Why is the development of new antibiotics so difficult?

Antibiotic resistance is a serious health crisis in the world and it is predicted to intensify in the near future. An issue which historically only affected the sickest patients in intensive-care units, antibiotic-resistant bacteria are now pervasive in global communities, threatening health worldwide. If nothing changes, drug-resistant diseases could cause 10 million deaths yearly by 2050, an exponential increase from the 700,000 people who die yearly from it now.[1] The increasing spread of resistance worldwide due to antibiotic overuse, compounded by the lack of new antibiotic development is causing this global crisis.

Importance of New Antibiotic Development to Combat Antibiotic Resistance

Antibiotics are immeasurably significant in modern medicine: they are a cheap, safe and effective class of drugs used to prevent and treat infections. They enable surgeries with high risks of infection and drastically increase survival rates of tuberculosis and malaria. Without them, routine surgeries, minor injuries and common infections can become life threatening and result in longer hospital stays.[2]

Over the last 50 years, medicinal chemists have effectively remodelled prior antibiotics; for instance, today's antibiotics include the fourth generation of beta lactams and the third generation of macrolides,[3] yielding analogues with increased potency and an enhanced ability to elude existing resistance.

Unfortunately, antibiotic resistance still persists in these remodelled antibiotics. For example, beta-lactam antibiotics work by preventing peptidoglycan synthesis and hence the formation of the bacterial cell wall, by acylating the transpeptidase involved in cross-linking peptides to form it. However, bacterial resistance has since been developed, producing beta-lactamases to inactivate beta-lactam as seen in Figure 1.[4] Exacerbating this issue is the fact that unlike remodelled antibiotics, the development of novel classes of antibiotics, which are critical to staying ahead of antibiotic resistant bacteria have not been forthcoming and almost all classes of antibiotics currently in use were discovered in the 1950s. Although 41 new antibiotics are currently under clinical development, a mere 13 have the potential to combat bacteria on the WHO's critical threat list.[5]

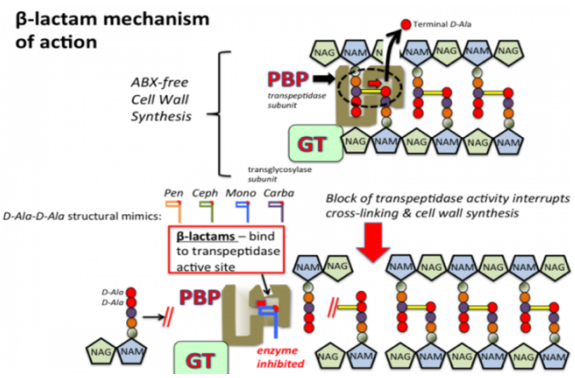

Figure 1: Mechanism of Beta-lactam Antibiotics[20]

After a few years of widespread medical use of an antibiotic, antibiotic resistance is usually reported.[6] This then regularly drives the need for new antibiotics to be formulated to replace that which bacteria have grown resistant to - something that the world is already struggling to do. For instance, an antibiotic resistant strain of *Klebsiella pneumoniae* spread globally, from the USA, to Europe, North America and the United Kingdom in just five years.[7] Industrialisation and the interconnectedness of today's world is no doubt a factor in the rapid spread of antibiotic resistance. As a result, rapid antibiotic resistance further creates the need for the development of more new effective antibiotics which are essential for global health.

A bacterium in the bacterial population with antibiotic resistance is more likely to survive than other "normal" bacteria, which are killed or inhibited by an antibiotic, resulting in aselective pressure on resistant strains of bacteria. Antibiotic resistance is hence accelerated when bacteria are unnecessarily exposed to medicines; such as in the overuse of drugs in animal medicine and food

production and the over-distribution of antibiotics where they are not necessary, creating more opportunities for bacterial mutations to develop and spread. Antibiotics work by targeting things in bacterial cells that are required for their survival that don't exist in our own human cells.

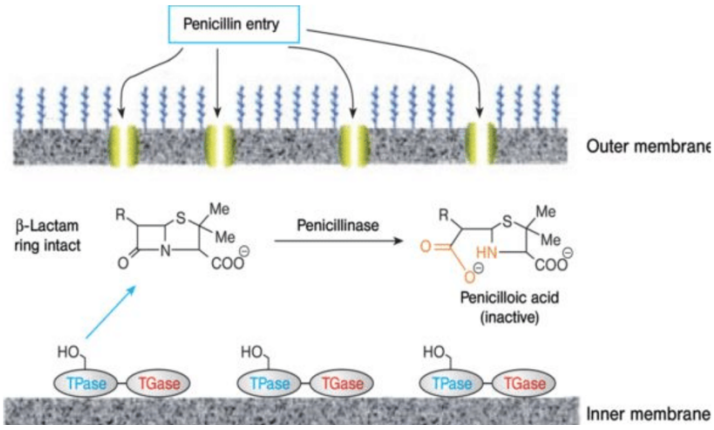

Figure 2: Mechanism of Penicillinases against Penicillin[21]

