Understanding Antibiotic Resistance: Challenges and Opportunities to Overcome the Growing Public Health Crisis

Understanding Antibiotic Resistance: Challenges and Opportunities to Overcome the Growing Public Health Crisis

Jennifer M. Broder
Harvard Law School, Class of 2011
May 22, 2011

Submitted in satisfaction of the Food and Drug Law course requirement

Supervisor: Professor Peter Barton Hutt

Abstract

Antibiotic drugs have been one of modern medicine's success stories, yet the underpinnings of that success are being unraveled by the alarming rate of bacterial resistance, coupled with the abandonment of antibiotic research and development programs by the large pharmaceutical companies. In order to mitigate the human and economic toll associated with antibiotic resistance, policymakers need to develop appropriate incentives for both antibiotic development and antibiotic usage. This paper reviews the unique problems inherent in the antibiotic market and discusses the current policy options proposed by the medical community as well as by legal scholars. Finally, the paper proposes a solution based on de-linking the financial incentives for innovation from the market-based incentives for consumption.

[It] is time to close the book on infectious diseases and declare the war against pestilence won.[1]

INTRODUCTION

Antibiotic resistance is one of the most threatening public health crises to face modern medicine today. We are long past the golden age of antibiotic therapy development lasting from the 1940s through the 1980s, where the pharmaceutical industry successfully introduced more than 100 antibiotics to the market and where resistance was not yet an issue.[2] Today, we face the grim reality of climbing bacterial resistance to antibiotics coupled with a decline in antibiotic innovation, potentially leading to what some scholars refer to as the "pre-antibiotic era."[3]

Beginning with the discovery of penicillin in 1928, the widespread and successful dissemination of antibiotic treatment was "among the most important public health interventions in the last century."[4] Health outcomes improved dramatically as once fatal infections were brought under control through the use of these drugs.[5] Indeed, the foundation of modern medicine presupposes the ready availability of effective antibiotics in order to perform a host of

---

[1] This is a statement allegedly made by the United States Surgeon General William H. Stewart in the 1960s, after a wave of antibiotic therapy successes. *See* Brad Spellberg et. al., *The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America*, 46 CLINICAL INFECTIOUS DISEASES 155, 156 (2008) [hereinafter Spellberg et. al., *A Call to Action*]; *see also* William M. Sage & David A. Hyman, *Combating Microbial Resistance: Regulatory Strategies and Institutional Capacity*, 84 TUL. L. REV. 781, 784 (2010) (attributing quote to Stewart). One commentator, however, has been unsuccessful in locating a trustworthy primary source for the quote. Although it might turn out to be the case that this particular phrase is merely an "urban legend" in the infectious disease community, commentators agree that the statement reflected a more confident era regarding the success of antibiotics. *See* Brad Spellberg, *Letter to the Editor, Dr. William H. Stewart: Mistaken or Maligned?*, 47 CLINICAL INFECTIOUS DISEASES 294, 294 (2008).

[2] *See* Eric Kades, *Preserving a Precious Resource: Rationalizing the Use of Antibiotics*, 99 NW. U. L. REV. 611, 616 (2005).

[3] *See* Roger M. Echols et. al., *Editorial Comment*, *Antibiotic Development – Déjà vu: Are We Facing the "Preantibiotic Era" Again?*, 15 INFECTIOUS DISEASES IN CLINICAL PRACTICE 75, 75 (2007); Otto Cars & Per Nordberg, *Antibiotic Resistance – The Faceless Threat*, *in* THE GLOBAL THREAT OF ANTIBIOTIC RESISTANCE: EXPLORING ROADS TOWARDS CONCERTED ACTION 1 (2004), *available at* http://www.Dhf.Uu.Se/Antibiotics-Participant/New-Pdf/Faceless-Threat.pdf ("[A] potential post-antibiotic era is threatening present and future medical advances.").

[4] Conan MacDougall & Ron E. Polk, *Antimicrobial Stewardship Programs in Health Care Systems*, 18 CLINICAL MICROBIOLOGY REVIEWS 638, 638 (2005).

