wang 2019).

Education and proper stewardship are at the heart of most AMR interventions. The WHO has listed that Objective 1 for the Global Action Plan on Antimicrobial Resistance is “to improve awareness and understanding of AMR through effective communication, education, and training” (World Health Organization 2023c).

To address AMR, all clinicians and other members of the patient care team must become good stewards of the antimicrobial armamentarium. The best way to guide antibiotic use properly and promote stewardship is to have practices in place that facilitate appropriate prescriptions and to inform patients receiving treatment of the ways they can help guard increasingly antibiotic resources (Al Sulayyim 2022; Vaughn 2021).

GLOBAL INEQUITIES IN AMR

Along with incentive policies like the PASTEUR Act and the UK "Netflix model," as well as with increased antimicrobial stewardship education, the global community will need to address the disproportionate burden of AMR in low- and middle-income countries, which have the highest global AMR-associated death rates.

In a recent study, researchers found that five regions—South Asia and the four regions of sub-Saharan Africa—had AMR-associated all-age death rates higher than 75 per 100,000 people. All-age death rates attributable to AMR were highest in western sub-Saharan Africa, at 27.3 deaths per 100,000 people. The lowest observed all-age death rates attributable to AMR were observed in Australasia, at 6.5 deaths per 100,000.

This disproportionate presence of antibiotic-resistant pathogens and antimicrobial-resistance genes (ARGs) is largely due to the inequalities between poorer nations and their wealthier counterparts (Fuhrmeister 2023). Poor sanitation, a lack of proper laboratory equipment and infrastructure, the availability of counterfeit medications, and inadequate regulations on antibiotic use all contribute to higher levels of AMR and ARGs. Improving conditions in these countries would very likely help to drive down AMR and AMR-associated death rates.

CONCLUSION

AMR is a global concern, and, much like climate change, we largely have our own influence to blame. While antimicrobials have been used for only the last century or so, their impact on our planet and its microenvironments is undeniable. Through poor stewardship, inappropriately designed markets, and a true lack of understanding, infections that were once treatable are now leading to serious illnesses or even death.

All hope is not lost, however. Novel treatments can be designed through collaboration between the international scientific community and the pharmaceutical industry, and, with proper stewardship of these new antimicrobials, the threat of AMR may be mitigated. Incentive policies that reward ingenuity and patience would signal to other drug companies that antimicrobial research and development can be lucrative, albeit not likely in the traditional manner.

Thus, through collaboration, stewardship, and education, AMR may be prevented from undermining the backbone of modern medicine.

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