For example, Penicillin prevents the cross-linking of peptides on mucosaccharide chains, inhibiting bacterial cell wall synthesis (a bacterium without a cell wall bursts and dies). However, after the widespread use of Penicillin, bacteria began to combat its effectiveness by producing Penicillinases, rendering Penicillin ineffective by hydrolysing the peptide bond in the beta-lactam ring of the nucleus.[8] Figure 2 displays this mechanism.

Additionally, bacteria can acquire resistance from other bacteria by conjugation, where bacteria can transfer antibiotic resistant genes from a DNA plasmid to another bacterium via a pilus, bypassing the usual parent-to-progeny route of genetic migration.[3] In this way, organisms can often collect several resistance traits over time, giving rise to multiple-drug-resistant (MDR) bacteria such as MRSA (Methicillin-resistant *Staphylococcus aureus*).[19] The formulation of new antibiotics to combat MDR bacteria is even more challenging and there is a growing need for antibiotics to combat these "super-bugs", resulting in more challenges for antibiotic development.

Antibiotic Development Process

The development process of a new antibiotic is lengthy and expensive. Firstly, basic research is required for the identification of organisms that produce antibiotic substances. Thousands of possibilities emerge which are then tested. It's relatively easy to find substances that kill bacteria, but significantly more challenging to then develop these substances such that they are not also harmful to humans. To quote and disprove Trump's suggestion, we simply can't just drink disinfectant solutions to rid ourselves of coronavirus, as disinfectant is toxic to our own cells too.[10] Promising drug candidates from pre-clinical developments then move onto clinical trials, which are even more costly - requiring resources generally only accessible to pharmaceutical giants. Should a new drug prove to be functional, it then still needs to be approved by a government drug regulator before it can be legally prescribed. This approval process is usually laden with regulatory hurdles, which contributes to the costs and timeline of antibiotic development. As such, the development of a new antibiotic can often be seen as a mammoth task, that few pharmaceutical companies wish to embark upon,[2] hampering new antibiotic development.

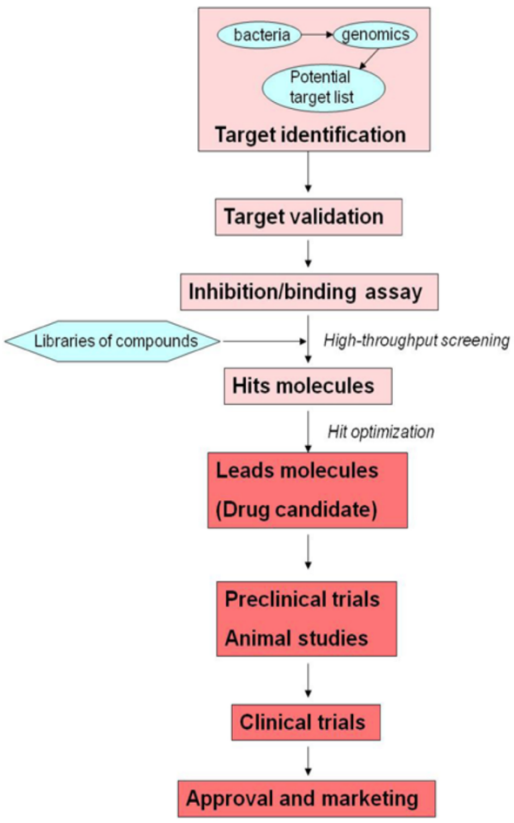

Figure 3: Antibiotic Development Process[22]

Scientific Challenges

There are currently several key scientific barriers that are hindering the development of new antibiotics; one of which is the lack of knowledge on how to combat drug-resistant Gram-negative bacteria, which have a double membrane and a range of efflux pumps that expel drugs out of the bacterium, making it a difficult target for antibiotics.[11] Gram-negative pathogens make up many serious and deadly bacterial infections, such as pneumonia and meningitis. Efforts to discover new antibiotics to transverse gram-negative bacteria's built-in defence mechanisms in order to attack these pathogens have been widely unsuccessful and scientists require a deeper understanding of techniques to tailor antibiotics to do so.[12] Figure 4 displays several mechanisms of antibiotic resistance in gram-negative bacteria which make it a difficult target for antibodies.

