Antimicrobial Resistance: Learning from the current global health crisis to prevent another one

By Gunnar Esiason
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Table of Contents

Introduction 4
Why is it Critical to Address AMR? 4
The Market Problem 5
What is Being Done? 6
What Needs to be Done? 7
Conclusion 8
**Introduction**

As one infectious pathogen has driven the world to a screeching halt, another health crisis looms in the not so distant future. The nemesis is well known, antimicrobial resistance (AMR). It is estimated that as many as 700,000 people die each year from drug resistant infections. The fear is it can get much worse. It is forecast that as many as 10 million people per year could succumb to this deadly crisis, while a cumulative $100 trillion of economic output could be lost by 2050 if it is left unchecked.4

Within the broad definition of AMR is the troubling trend of antibiotic resistant bacteria. Antibiotics are a class of drugs designed to kill bacteria. The CDC considers antibiotic resistance to be “one of the biggest public health challenges of our time.” In the US, some two million people contract infections that are resistant to antibiotics each year, and as many as 23,000 of them die.5 Those drug resistant infections already account for $20 billion in healthcare costs.6

Driven largely by decades of overuse and misuse of antibiotics, commonly treated infections are evolving to become impervious to our medication arsenal. Antibiotic resistance is the result of strains of bacteria “surviving exposure to a medicine that would normally kill them or stop their growth. This allows those strains to grow and spread, due to the lack of competition from other strains.”7 8 As these resistant strains of bacteria flourish, medicines that would have been able to eradicate an infection are no longer able to do so. The result is a deadly combination of weaker medications and stronger infections. When bacterial infections eventually evolve to become nearly impossible to treat, they are sometimes referred to as “superbugs.”

The pipeline for new antibiotic therapies to complement the existing arsenal and treat superbugs is on fragile ground. In a perfect world, infectious disease experts and doctors do not want a sudden rush of new antibiotics to the market. Instead they want access to a “slow and steady drip” of new antibiotics from drug makers.1, 6 2 That of course, assumes a market that can sustain new entries.

The market and current reimbursement methods, combined with the way antibiotics are used to treat illness, make them a risky investment for pharmaceutical companies and Wall Street.4 Compounding the issue is the fact that “Over 95 percent of [antibiotics] in development today are being studied by small companies rather than the large pharmaceutical firms that once dominated this field,” and they aren’t all targeting the World Health Organization’s critical threat pathogens, some of the most deadly bacterial strains facing humanity.5 It’s also noted that “nearly 75 percent of the companies developing antibiotics are considered pre-revenue, meaning that they have no products on the market” and are vulnerable to becoming destabilized.5 While it is admirable that small companies are trying to take on this challenge, it should be no wonder that infectious disease experts are nervous about the huge risks these firms are taking on.

There are fears the coronavirus pandemic may be accelerating this crisis. While antibiotics do not treat viruses like the novel coronavirus, they can provide protection or treatment for secondary infections patients may acquire when they are in the hospital as a result of respiratory illness. The recent influx of hospitalized coronavirus patients has led to an increase in antibiotic prescriptions. As one report noted, “early data from hospitals shows that very high proportions of patients—more than 90 percent in some cohorts—are being treated with those drugs to cure or protect against secondary infections during respiratory illnesses or hospitalization.”6

The growth of antibiotic resistance is a problem that everyone knows is coming, but we have been unable to conquer.

**Why is it Critical to Address AMR?**

Antibiotics are the thread that strings together the medical industry. They are “fundamental to modern medicine, essential for treating everything from routine skin infections to strep throat, and for protecting vulnerable patients receiving chemotherapy or being treated in intensive care.”7 They are also used tangentially to most surgical procedures, following transplant operations and in chronic care. Prior to Sir Alexander Fleming’s discovery of penicillin, the first antibiotic, in 1928, infectious diseases were rampant and difficult to treat.8 Penicillin marked the dawn of the antibiotic revolution. A post-antibiotic era, when the drugs are no longer able to treat bacterial infections, threatens to undermine decades biomedical progress since the dawn of the antibiotic revolution.9