[5] *See* Sage & Hyman, *supra* note 1, at 783 (describing how the same infection that killed President Calvin Coolidge's son was contracted by President Roosevelt's son, but was successfully treated by a sulfa-based antibiotic).

advanced procedures, such as cancer treatments, organ transplants, and other complicated surgeries, that carry the risk of infection.[6] Over time, though, bacteria began to develop resistance to these drugs. While bacterial resistance is not a new phenomenon,[7] in the past the pharmaceutical industry has supplied a sufficient number of new antibiotics to cover the resistance rate.[8] Today, however, we face a mutually reinforcing problem. Not only has the rate of resistance been on the rise, but the pipeline of new antibiotics to combat these resistant bacteria has largely run dry.[9] Large scale-pharmaceutical companies have slowed, if not halted altogether, their antibiotic research and development programs due to the drug's low profitability profile, and the medical community is worried that the small pharmaceutical companies and the biotechnology firms that remain in the space will not be able to serve as a long-term viable replacement. The need for new antibiotics is at the greatest it has ever been, as we are even beginning to see some bacterial strains that are resistant to *all* modern antibiotics.[10]

How did we find ourselves in such a predicament? It is certainly not for a lack of attention to the matter: the Infectious Diseases Society of America (the "IDSA"), the Centers for Disease Control and Prevention (the "CDC"), the Food and Drug Administration (the "FDA"), the National Institutes of Health (the "NIH"), members of the medical community, and legal scholars have all been alerting policymakers to the problem of antibiotic resistance.[11] Despite

---

[6] *See* Cars & Nordberg, *supra* note 3, at 1.
[7] English hospitals detected bacteria that were resistant to penicillin within 10 years of the drug's introduction to patients. *See* Cars & Nordberg, *supra* note 3, at 1.
[8] *See* MacDougall & Polk, *supra* note 4, at 638.
[9] *See* ABIGAIL COLSON, EXTENDING THE CURE: POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE 1 (2008).
[10] *Acinetobacter* and *Stenotrophomonas* are both multi-drug resistant pathogens that in some cases cannot be treated by modern antibiotics. The only remaining option has been an old antibiotic, colistin, whose use has been greatly discouraged due to its high toxicity levels. *See* Cars & Nordberg, *supra* note 3, at 2.
[11] *See* Interagency Task Force on Antimicrobial Resistance, *A Public Health Action Plan to Combat Antimicrobial Resistance; Part 1: Domestic Issues* (June 5, 2002), *available at* http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf. The Task Force consisted of the CDC, the FDA, the NIH, the Agency for Healthcare Research and Quality, the Health Care Financing Administration, the Health Resources and Services Administration, the Department of Agriculture, the Department of Defense, the Department

these multiple calls to arms, little has been done to move the issue outside the realm of scholarly debate into tangible action.[12] There are perhaps several explanations for this lack of movement, from insufficient levels of coordination among the relevant parties to considerable dissension within the field as to the appropriate remedial measures.[13] Moreover, attempts by members of Congress to propose legislation designed to address antibiotic resistance, albeit primarily in the context of anti-bioterrorism, have thus far proved futile as none of the proposed bills have been enacted into law.[14]

Combating antibiotic resistance is not only a medical necessity, but an economic one as well. Resistant infections are much more expensive to treat than non-resistant ones, as those patients require longer hospitalization stays and treatment programs.[15] The risk of mortality is also greater for patients with resistant infections, which, aside from the human loss, imposes an additional economic cost on society.[16] Moreover, the cost of continually researching and

---

of Veterans Affairs, and the Environmental Protection Agency. *See also* INFECTIOUS DISEASES SOC'Y OF AM., BAD BUGS, NO DRUGS: AS ANTIBIOTIC DISCOVERY STAGNATES ... A PUBLIC HEALTH CRISIS BREWS (July 2004) [hereinafter BAD BUGS].

[12] *See* John S. Bradley et. al., *Infectious Diseases Society of America*, *Anti-Infective Research and Development – Problems, Challenges, and Solutions*, 7 LANCET INFECTIOUS DISEASES 68, 68 (2007) (noting that two years after the IDSA's publication of *Bad Bugs, No Drugs*, "very little has changed"); Sage & Hyman, *supra* note 1, at 785 ("Federal and state regulators have not ignored these issues, but they have had limited success in solving them."); Spellberg et. al., *A Call to Action*, *supra* note 1, at 156 ("Unfortunately,...the resulting publicity and efforts to stimulate the adoption of solutions to spur new antibiotic discovery have failed.").

[13] An example of internal policy discord within the medical community is the debate over the effectiveness of antibiotic cycling as a method to slow resistance. Cycling programs use a scheduled rotation of antibiotics to minimize the emergence of resistant strains and are generally limited to intensive care units. *See* MacDougall & Polk, *supra* note 4, at 650. While some in the medical community champion cycling programs, *see* Marin H. Kollef, *Is Antibiotic Cycling the Answer to Preventing the Emergence of Bacterial Resistance in the Intensive Care Unit?*, 43 CLINICAL INFECTIOUS DISEASES S82 (2006), others doubt these programs' effectiveness due to poor compliance and to the lack of data supporting their validity. *See* MacDougall & Polk, *supra* note 4, at 651; *see also* Erwin M. Brown & Dilip Nathwani, *Antibiotic Cycling or Rotation: A Systematic Review of the Evidence of Efficacy*, 55 J. ANTIMICROBIAL CHEMOTHERAPY 6 (2005).

