How the political economy hinders antibiotic discovery and how that can be changed

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Jack Stalfort

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Advisor

Sean M. Ferguson, Department of Engineering and Society

Introduction

Microscopic organisms, or microbes for short, are a double edged sword for human health. They colonize the gut of every single person on the planet, providing digestive and immune system support, while also being an indispensable part of the food chain. However, microbes are also the cause of almost all known infectious diseases, from the plague to COVID-19. There are different types of treatments for these diseases based on what type of microbe is causing it. Bacterial infections are treated with antibiotics, viral infections are treated with antivirals, fungal infections are treated with antifungals, and parasites are treated with antiparasitics.

Since microbes compete with other bacterial species for resources, some have evolved to produce antibiotics to literally kill their competition. This is what Alexander Fleming witnessed when he accidently let a mold grow on a plate of harmful bacteria, which led to the discovery of the first antibiotic: penicillin (Kalvaitis, 2008). This led to the golden age of antibiotics: where others, inspired by Fleming, discovered new antibiotics from microbes they grew in their laboratories. Antibiotics are often praised, with scientists saying things like "The discovery of potent and safe antimicrobial agents is arguably the single greatest health care advance in history." (Rice, 2008)**.**

However, the discovery of new antibiotics has been declining. There were only 6 new antimicrobial drugs approved from 2010-2014, which compared to the 19 approvals made from 1980-1984, seems small (Ventola, 2015). While this decline is happening, disease-causing bacteria are evolving resistance to the antibiotics we do have, causing something called the Antimicrobial Resistance Crisis (AMR) (Ventola, 2015). This is a problem because in the time it takes to pick out an appropriate treatment, the patient could die (Bassetti & Righi, 2013). There are even more dire examples of antibiotic resistance. While examples like this are uncommon, a woman died in 2017 after 26 different antibiotics didn't work to rid her of an infection (Branswell, 2017). This is why we need new antibiotics: resistance to the ones we do have is already here.

In 2014 it was estimated that deaths caused by AMR would increase from 700,000 to 10,000,000 annually, which would eclipse 2014 cancer caused deaths by 1.8 million (O'Neill, 2014). While bacterial infections aren't the whole picture, one would think this pressing issue would compel pharmaceutical companies to develop more antibiotic drugs. However, in addition to the decrease in improved antibiotics, 15 of the 18 largest pharmaceutical companies have left antimicrobial research over the last 20 years (Finlay et al., 2019). Why are there less antibiotics being produced, why are big pharmaceutical companies leaving the antibiotic development space, and what can we do to fix this? AMR is a multi-faceted issue, but my thesis is going to be focused on just the novel antibiotic production side. Specifically, how the political economy shapes the development of antibiotics, and how the political economy can be reconfigured to promote their production.

To tackle this problem, I am going to use the Framework presented in the paper "The political economy of technoscience: An emerging research agenda" by Kean Birch. In this paper he describes factors that influence the development of technology and science, commonly referred to as technoscience, as well as factors that technoscience influences. For instance, an example of moral values influencing technoscience would be the development of an antibiotic: we as a society deem it moral to develop cures for potentially deadly infections. An example of technoscience influencing the capital economy would be the creation of new professions due to the development of a technology, such as the smartphone. These are typical examples of what factors can influence technoscience and what factors technoscience can influence, yet Birch argues that this does not capture the full picture. To capture the full picture, one has to look at ways the political economy (meaning how the economy is organized in a moral, social, and political way) influences technoscience (Birch, 2013).

Problems With Antibiotics

Given the complexity of combating AMR, there are many areas which need addressing. One article lists 7 areas: restrict antibiotic use in farm animals, prevent hospital acquired infections, improve the use of antibiotics in hospitals (antibiotic stewardship), don't treat viral infections with antibiotics, develop better diagnostic tests so it becomes known what has to be treated, and promote antibiotic development (Bartlett et al., 2013). Each one of these could be its own thesis, therefore, I am going to focus on just the development of new antibiotics. This section will focus on problems that are causing a lack of new antibiotics, and the next section will be on solutions. That being said, this section won't focus on the technical reasons as to why it is difficult, but on the political economy surrounding antibiotics and the nature of antibiotics themselves, which will allow the framework to be used to evaluate already proposed solutions.