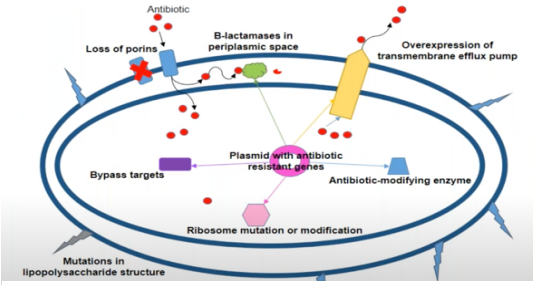

Figure 4: Antibiotic Resistance in Gram-negative bacteria[23]

Another scientific barrier is in the search for molecules that would work as effective antibiotics. As compared to 50 years ago, new and promising molecules are much less prevalent and easy to find as many have already been discovered and used. Heightening this barrier is the new antibiotic screening strategy in use - developed when the pharmaceutical industry faced difficulties identifying new leads in the 1990s. Though the strategy appears to be more sophisticated, combining genomics with high-throughput screening of existing compound libraries, it has proven to ultimately be less successful. The new strategy places an over-emphasis on identifying targets and the molecules bound to them, instead of focusing on the ability of molecules to permeate bacteria, evade efflux and avoid mutational resistance, which is just as crucial. As such, compounds discovered by this method that are initially effective eventually turn out not to be. Another problem with this strategy is that finding a compound which binds to a conserved target does not compare to finding one with antibiotic activity. Additionally, drugs with single targets are particularly vulnerable to mutational resistance. It is hence ideal that antibiotics should bind with multiple targets, similar to aminoglycosides, beta-lactams and quinolones. This new strategy has not produced any new antibiotics which have entered clinical use and many pharmaceutical companies have consequently abandoned antibiotic discovery,[11,12] curbing new antibiotic development.

Antibiotics have to be formulated in a chemically complex way, which can be very challenging. Not only do they have to be remarkably non-toxic, as daily dosages of antibiotics are a lot higher than other pharmaceuticals, they must work in multiple body compartments and should preferably be broad-spectrum to inhibit a wide range of bacteria, as at present it is difficult for doctors to promptly identify specific bacteria causing infection.[12] This chemical complexity is something that is not demanded in the formulation of other drugs, such as with Alzheimer's where a drug is specific, working only to boost amounts of acetylcholine in the brain.[13] It thus takes more time to optimize antibacterial activity and the safety of antibiotics, which are also prone to resistance by bacteria. These criteria have limited the number of substances suitable as antibiotics and restricted the strategies used to discover them, making the development of new antibiotics exceptionally difficult. Advances in molecular diagnostics could potentially allow doctors to make a more specific diagnosis of infection before choosing an antibiotic, allowing for future production of more narrow spectrum antibiotics instead, which would be easier to formulate.[3]

Regulatory Challenges

Once a new antibiotic is formulated, there are still numerous regulatory hoops that pharmaceutical developers have to jump through. Primarily, there is a need to verify that the new antibody has merit in the face of drug resistance and that it is safe for use. Regulatory bodies, such as the European Medicines Agency, have the overarching intent to protect patient safety and hence

maintain strict guidelines and criteria for new drugs to pass. Though it can be difficult to have new medications approved, lowering the standards for drug safety and efficacy is still not a reasonable path for scientific agencies to go down, as this will certainly not address this crisis. Furthermore, challenges in the regulatory capacity of antibiotics in certain countries can lead to the acceleration of the antibiotic resistance of new antibiotics. For example, countries may lose control of antibiotic distribution and antibiotics reserved as a last-resort treatment option are sold without a prescription, speeding up antibiotic resistance to new drugs.[17]

Economic Challenges

If these scientific challenges didn't sound difficult enough, there are still enormous economic challenges in the production of antibiotics. In total, it can cost over $1 billion to develop a new antibiotic.[2] Despite this large economic effort and scientific breakthrough, depending on the healthcare system, it can still be tremendously difficult to persuade health systems to purchase these new antibiotics, due to their nature; limited lifespan because of the emergence of drug resistant pathogens, short-course treatments usually spanning 1-2 weeks and traditional low selling price. As such, there is little economic incentive for pharmaceutical companies to invest in creating new antibiotics as it is very unlikely that they will be able make a profit, which is after all the eventual aim in the pharmaceutical industry. Antibiotics are the only drug class that when a scientific breakthrough is made, sales are kept as low as possible.[2,14] The development of new antibiotics is now mainly directed by small biotechnology companies. However, these companies still experience monumental challenges in bringing new drugs to market and making them accessible. Even companies that have brought new antibiotics to the market, such as Archaogen and Melinta Therapeutics have gone bankrupt.[15] Given these factors, pharmaceutical companies struggle to find investors for new antibiotics, given the low probability of its successful production– scientifically and economically. Consequently, tangible gains expected by potential investors are extremely high to account for this risk, which these small companies simply can't afford to give.