[14] See Jessica P. Schulman, *Patents and Antibiotic Resistance*, 59 DEPAUL L. REV. 221, 230-33 (2009), for a discussion of the legislative history of the Protecting America in the War on Terror Act of 2005, the Project BioShield II Act of 2005, and the Medical Innovation Prize Act of 2007.

[15] *See* Ramanan Laxminarayan, *Introduction* to BATTLING RESISTANCE TO ANTIBIOTICS AND PESTICIDES: AN ECONOMIC APPROACH 3 (Ramanan Laxminarayan ed. 2003); Kades, *supra* note 2, at 625 (estimating that a patient with penicillin-resistant gonorrhea costs twelve to fifteen times more than treating a patient with a non-resistant strain).

[16] Such economic loss would include lost productivity. *See* Laxminarayan, *supra* note 15.

developing new drugs to replace old ones that have lost their effectiveness diverts money and resources that could be used to develop drugs for other diseases.[17]

This paper seeks to examine the unique problems inherent in the antibiotic market, briefly review current policy options, and propose an optimal mix of solutions aimed at increasing financial incentives for innovation and decreasing inappropriate antibiotic usage. The paper proceeds as follows. Part I reviews the relationship between antibiotic use and antibiotic resistance. Part II focuses on the benefits and drawbacks of using a conservation-based approach to combat antibiotic resistance. Part III discusses why the financial incentives for pharmaceutical companies to develop antibiotics and for patients to use them appropriately are suboptimal. Part IV engages in a policy analysis and proposes ways to financially incentivize both antibiotic research and development and antibiotic conservation by relying on market signals. The paper then concludes.

It is important to keep in mind that that neither "more antibiotics" nor "less antibiotic usage" are end goals themselves; they are only *intermediate* goals towards the real objective of reducing the harmful effects of antibiotic resistance.[18] It should not matter, then, whether this outcome is achieved through the development of new drugs, through the slowing of bacterial resistance itself via conservation programs, or through some combination thereof. What complicates this discussion, though, is that these pathways can often work at cross-purposes. Thus, it will be crucial for an effective policy analysis to understand how innovation and conservation interact in order to craft an overall effective solution towards battling antibiotic resistance.

---

[17] *Id.* However, most commentators would argue that there is *not enough* expenditure on antibiotic research and development, especially as compared to drugs for chronic and lifestyle conditions. See *infra* Part III.A for further discussion on the challenges facing antibiotic development.

[18] *See* Kevin Outterson, *The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Intellectual Property Law*, 67 U. PITT. L. REV. 67, 67-69 (2005) [hereinafter Outterson, *Vanishing Public Domain*].

I. ANTIBIOTICS AND RESISTANCE: A BRIEF BACKGROUND

The story of the development of antibiotics has a well-known introduction. In 1928, Alexander Fleming inadvertently discovered penicillin when one of his bacterial cultures of *Staphylococcus aureus* was killed off by bread mold that had contaminated the dish.[19] Subsequently in the 1930s, researchers discovered the antibacterial properties of another compound: sulfonamides.[20] Sulfa drugs, as they were called, were the first antibiotics to be prescribed to the public and were effective against a range of infections, especially those caused by *streptococci* bacteria.[21] Since then, antibiotic research has produced numerous antibiotic therapies to treat human, as well as animal, infections.[22] Along with general improvements to sanitation, the availability of effective antibiotics helped to usher in a new era of public health and welfare. Within the first twenty years of antibiotics' introduction, the median life span in the United States improved by eight years, from 62 to 70.[23]

---

[19] *See* Kades, *supra* note 2, at 614; COLSON, *supra* note 9, at 1. It was not until the late 1930s that a team of researchers was able to purify the penicillin and scientifically prove its antibacterial properties. *See* David Ho, *Scientists & Thinkers: Alexander Fleming*, TIME, Mar. 29, 1999, *available at* http://www.time.com/time/magazine/article/0,9171,990612-1,00.html. Penicillin was subsequently introduced to the market in the early 1940s. *See* BAD BUGS, *supra* note 11, at 10.

[20] *See* COLSON, *supra* note 9, at 1.