Further, the financial toll of growth in antimicrobial resistance cannot be overlooked. As noted, resistant infections already account for an additional $20 billion in US healthcare spending and a forecast $100 trillion of lost economic output if we are unable to catch up to the problem. One need not look further than the coronavirus pandemic to see the immense cost of infectious disease on such a macro scale. Mere months into the global pandemic, the United States has already spent trillions on economic relief and efforts to tackle the virus.10

A recent study attempted to quantify the cost of the pandemic’s economic toll. Understanding that the pandemic...
is forecast to reduce economic output across the globe by $9 trillion, researchers suggested that spending in the neighborhood of $110 billion to procure enough vaccine doses to curb it would provide a net benefit of $2.8 trillion in salvaged economic output.11 That $110 billion represents the needed investment.

The differences between the current pandemic and the gradually increasing threat from antibiotic resistance are vast, but the common byproduct of the two—one we are currently living with and one forecast—are worth considering. From the perspective of dollars and cents, infectious diseases have quite a record of creating economic catastrophes.

The Market Problem

The failure to address the growth of antibiotic resistance is due to the disincentivized antibiotic market, and the proof is in the numbers. Between 1980 and 2009, the FDA approved 61 new antibiotics, while only 15 have since made it through approval in the past decade.12 The byproduct is investors hesitating to dip into the awesome innovative power of the biopharmaceutical industry.13 In the United States, antibiotics are, as one journalist described, seen as “commodities” in the eyes of hospitals and payers.14 When considering the crisis relative to payers, Medicare is worth mentioning because it “is the nation’s largest payer and Medicare recipients account for the majority of new AMR cases.”15 The federal payer does not reimburse antibiotics when they are used on an inpatient basis as they would traditionally reimburse drugs, much less breakthrough drugs.

The problem is that Medicare has historically reimbursed hospitals the same amount regardless of whether an older, generic drug or a newly minted—and likely more costly—branded medication is prescribed to people who are inpatient.16 Because antibiotics are often used tangentially to many surgical procedures or as first lines of treatment for inpatients, the formula leads to a big loss for hospitals when they prescribe branded drugs that have yet to transition to generic after their exclusivity period ends.17 Under the Diagnostic Related Group (DRG) model that Medicare uses to pay for patients in the hospital, “hospitals receive a fixed fee for each Medicare patient they treat.”18 Mounting losses for hospitals create an incentive to prescribe older medications that may not treat a patient’s infection as effectively as a newer medication might, or on the flip side, may force a hospital into unnecessarily using too strong a drug, as has been the case with a drug called colistin, which is an antibiotic of last resort that has seen a troubling prescription trend.19

Hospital financial incentives commonly result in any of three possible scenarios. First, too strong of a drug is used to clear an infection that may not require an older last-resort drug. Second, a novel drug sits on the shelf and goes unused. Third, a less effective antibiotic is used and could end up contributing to that patient’s resistance factor.20 Put another way, Medicare DRG payments do not recognize the long-term value of inpatient antibiotic use because it treats all antibiotics as equals instead of as medications whose efficacy depreciates over their lifetimes. The Centers for Medicare and Medicaid Services has recognized this problem, and last year implemented a rule that creates add-on payments to novel antibiotics as way make market entry for new drugs more appealing.21 Experts, however, call this rule change an “important step,” but say more reform is needed.22 It should not come as a shock when drug makers have more interest in developing drugs that are reimbursed outside the DRG payment model.23 In the absence of proper reimbursement for new drugs, developers and investors recognize that the drug development process is a financially risky proposition. The result is a weak pipeline for new antibiotics and pharmaceutical companies leading an exodus from development.