The first and most obvious problem is monetary: it costs an estimated $1.581 billion 2011 dollars to develop a new antibiotic that would fight a multidrug resistant bacteria, with 708 million of that coming from pre-clinical research and design (Towse et al., 2017). While this is undoubtedly a large number and still an obstacle to overcome, the cost of development is not an antibiotic-specific problem. There are many estimations on how much the average drug costs to develop, but one estimate puts it at $1.3 billion (Loo, 2014).

These estimations of cost vary between $314-$2800 million (Wouters et al., 2020), yet analyzing these values by the type of drug provides further evidence that cost is not the issue. Research from 2020 calculated the average cost of development for different groups of therapies that were FDA approved between 2009 and 2018 (Figure 1). They found the group titled "antiinfectives for systemic use", which includes antibiotics, had an average development cost of $1297.2 million and a very similar median of $1259.9 million, which is comparable to the other 2011 estimate of $1.581 billion (Wouters et al., 2020). Anti-infectives had the fifth highest development cost out of the 10 categories included in the research. It was below the mean cost of development for any drug regardless of category ($1335.9 million), yet it was

above the median ($985.3 million) (Wouters et al., 2020). The similarity between the cost to develop an antibiotic and the cost to develop any type of drug, along with the fact that the “antineoplastic and immunomodulating agents" category are the outliers in terms of cost (Figure 1), indicate the cost to develop an antibiotic is not driving the decrease in new antibiotics. In other words: cost is still a problem to develop pharmaceutical drugs, yet every type of drug has to deal with it.

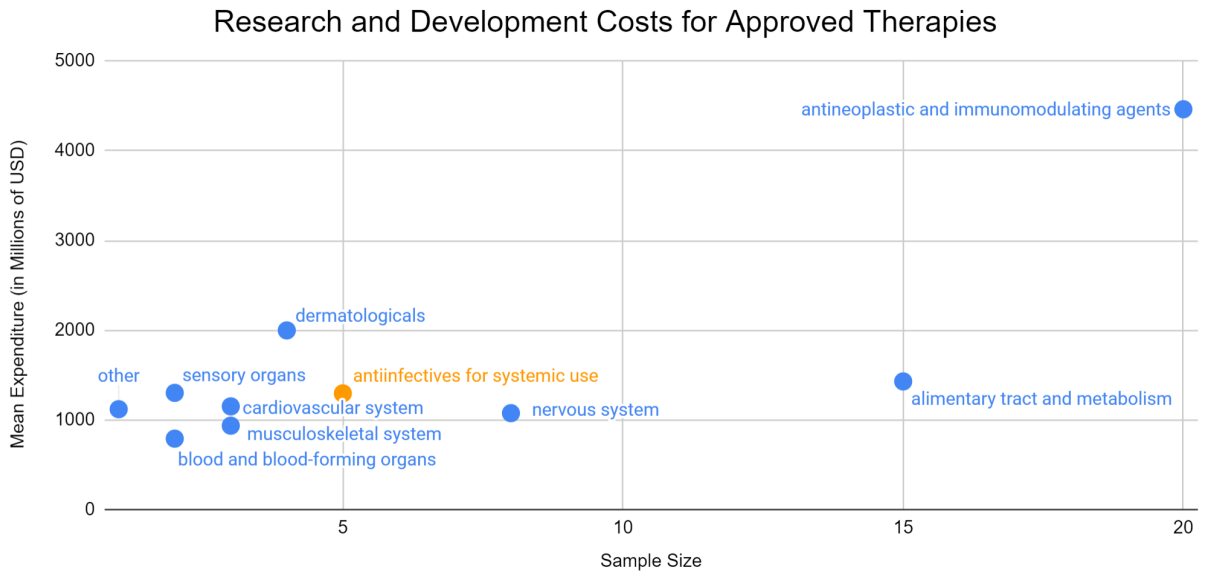

Figure 1: Mean expenditure to bring different types of drugs to market. Antiinfectives are colored in orange to illustrate that cost is not the driving issue. Data taken from (Wouters et al., 2020)