[21] The massive production of sulfa drugs by numerous manufacturers, coupled with a lack of testing requirements, resulted in the 1937 Elixir Sulfanilamide disaster, where upwards of 100 people were poisoned by certain manufactures of the drug. This tragedy helped fuel public outcry that led to the passage of the Federal Food, Drug and Cosmetic Act of 1938. *See* Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAGAZINE (June 1981), *available at* http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm. For accounts of the crisis written in 1937, see *Medicine: Post-Mortem*, TIME, Dec. 20, 1937, *available at* http://www.time.com/time/magazine/article/0,9171,758704,00.html (last visited Apr. 25, 2011); *Death Drug' Hunt Covered 15 States; Wallace Reveals How Federal Agents Traced Elixir To Halt Fatalities*, N.Y. TIMES, Nov. 26, 1937, *available at* http://select.nytimes.com/gst/abstract.html?res=F40C15F93B59177A93C4AB178AD95F438385F9 (last visited Apr. 25, 2011).

[22] This paper does not address the important issue of reducing antibiotic usage in animals. *See* Kades, *supra* note 2, at 618 n.36-39 and accompanying text for further discussion on the topic.

[23] The relevant time span for this estimate is from 1933 to 1955. David Schlessinger, *Biological Basis for Antibacterial Action*, *in* MECHANISMS OF MICROBIAL DISEASE 78 (Moselio Schaechter et. al. eds., 1993), *quoted in* Kades, *supra* note 2, at 615.

Bacteria, however, began showing signs of resistance early on.[24] Antibiotic resistance is a natural evolutionary consequence to antibiotic exposure, whereby bacteria genetically adapt to become less susceptible to the antimicrobial agent in use.[25] One commentator attributes the adaptability of bacterial populations to their "genetic plasticity" and "rapid replication" rates, noting that "it takes many bacteria only 20-30 min[utes] to replicate."[26] Because of their quick rate of reproduction, bacteria that develop genetic characteristics that render them invulnerable to a certain antibiotic can survive and quickly generate new populations carrying these resistant characteristics. Thus, the more a strain of bacteria is exposed to an antibiotic, the more likely it is to both develop and spread resistance to that antibiotic.[27]

A consequence of bacterial resistance is that antibiotics have a finite shelf-life. Antibiotic drugs present a unique challenge precisely because their *absolute* effectiveness decreases over time, not merely their *relative* effectiveness as compared to competing drugs on the market.[28] Commentators often refer to antibiotics as an exhaustible resource,[29] or a common pool resource,[30] "prone to depletion and collapse through uncoordinated withdrawals."[31] As seen through this framework, uncoordinated withdrawals include our overuse and misuse of

---

[24] As noted earlier, bacteria began showing resistance to penicillin within ten years of the drug's introduction. *See* Cars & Nordberg, *supra* note 3, at 1.

[25] *See generally* Kades, *supra* note 2, at 617-25; Spellberg et. al., *A Call to Action*, *supra* note 1, at 2; I.M. Gould, *Antibiotic Resistance: The Perfect Storm*, 34 INT'L J. ANTIMICROBIAL AGENTS S2, S3 (2009) ("Whether it be a resistant Gram-positive or Gram-negative organism that is causing a therapeutic problem, one of the most likely causes is prior exposure of that patient to one or more broad-spectrum antibiotics.").

[26] Spellberg et. al., *A Call to Action*, *supra* note 1, at 155-56 ("There is no doubt that microbes are the most numerous, diverse, and adaptable organisms that have ever lived on the planet."); *see also* MacDougall & Polk, *supra* note 4, at 638 ("This [microorganisms' ability to rapidly develop resistance to antimicrobials] is a testament to the impressive reproductive rate of most microorganisms, the tremendous selective pressure that antimicrobial agents apply to these populations, and the huge number of unculturable organisms in the environment that may be serving as reservoirs of antimicrobial resistance genes.").

[27] *See generally* RAMANAN LAXMINARAYAN ET. AL., EXTENDING THE CURE: POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE 3-4 (2007) [hereinafter EXTENDING THE CURE]; Sage & Hyman, *supra* note 1, at 787-90; Spellberg et. al., *A Call to Action*, *supra* note 1, at 156-57.

[28] Kevin Outterson, *The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation*, 31 CARD. L. REV. 613, 637 (2010) [hereinafter Outterson, *Legal Ecology of Resistance*].

[29] Kades, *supra* note 2, at 629.

[30] Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 614.