Further complicating the market is the essential practice of antibiotic stewardship. Stewardship dictates the appropriate use of antibiotics and has been an enormously valuable tool in slowing the spread of antibiotic resistance.24 Stewardship is necessary because it is known that antibiotic overuse and misuse—for example, treating a viral infection with an antibiotic or treating a bacterial infection with the wrong antibiotic—contributes to an increase in antibiotic resistance.25

An antimicrobial steward, an official position in a medical center, maintains the critical role of determining if an antibiotic is appropriate for use, and if it is even the right one. Seen almost as a gatekeeper, these stewards can prevent scores of unnecessary prescriptions or rewrite prescriptions.26

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drug being used.\textsuperscript{16} Compared to long-term use medications, short courses lead to less revenue for drug developers trying to recoup their investment in drug development. Antibiotics are unlike highly specialized drugs that have huge impacts on small patient populations, which have recently dominated FDA approvals thanks to incentives provided by the Orphan Drug Act.\textsuperscript{17} The irony is that limited instead of broad use for antibiotics can reduce the rate of infections of superbugs in the population, but the practice is precisely the opposite of what drug makers and investors want. It understandably serves as a deterrent for potential market entry.\textsuperscript{\textsuperscript{1}\textsuperscript{p.127}}

When the cost to develop a new antibiotic can reach $2.6 billion with research and development and clinical trial costs, drug makers crave revenue to recoup costs over the lifetime of a drug before patented exclusivity expires.\textsuperscript{\textsuperscript{4}} Stewardship, from an economic perspective, serves as an externality that can make it impossible for a small or medium-size company to recoup those costs and then turn a profit before exclusivity ends. Of course, the Medicare DRG payment model does not help, but neither do the market sizes for individual antibiotic indications, regardless of how payers reimburse patients or hospitals.

University of Pittsburgh researchers looked to a specific market as a case study that quantifies these problems. They studied the market for new antibiotics with activity against carbapenem-resistant Enterobacteriaceae (CRE), which is considered a medical priority. While there are a handful of drugs with activity against CRE, the pathogen was responsible for more than 1,000 deaths in 2017 and accounted for more than 10,000 cases in the United States each year from 2012–2017.\textsuperscript{17, 29} The idea, of course, is that the current suite of anti-CRE drugs will develop resistance profiles and need to be replaced. For some patients, that time has already come as their cases have already developed resistance to last resort drugs.

The researchers calculated the current annual U.S. market for this class of drugs to be $289 million, of which various players carve out a piece.\textsuperscript{\textsuperscript{17 }p.2} As a benchmark, the researchers note that biopharmaceutical companies “target about $300 million in annual revenue” to be profitable and sustainable. The problem is that new and eventually necessary drugs cannot be sustained under the current conditions because there is not enough room for them in the market.\textsuperscript{\textsuperscript{11 }p.2} Yes, there are generic antibiotics that work for this indication, but the nuanced piece of this market is such that everyone with a CRE infection may not respond to them. As anti-CRE drugs become weaker and weaker, novel drugs will be an even more critical need, but there is no room for them.

Within that market specifically, a pharmaceutical company called Achaogen declared bankruptcy less than a year after its antibiotic plazomicin was approved by the FDA.\textsuperscript{18} Achaogen has not been the only drug maker to suffer this fate. Since 2009, and across several indications, “6 of 16 antibiotics approved since 2009 have fallen to zero value.”\textsuperscript{19} The list includes Baxdela/derafloxacin, Minocycline/Minocin, Orbiactin/oritavancin, Vabomere/meropenem-vaborbactam, Xerava/eravacycline, and, of course, Zemdri/plazomicin.\textsuperscript{19}

Beyond some of the very notable failures, experts are warning that bringing too many antibiotics to market at once could be a recipe for disaster of a new generation of drugs. Some experts suggest that prescribers don’t want a sudden “flood” of new drugs, but rather “a slow and steady drip” of new products.\textsuperscript{\textsuperscript{3}\textsuperscript{p.62}} A sudden “flood” could open up new drug candidates to resistance in tandem and set the crisis back to square one.\textsuperscript{3} \textsuperscript{p.62} Satisfying the crowded marketplace for specific infectious targets as well as preserving efficacy calls for a slow and steady approach combined with an incentivized reform.

The notably short treatment courses, stewardship programs, inpatient payment models, and small but crowded markets have led researchers to calculate “the average antibiotic R&D project has been estimated to be ~$50 million as compared to +$1150 million and +$720 million for musculoskeletal and neurologic R&D projects, respectively.”\textsuperscript{16}

The current antibiotic market is a perfect storm of problems.