The issue with antibiotics then is not their cost of development, but the revenue which they bring in. With the average cost of development likely in the billions, it is estimated that the average antibiotic brings in a relatively low $46 million a year (Plackett, 2020). Figure 2A shows the average revenue for antibiotics each year after they were marketed to patients, while figure 2B shows the income for different cancer drugs since they were marketed to patients. Cancer drugs were chosen because new cancer drugs are being produced at a substantial rate nowadays (Meyers et al., 2022). Granted this data is over different time scales and is comparing revenue to income, yet it is still clear that cancer drugs make a lot more than

antibiotics. This difference is even evident within the drug class of anti-infectives. In 2014, research found that the antibiotic market increased by 4% annually, yet the vaccine market increased by 16.4% annually over the same 5 year period (So & Shah, 2014).

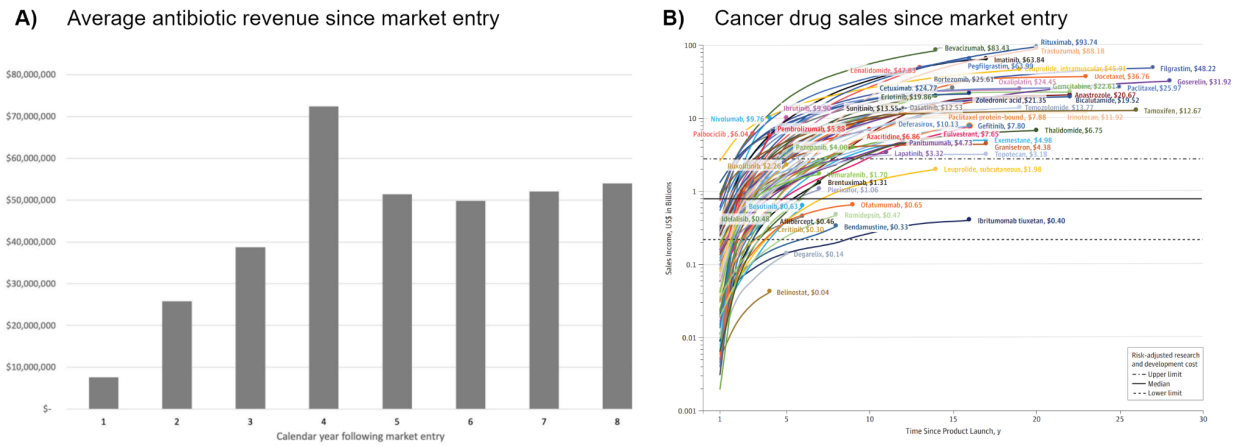

Figure 2: Comparing the revenue by year after market entry of A) antibiotics to B) the income of cancer drugs by year after market entry. A) is from (Rahman et al., 2021), while B) is from (Tay-Teo et al., 2019)

The pharmaceutical political economy is built on the idea that pharmaceuticals need to make at least as much as they cost, no matter how many lives they may save. That means the fact that antibiotic revenues are so low certainly hampers their development. The main way pharmaceutical companies decide whether or not to invest in a biotechnology (such as an antibiotic) is by the risk-adjusted net present value or rNPV, which is how much a biotechnology is monetarily worth (Stewart et al., 2001). Unfortunately for antibiotics, the net present value for a new injectable antibiotic is estimated to be -50 million dollars (Spellberg, 2014).

So why don't antibiotics make that much money? It has to do with the nature of antibiotics themselves. In other words, being an antibiotic comes with certain challenges other drugs don't face. One

of those challenges is the short duration of treatment. The duration of treatment varies by infection, but examples of durations for common bacterial infections are 5 to 7 days for community acquired pneumonia, and 3-7 days for uncomplicated urinary tract infections (Wilson et al., 2019). Add on to this fact that antibiotics are really cheap, with the highest costs for a course of treatment being $1,000-$3,000 (Bartlett et al., 2013). Kalydeco, a treatment for cystic fibrosis, is a great juxtaposition for this part of the problem: patients have two take two pills a day, are on it for life, and it costs $294,000 a year (Kaiser, 2012).