[31] *Id.* Typical examples of common pool resources include fisheries and forests. *See id.*

antibiotics, which threaten to "prematurely destroy these important drugs."[32] Approaching antibiotic resistance as a resource issue serves not only a helpful explanatory function, but it also helps shape the prescriptive debate by focusing on which solutions will be most effective at the patient level, facility level, and ecological level.[33]

II. CONSERVATION AS AN APPROACH TO RESISTANCE

Resistance may not be preventable by human efforts – but it can be slowed. By reducing the "selective pressure" we put on bacteria "via exposure to the thousands of metric tons of antibiotics we have used...over the past half century,"[34] we can prolong the absolute usefulness of these drugs. It seems, though, that these years of overuse and misuse have taken their toll on antibiotic effectiveness and have contributed what the medical community considers to be alarming rate of resistance to certain drugs.[35]

A number of studies demonstrate the increased speed at which bacteria have been developing resistance. Two such studies described by Laxminarayan et. al. acutely illustrate the phenomenon. In 1987, only 2% of patients infected with *Staphylococcus aureus* (*S. aureus* or, more colloquially, "staph") showed resistance to methicillin, an antibiotic that had been on the market since the 1960s and was largely an effective treatment. By 2004, more than 50% of

---

[32] *Id.* Overuse refers to the unnecessary use of powerful antibiotics to treat minor or routine organisms. *See* Sage & Hyman, *supra* note 1, at 791. Misuse refers to the inappropriate usage of antibiotics. Examples of antibiotic misuse include: (1) the common problem of prescribing antibiotics for a viral infection, against which antibiotics are completely ineffective; (2) prescribing the wrong antibiotic for the bacteria at issue; and (3) prescribing the right antibiotic, but in a sub-therapeutic dose. *See id; see also* Ethan Rubinstein & George G. Zhanel, *The Hospital Physician*, *Anti-Infective Research and Development – Problems, Challenges, and Solutions*, 7 LANCET INFECTIOUS DISEASES 69, 70 (2007) (noting the near 40% inappropriate use of antibiotics in hospital settings).

[33] *See* MacDougall & Polk, *supra* note 4, at 639 (discussing the need to have the requisite understanding of the interaction between antibiotic use and antibiotic resistance at the various levels).

[34] Spellberg et. al., *A Call to Action*, *supra* note 1, at 157.

[35] BAD BUGS, *supra* note 11, at 9 ("'Antibiotic resistance is increasing too quickly and in too many organisms...'"); *see also* George H. Talbot et. al., *Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America*, 42 CLINICAL INFECTIOUS DISEASES 657, 657 (2006) (noting "an increasing frequency and severity of antimicrobial resistance").

patients infected with *S. aureus* did not respond to methicillin.[36] This particular pathogen – methicillin-resistant *S. aureus* (or MRSA) – causes many types of serious infections and can have fatal consequences if untreated.[37] MRSA strains are resistant not only to methicillin but to other classes of antibiotics as well.[38] Discouragingly, doctors have begun to report cases of MRSA that fail to respond to vancomycin, the antibiotic to which doctors most frequently resort in order to treat MRSA infections.[39] Another such study focuses on *Streptococcus pneumoniae* (*S. pneumoniae*), a bacteria which can cause bacterial meningitis as well as bacterial pneumonia.[40] In 1987, only .02% of patients infected with *S. pneumonia* did not respond to penicillin. By 2004, this number had jumped to a staggering 20%, representing a 1,000-fold increase in less than twenty years.[41] Additional pathogens that have exhibited dangerous forms of resistance today have been identified as *Acinetobacter baumannii*; *Aspergillus* species; extended spectrum b-lactamase (ESBL)–producing Enterobacteriaceae; vancomycin-resistant *Enterococcus faecium*; and *Pseudomonas aeruginosa.*[42]

The growth of antibiotic-resistant bacteria implicates serious health concerns. Infectious diseases already account for the third-leading cause of death in the United States,[43] and the second-leading cause of death in the world,[44] a figure that is likely to increase as resistant

[36] EXTENDING THE CURE, *supra* note 27, at 1.
[37] *See generally* Talbot et. al., *supra* note 35, at 665. MRSA has become one of the more popularly recognized resistant pathogens, as it has spread from being a primarily hospital-acquired infection to one that is community-acquired as well. *See id.*
[38] *See* Kades, *supra* note 2, at 616 (noting that MRSA developed resistance to the antibiotic Cipro, which is in the fluoroquinolones class, after only three years). A class of antibiotic refers to a group of drugs that exhibit the same "novel mechanisms of action" to fight bacteria. COLSON, *supra* note 9, at 1.
[39] *See id.*; Talbot et. al., *supra* note 35, at 665.
[40] EXTENDING THE CURE, *supra* note 27, at 1.
[41] *Id.*
[42] See Talbot et. al., *supra* note 35, at 658-665, for further details about these specific pathogens.
[43] *See* Brad Spellberg et. al., *Trends in Antimicrobial Drug Development: Implications for the Future*, 38 CLINICAL INFECTIOUS DISEASES 1279, 1279 (2004) [hereinafter Spellberg et. al., *Trends*].
[44] *See id.*