What is Being Done?

The rise of antimicrobial resistance, the dwindling pipeline and the broken market have not gone unnoticed. Both governments around the world and the biopharmaceutical industry recognize the need for reform. The two most broadly endorsed fixes to the market come in the shape of “push” and “pull” funding. Push incentives pay for input.\textsuperscript{11} They are financial rewards that aim to de-risk the drug development process before a drug is approved. It is a type of cheap financing. Pull funding, which is more difficult to implement, is payment for outcomes conditional on success.\textsuperscript{11} It is essentially a commitment to buy novel antibiotics, hold them, and then deploy them when the need arises.

Boston based CARB-X and the newly established AMR Action Fund are two examples of push funding mechanisms. CARB-X’s mission is to “Accelerate a diverse portfolio of high-quality antibacterial products towards clinical development, focusing on the priority bacterial pathogens identified by the WHO.
The organization was launched in 2016 by the US Department of Health and Human Services and Biomedical Advanced Research and Development Authority (BARDA). It is funded by a coalition of nonprofits and worldwide government agencies. Its primary focus is providing funding, scientific and business support to accelerate products through the early stages of development and Phase I trials. It is hoped their support leads to further outside investment.

Similarly, the AMR Action Fund was created by leading pharmaceutical companies as a sort of industry coalition fund to address antimicrobial resistance. It is a clear indicator that the pharmaceutical industry recognizes antimicrobial resistance threatens other biomedical advances. The fund aims to “invest more than $1 billion in smaller biotech companies and provide industry expertise to support the clinical development of novel antibiotics” with the goal of delivering two-to-four new antibiotics by 2030 via push incentives through phase II and III clinical trials.

Push funding can be best described through a case study. There is successful precedent for de-risking drug development by way of cheap financing from nonprofit organizations for early stage drug developers. Beginning in 2000, the Cystic Fibrosis Foundation provided seed funding via an investment of $47 million over a five-year period into a then small biotech company to kick off development of a class of personalized medications designed to treat the underlying cause of cystic fibrosis. That initial investment has since led to four breakthrough drugs for cystic fibrosis patients. The difference there is the end market. Cystic fibrosis is an orphan disease with a sustainable and lucrative market. In the antibiotic market, push incentives only satisfy one piece of a larger problem.

In the absence of market reforms, pull incentives aim to create a revenue stream via financial reward. They are complements to push incentives. An example of pull incentives are the Medicare add-on payments mentioned above.

To further illustrate what pull funding could look like for novel antibiotics, and why it would be so difficult to achieve, consider the coronavirus pandemic as a parallel. An existing cache of readily available vaccine doses with efficacy against SARS-CoV-2 would have helped humanity stave off the crushing caseloads and economic meltdown at the hands of the virus. Using that vaccine would have, of course, required substantial investment into its development before it was ever widely used. Consider what governments around the world are already doing: buying SARS-CoV-2 vaccine supplies before they have been proven safe and effective with vast sums of money.

Some call for antibiotics to be treated in a similar way. It would amount to awarding the successful development of an antibiotic with efficacy against resistant bacteria strains without using them until necessary. The pull incentive would act as a reward—from governments or hospitals—to create a revenue stream for developers in the absence of near-term prescriptions. The Review on Antimicrobial Resistance suggests a “market entry reward” to the tune of $1 billion as a meaningful and impactful amount. The appropriate price for a pull incentive is up for debate, but it should be seen as a ballpark amount to recognize the cost required to establish such a mechanism.

Also consider that the Review on Antimicrobial Resistance sets a goal for 15 new antibiotics per decade through 2050. Their goal is an important one that maintains the need for a steady stream of new drugs. It is also worth stating that these pull incentive payments can balloon quite quickly, and one need not look further than what governments are paying for vaccines today.