However, vaccines have a short duration of treatment yet are still profitable (Dutescu & Hillier, 2021), so there has to be some other factor at play. That factor is the fact that infectious diseases can acquire resistance *and* spread to other people. Other types of drugs do not have both of these problems. Cancer drugs can develop resistance, but they don't spread to other people. Genetic disorders that are the targets of gene therapy, like sickle cell disease, are problems with our body and therefore don't develop resistance and don't spread to other people. Resistance to vaccines isn't seen immediately because they are a preventative treatment, meaning nothing is there to generate resistance.

Since the pathogens antibiotics treat can generate resistance and spread, doctors like to wait to prescribe them so that resistance develops as slowly as possible (Plackett, 2020). So if a new antibiotic comes to market, they are not going to be eager to prescribe it. Once the public needs it, the patent on that antibiotic, which lasts for 20 years since they are filed (Petrova, 2014), already has a chunk of time gone. Current patents are protecting against times where antibiotics are not at their peak use.

Generating New Antibiotics Through the Political Economy: Incentives and Regulation

While short treatment durations and low costs are great for the patient, they aren't good for pharmaceutical companies. Thus the pharmaceutical political economy needs to be reorganized in a way such that the relationship between consumers and producers is mutually beneficial, otherwise nobody will

benefit. Currently the political economy is only allowing for therapies to be made that make a profit, which inhibits the production of novel antibiotics, despite their ability to save lives. It is important to note that this is not an issue of morals: whatever a pharmaceutical company decides to focus on will save or improve lives.

With all the ways the political economy is discouraging new antibiotic development and the dire consequences of inaction, the future on this topic might appear grim. However, that hasn't stopped some from proposing and even implementing some solutions. Given the framework and the reasons for a lack of new antibiotics, solutions others have proposed or implemented related to how the economy influences technoscience can be evaluated.

In an attempt to reshape the pharmaceutical political economy, The GAIN (Generating Antibiotic Incentives Now) act was passed in 2011. One thing it does is give 5 extra years of protection against competition to companies who discover an antibiotic (Ambrose, 2011). Before the GAIN act was passed, the FDA wouldn't approve another version of many types of drugs for between 4 to 7.5 years. Now that timeframe is bumped up an extra 5 years, but only for qualified infectious disease products (QIDP) (Sherkow, 2012).

The GAIN act was created to act as an incentive for the production of novel drugs that would "conquer…germs that are resistant to antibiotics" (Darrow & Kesselheim, 2020). While it is certainly a step in the right direction and is a large accomplishment, when looking at the cost of antibiotic development, this additional five years does very little. An associate professor at Harvard Medical School Aaron said "Now almost 6 years later, I don't see any evidence that the GAIN Act has led to any change at all in the antibiotic pipeline." (Brennan, 2018).

A lot of work has been done looking at financial incentives, which can broadly take two forms: those that lower research and design costs are called push incentives, while ones that increase revenue are called pull incentives (Cama et al., 2021). One paper published in 2021 did a systematic review of the opinions of previous literature (Dutescu & Hillier, 2021). Models that favored both push and pull incentives were more popular overall with 20 mentions in favor in the literature. This is compared to 12 in favor of just push incentives, 5 in favor of just pull incentives, and 1 that was in favor of neither. However, the authors note that the models where both types of incentives are favored varied widely, with some not being specific on the push or pull incentive, just that there should be one. Given that the vast majority are in favor of at least one of these financial incentives, this warrants a further discussion on these incentives.