bacteria become more prevalent.[45] Those infected with resistant bacteria experience a higher mortality rate and higher rates of secondary complications than those whose infections respond to antibiotics.[46] Moreover, the cost of treating antibiotic-resistant bacteria is much higher than treating antibiotic-susceptible bacteria, because the treatments are longer and more expensive.[47] As such, concerned efforts to conserve antibiotic use are essential to mitigating the human and economic toll of antibiotic resistance.

Translating these observations, however, into targeted solutions aimed at an optimal rationalization of antibiotic use has proved to be difficult. The main complicating factor is the fact that the empirical relationship between antibiotic use and antibiotic resistance is incredibly complex and not yet fully understood.[48] Some drugs remain effective against certain bacteria even after decades of use, but lose their effectiveness against other bacteria rather quickly. For instance, the *group A streptococci* bacteria remain fully susceptible to penicillin, while more than 90 percent of *S. aureus* strains and 30 percent of *Streptococcus pneumonia* strains are resistant to penicillin.[49] Likewise, even though a pathogen will often develop resistance to multiple drugs within the same class of antibiotics,[50] in some cases, a pathogen will develop resistance across

[45] *See* Cars & Nordberg, *supra* note 3, at 1.
[46] *See id.* at 4; *see also* Rubinstein & Zhanel, *supra* note 34, at 69 (noting that drugs to treat resistant strains can be "hampered with adverse effects").
[47] *See* BAD BUGS, *supra* note 11, at 3, 13; *cf.* Talbot et. al., *supra* note 35, at 658 ("[T]he toll of antimicrobial resistance: the loss of thousands of lives and the avoidable costs of billions of health care dollars.").
[48] *See* Cars & Nordberg, *supra* note 3, at 3 ("The relationship between antibiotic use and resistance is complex."); MacDougall & Polk, *supra* note 4, at 639 (describing studies that illustrate how the medical community's understanding of the relationship between antibiotic use and resistance is incomplete).
[49] *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 634 (quoting *CDC's Role in Monitoring and Preventing Antimicrobial Resistance: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 110th Cong. 2 (June 24, 2008)).
[50] As mentioned earlier, a class of antibiotics refers to a group of drugs that display the same distinct "mechanis[m] of action" against bacteria. *See* COLSON, *supra* note 9, at 1; Outterson, *Legal Ecology*, *supra* note 28, at 634.

multiple antibiotic classes.[51] Moreover, sometimes resistance can even be passed from one species of bacteria to another.[52]

The numerous ways in which resistance can develop makes it difficult to come up with a consistent antibiotic usage policy: strategies that may reduce resistance in some pathogens may be ineffective, or even counterproductive, in others.[53] Furthermore, even when efforts to reduce the usage of one antibiotic have been successful, that reduction is often merely substituted with the increased use of another antibiotic in its stead. This is known as the "squeezing the balloon" phenomenon, which only results in "swapping one resistance problem for another."[54] To avoid this fate, total reduction in antibiotic consumption must be part of any effective strategy for reducing resistance, rather than relying on piecemeal efforts of conservation which ultimately may not prove to be as fruitful.[55] In short, scientists are continually updating and revising their understanding of the biology of antibiotic resistance.[56] The policy implications of this are such that we need a response to antibiotic resistance that does not *solely* rely on altering antibiotic usage to reduce resistance outcomes. Stated otherwise, until we have the knowledge to differentiate one pathogen's reaction path from another, any policy that tries to modulate