The question remains, who will pay for pull mechanisms? What is troubling is that these interventions have yet to make a lasting impact. Achaogen, the bankrupt antibiotic developer mentioned above, received financial awards from CARB-X and still failed. Both CARB-X and the AMR Action Fund recognize that their financial awards, while significant, are not enough to stabilize the drug development pipeline, market and future success of the antibiotic playing field. They are, as one industry commenter said, “not a complete fix but rather… a clarion call for action by governments to create the strong Pull incentives that will sustain new antibiotics in the marketplace.”

What Needs to Be Done?

Market reform is the key to creating a sustainable antibiotic ecosystem. One need not look further than the large pharmaceutical companies abandoning antibiotic development. The market must be fixed.

One proposal is the DISARM Act. It is a bill “introduced in Congress in 2019 that would create higher Medicare reimbursement for new antibiotics, while also requiring the hospitals that receive the increased payments to use the drugs appropriately.” Simply, DISARM would carve important and novel antibiotics out of the Medicare DRG payment scheme. It would force Medicare to value antibiotics as breakthrough drugs instead of commodities, as they are currently seen. The act “would ensure that every antibiotic will be reimbursed regardless of its price to allow doctors to make decisions scientifically and not financially.” It maintains that doctors are instruments of healing and should be allowed to prescribe courses of treatment that would help patients facing serious infectious
in the drug ecosystem, it is when drug makers seek the revenue to recoup losses incurred during the development phase. Regulatory, educational and stewardship actions now will pay dividends later.

Conclusion

The underlying feature of the dysfunction in the antimicrobial market is artificial economic disincentives. New antimicrobials, and specifically antibiotics, are forced to survive in a less than perfect market that severely undervalues their contributions to society. The way antibiotics are used over short courses and billed as a commodity below their market value is driving investment away at precisely the wrong time.

Antibiotics are among a special class of drugs that tie together much of the health industry and our biomedical progress. Locally, a mounting antibiotic crisis not only threatens livelihoods, but also the robust Massachusetts pharmaceutical industry. Antibiotics are used tangential to many of the innovative therapies developed in the Bay State, and their collective failure threatens the biomedical success that has been achieved in the antibiotic era.

The critical factor is that if left unchecked, antimicrobial resistance could kill as many as 10 million people per year, with the potential of a cumulative $100 trillion in lost economic output by 2050.1 The lessons from the current coronavirus pandemic are worth paying attention to. Falling behind an infectious pathogen comes at the cost of too many lives lost, too many homes destroyed and untold financial ruin. Regulators need to disentangle the antibiotic market now so another disaster does not strike soon.

Action is needed now. It can take over a decade from the time when an antibiotic candidate is identified to clinical use and regulatory approval.28
ANTIMICROBIAL RESISTANCE: LEARNING FROM THE CURRENT GLOBAL HEALTH CRISIS TO PREVENT ANOTHER ONE

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About the Author

Gunnar Esiason is a cystic fibrosis and rare disease patient leader, who is passionate about early stage drug development, patient empowerment and health policy. He is a second-year M.B.A. student at the Tuck School of Business at Dartmouth and is also working towards a Master of Public Health degree at the Dartmouth Institute for Health Policy and Clinical Practice. At Tuck, Gunnar serves as a Tuck Center for Health Care MBA Fellow, a health care club co-chair and a club hockey captain. His first-year course work included a First-Year Project with a health insurance start-up. Prior to Tuck, Gunnar received a BA form Boston College in 2013, worked on an enteral feeding product at a medical nutrition company, was appointed to the board of directors at the Boomer Esiason Foundation, and was the head coach of his high school alma mater’s varsity hockey team. Gunnar maintains the roles of patient advocate and director of patient outreach at the Boomer Esiason Foundation.

He has consulted on clinical trial development, a real-world evidence population health study, and a cystic fibrosis-specific mental health and wellness screening tool. In 2019, Gunnar delivered the pre-commencement address at the St. Louis University School of Medicine commencement exercises. He has also been featured as a keynote speaker at more than two-dozen top medical centers, biotech conferences, and health industry events across the United States. His health policy opinions have been featured in Newsweek, The New York Daily News, The Hill, US News & World Report, and Morning Consult.

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