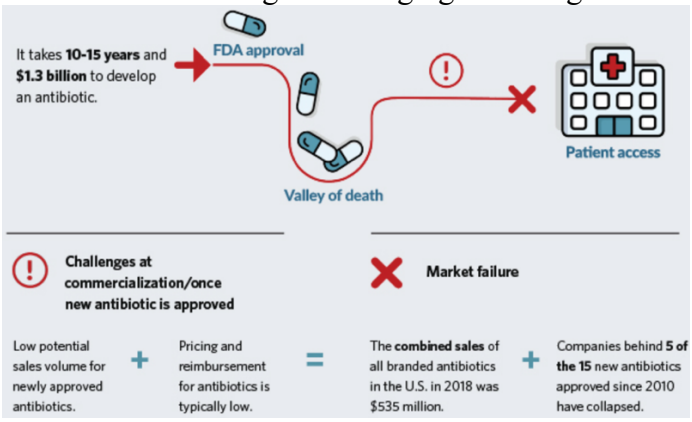

Figure 5: Market Challenges Jeopardize Antibiotic Access[24]

Investments by the pharmaceutical industry for the development of new antibiotics are hence diminishing. There is simply no viable route to market for new antibiotics, however valuable they may be to society, especially when there is much more economic incentive in the sale of other drug classes, such as drugs for the management of chronic conditions and immune-oncology therapeutics, thereby prompting pharmaceutical companies to invest in these.[14,15] Figure 5 displays these economic challenges in the production of antibiotics, which prevent new antibiotic development.

Societal Challenges

Moreover, there are many societal challenges in the formulation and distribution of antibiotics. Antibiotics are undervalued precisely because of how effective they have been for the past 50 years and most do not appreciate how important they actually are. As such, society now expects all pathogens to be cured at a small cost with a handful of pills, promoting a false sense of security and potentially also encouraging the overuse of antibiotics because of the attitudes of the public towards them.[14]

Urgency for New Antibiotic Development

The number and efficacy of antibiotics in development today simply aren't enough to deal with the growing threat of antibiotic resistance. Most in clinical development will not bring substantial benefits as compared to existing treatments and only a select few target gram-negative bacteria. Though there are more innovative and potentially effective candidates currently in the pre-clinical stage of development,[16] the first of these drugs may take up to 10 years to make it to market and many promising candidates will fail along the way due to a myriad of reasons. Given the slow rate at which new antibiotics are being developed and the increasing rate of antibiotic resistance, there is an urgent need for a new specific and collaborative research model. Only with global coordination efforts, can the world successfully overcome the foundational scientific barriers which block the discovery and development of new antibiotics which are fundamental in combatting the worldwide problem of antibiotic resistance. Health care centres, governments and philanthropic organisations across the globe should ideally collaborate and share information on their antibiotic development efforts, to aid new antibiotic development and distribution, ensuring a sustainable pipeline of new drugs.[17] Furthermore, as low income countries with weaker and overburdened healthcare systems may face difficulties in stopping antibiotic resistance, countries can work together to ensure infections are treated appropriately and effectively with existing antibiotics, with the help of affordable resistance diagnostics. With the interconnectedness of the globe, antibiotic resistance in one country will become a global health issue. However, global change to combat this problem is still not occurring at the degree required in order to turn the tide against antibiotic resistance.

The unfortunate truth is that antibiotic resistance will always re-emerge as bacteria continuously evolve. Consequently, the world needs to combat antibiotic resistance in more ways than just with the formulation of new antibiotics. For instance, due to diagnostic advancements, the targeting of resistant bacterial strains with directed interventions to reduce transmission is becoming possible.[17] An example of this is community-associated penicillin-resistant pneumococcus in Sweden.[18] Additionally, personalised treatment technologies for identified infections are being developed, to maintain the effectiveness of existing antibiotics and to reverse the rise of resistance. Namely, CRISPR-modified bacteriophages.[19] Even the most innovative antibiotics will eventually become obsolete with antibiotic resistance emergence. It is hence worthwhile to conceive other options to combat antibiotic resistance.[3]

From the quick and effective formulation of Covid-19 vaccines, we know that progress is in fact possible when it becomes a global priority, with global collaboration and sharing of information. In the same way, new antibiotics can surely be developed, despite the extensive scientific, economic, regulatory and social challenges that currently stand in its way.

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