---

[51] Outterson, *Legal Ecology*, *supra* note 28, at 634.
[52] *Id.*; *see also* Kades, *supra* note 2, at 623 ("'[A] single antibiotic to treat an infection can provoke resistance to other drugs...'") (citation omitted).
[53] *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 635 (noting how optimal dosing strategies depend on an accurate understanding of whether the particular bacteria develops resistance through single-point mutations or through a more complex genetic process); Rubinstein & Zhanel, *supra* note 34, at 70 ("We also need to acknowledge that our understanding of when and how to best use combination antibiotic therapy is lacking."). *Compare* Michael D. Tino, *A Primary Care Physician*, *Anti-Infective Research and Development – Problems, Challenges, and Solutions*, 7 LANCET INFECTIOUS DISEASES 70, 71 (2007) (proposing new course of treatment for community based sinusitis and chronic bronchitis) *with* Glenn S. Tillotson, *Bad Bugs Still Need Drugs*, *Anti-Infective Research and Development – Problems, Challenges, and Solutions*, 7 LANCET INFECTIOUS DISEASES 76, 77 (2007) (describing Dr. Tino's approach, which suggests that "it might be beneficial to use more potent antimicrobial agents" to "eradicate a pathogen more efficiently" as a concept that has "yet to be more widely accepted").
[54] Gould, *supra* note 25, at S4; *see also* MacDougall & Polk, *supra* note 4, at 647 (describing studies where reducing one antibiotic had the effect of reducing resistance in the targeted pathogen, but the subsequent increased usage of a replacement antibiotic was accompanied by the increased incidence of resistance in other pathogens).
[55] *See* Gould, *supra* note 25, at S4.
[56] MacDougall & Polk, *supra* note 4, at 639 (discussing the continuing evolving body of scientific knowledge about the relationship between antibiotic use and resistance).

antibiotic usage will be suboptimal. To be sure, antibiotic conservation is a necessary element to a resistance reduction strategy; it just should not be the only one. This author submits that we cannot depend on a use-based conservation strategy to the exclusion of all others when (1) the marginal impact varies dramatically from one use to the other[57] and (2) we cannot adequately distinguish between the two in the *ex-ante* world.

III. CHALLENGES FACING THE ANTIBIOTIC MARKET

A. Declining Investments in Antibiotic Research and Development

The rising rates of bacterial resistance, coupled with our incomplete understanding of the relationship between antibiotic use and resistance, necessitates a policy response that emphasizes the development of new drugs to target pathogens no longer susceptible to current treatments.[58] In spite of this urgent need for novel therapies, the antibiotic pipeline is running dry.[59] Between 1930 and 1970, scientists introduced fourteen different classes of antibiotics.[60] Since 1970, only five new classes have been discovered (mupirocins, streptogramins, oxazolidinones, lipopeptides, and pleuromutilins),[61] two of which (mupirocins and pleuromutilins) are only available for topical use.[62] The infectious disease community also warns of declines in four key measures of antibiotic innovation: the number of new drug applications,[63] the diversity in class among those drugs being developed,[64] the diversity in infections the drugs are indicated to treat,

---

[57] See Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 634-5 ("Resistance within classes and between classes differs by both pathogen and drug...") (citation omitted).
[58] *See generally* BAD BUGS, *supra* note 11, at 3.
[59] *See id.* at 14.
[60] COLSON, *supra* note 9, at 1.
[61] *Id. But see* Kevin Outterson et. al., *Will Longer Antimicrobial Patents Improve Global Public Health?*, 7 LANCET INFECTIOUS DISEASES 559, 559-61 (2007) (arguing that ketolides and glycylcyclines (introduced in 2004 and 2005, respectively) should be considered novel antimicrobial classes even though they are related to existing classes) [hereinafter Outterson et. al., *Antimicrobial Patents*].
[62] COLSON, *supra* note 9, at 1. Topical antibiotics remain important for their ability to treat skin infections, especially those caused by MRSA. *Id.* at 2.
[63] *Id.* at 1-2.
[64] *Id.* at 2 (noting that over seventy-five percent of new drug applications were in two classes).

and the diversity in pathogens targeted by the drugs.[65] To be sure, there has been some recent progress in the development of drugs to treat infections due to MRSA, VRE (vancomycin-resistant *enterococci*), and ESBL-producing bacteria (E. Coli and Klebsiella spp.), but the situation for infections caused by gram-negative bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which often show immunity to all antibiotics currently on the market, remains much more grim.[66]

Although antibiotic research has not stopped, it has slowed and narrowed in scope.[67] What accounts for this decline in clinical research and development efforts? Commentators point to several contributing factors.