One type of pull incentive is the Market Entry Reward (MER), which was a part of 5 of the hybrid models reviewed and 14 models overall (Dutescu & Hillier, 2021). The way a MER works is that if an antibiotic is brought to market that meets certain criteria, the company that did that gets a monetary award. The reward has been suggested to be tied to its public health value and be large enough to give a return on investment, which might cost 1-2 billion (Daniel et al., 2018). This makes sense when compared to the cost to develop a new antibiotic discussed earlier. The criteria antibiotics are evaluated on needs to be chosen carefully, yet this aspect is more of a scientific and medical problem than a political economy problem.

It is important to put the cost of a MER for antibiotics in perspective. Antimicrobial resistance costs the U.S. $55 billion annually (Dadgostar, 2019), meaning this type of MER would be financially beneficial for up to 27 antibiotics produced each year. One benefit of MERs is that they decouple the revenue a company receives from how much of the drug they can sell in a given time period. This concept is called delinkage, and it was originally intended to entice drug companies to develop medicines for diseases that are prevalent in low-income countries (ReAct, 2021). Interestingly, the same effect is

happening for antibiotics, but instead of the consumers not being able to pay, they are not being prescribed enough and are not being priced high enough.

One type of push incentive is a public-private partnership, which is when the public sector gives the private sector money for research and design. These have already been implemented, with the largest antibiotic public-private partnership in the U.S. being BARDA (Biomedical Advanced Research and Development Authority), which recently gave $200,000,000 to GlaxoSmithKline (Outterson et al., 2015). The funding BARDA gives is flexible: companies can change projects based on milestones missed, and can get more funding based on milestones hit. While this may seem like a lot of funding, remember that estimates to develop an antibiotic are commonly well over one billion dollars. Thus incorporating more public funding into the political economy must be implemented for initiatives like BARDA to work.

Another problem is with the regulatory process, which for all medications is governed by the food and drug administration (FDA). In 2006 it was discovered that the approved antibiotic telithromycin rarely would cause potentially fatal liver damage (Shlaes et al., 2013). This, along with statistical rethinking of clinical trials, would change how clinical trials were conducted for antibiotics. For instance, patients could not enroll in a clinical study if they had taken another antibiotic for their infection before enrollment, and the FDA would intentionally lower the reported percent of patients the treatment had a positive effect on (Shlaes et al., 2013).

Discussion: Applying the Framework

Given the problems facing antibiotic development, the framework can be applied to the current and potential solutions. While the GAIN act is beneficial, it is better to focus lawmakers' attention on other initiatives that more radically alter the pharmaceutical political economy. This is because prolonging the time antibiotics are protected from competition won't lead to antibiotic development becoming an

attractive investment, and as the framework indicates, these economic incentives influence the development of technoscience.

The initiatives lawmakers should focus on are push and pull incentives such as MERs and public-private partnerships. These interventions target the backbone of the problem without affecting aspects that are already working, such as the low price of antibiotics. Given the nature of new antibiotics being withheld to some extent from the antibiotic arsenal doctors have at their disposal, the only way for antibiotics to be profitable, and thus producible, is if funding comes from the government.

These two incentives affect different aspects of the problem, yet both of them are necessary. Public-private partnerships will push companies to get back into the antibiotic development space. Criteria to receive this type of funding can direct research efforts to focus on types of antibiotics that have novel uses. However, even with this type of funding, the political economy will choose the development of therapies that are highly profitable, such as cancer treatments. This is where MERs come in: they make antibiotics profitable so that companies will actually want to use the funding from private-public partnerships instead of focusing on something much more profitable. Changing the regulatory process will also help push companies back into the antibiotic development

Conclusion

Antibiotics are not a profitable business for pharmaceutical companies as the cost of development almost always outweighs the revenue they can bring. There are many reasons for this: antibiotics are generally cheap, they don't have long prescription times, and the prescription of new ones is hindered by how antibiotic resistance can develop and spread. Solutions to get companies back in the antibiotic development space fall into two categories: push and pull incentives. These have the capability to make antibiotic development profitable, allowing for the antibiotic pipeline to become full again and save many

lives and dollars along the way. We can't wait for the incentive to develop antibiotics to happen naturally, as by the time this happens many people would have died unnecessarily.

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