Industry dynamics. First, they note of the industry consolidation among the large pharmaceutical companies during the 1990s. A product of this consolidation was the decline in the total number of companies engaged in antibiotic research, from seventy entities to fewer than twelve.[68]

Lower profitability profile. Second, those remaining pharmaceutical companies began to leave the antibiotic space because it had become an unattractive market from a profitability standpoint relative to the markets for other drugs.[69] Even companies with well-known antibiotic programs, such as Roche, Abbott, and Eli Lilly, left the anti-infective market.[70] During the late 1990s and early 2000s, "the number of established companies working on antibacterial products

---

[65] *Id.*
[66] *Id.* For some positive news, Wyeth's new drug tigecycline, introduced in 2005, is active against both gram-positive and gram-negative bacteria. Outterson et. al., *Antimicrobial Patents*, *supra* note 61, at 560.
[67] COLSON, *supra* note 9, at 3.
[68] *See* Jeffrey L. Fox, *The Business of Developing Antibacterials*, 24 NATURE BIOTECH. 1521, 1521 (2006); *see also* DAVID SHLAES, ANTIBIOTICS: THE PERFECT STORM 13 (2010).
[69] *See generally* BAD BUGS, *supra* note 11, at 14-19; Paul H. Rubin, *The FDA's Antibiotic Resistance*, 27 REG. 34, 34 (2005).
[70] Fox, *supra* note 68, at 1521.

fell by about two-thirds, from at least 18 in the United States and Europe to only six."[71] Why did we see such an exodus from the market? The answer stems from the fact that antibiotics are a less attractive investment relative to other drugs, for several reasons.

One reason that antibiotics present a unique challenge to pharmaceutical companies is that, as noted above, their absolute effectiveness decreases over time, not simply their relative effectiveness vis-à-vis new competitors on the market.[72] This has the effect of reducing the overall value of the company's investment in the antibiotic, because as the antibiotic becomes less effective, doctors will (presumably) prescribe it with less frequency, which in turn lowers revenue. This is especially problematic when resistance to an antibiotic occurs *within* its patent period, as this is the time when pharmaceutical companies expect to reap most of their profits.[73]

To be sure, resistance is a double-edged sword when it comes to incentivizing antibiotic development. On the one hand, resistance lowers the antibiotic's net present value by diminishing the future stream of revenue, but, on the other the hand, resistance generates demand for novel antibiotics by creating bacteria that do not respond to current treatments.[74] Moreover, resistance has the added effect of continually clearing the competitive playing field of old antibiotics.[75] This is presumably a benefit for pharmaceutical companies, which would rather face less competition in the marketplace – as long, of course, as they are not the ones being swept away. Kevin Outterson refers to these twin effects as part of his "resistance stimulates

---

[71] *Id.*
[72] *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 637.
[73] *Id.* at 634; *see also* Schulman, *supra* note 14, at 234.
[74] *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 630 ("Resistance also encourages the production of antibiotics with novel features. Examples include new drug classes that bypass existing resistance mechanisms, such as ketolides, glyclycyclines, and some other antibiotics.") (citations omitted).
[75] *Id.* ("[R]esistance makes existing new drugs obsolete over time, creating marketing opportunities for new drugs. To the extent that competition within existing drugs discourages market entry by a new drug, resistance clears the field and facilitates introduction of new drugs.").

innovation" hypothesis.[76] He makes the empirical argument that resistance does more to stimulate innovation than it does to discourage drug companies from entering the market, thus offering the conclusion that perhaps antibiotics need fewer financial incentives for development than other types of drugs.[77] Even if Outterson's empirical claim is borne out, we are still left with the possibility that the future antibiotics may not be as effective as prior drugs,[78] that research and development efforts may not produce new drugs in time to meet patient needs, or that the pathogens displaying multi-drug resistance may constitute too small of a market to justify commercial expenditure.[79] Moreover, even if on balance resistance does more to spur innovation than to hinder it, it does not follow that resistance does enough to spur investment in antibiotics over investment in other classes of drugs that offer pharmaceutical companies a better return on investment ("ROI").

The major contributing factor to antibiotics' relatively low ROI is the limited duration of antibiotic treatment. Unlike medicines for chronic conditions (such as high blood pressure, cholesterol, or diabetes), which are taken regularly and over extended periods of time, antibiotics are taken only for a short length of time and only when an infection arises.[80] Pharmaceutical companies have accordingly weighted their research and development portfolios in favor of

[76] *Id.* at 617. He elaborates that there are three mechanisms by which resistance can spur innovation: (1) by "clearing out competitor drugs," and (2) by "steering innovation towards novel classes." *Id.* at 636. He argues that the innovation-generating effects of these two mechanisms outweigh the innovation-reducing effect of slowing down patent sales during the patent period due to increased resistance. *Id.* at 637-41.
[77] *Id.* at 641.
[78] *See* Rubinstein & Zhanel, *supra* note 34, at 69 (discussing the lower health outcomes associated with newer antibiotics).
[79] *See* Talbot et. al., *supra* note 35, at 666 ("Unfortunately, many of the problem pathogens we have identified are characterized by commercial markets that are relatively small, as well as unpredictable; these factors have deterred major pharmaceutical companies from investing in these unmet needs.").
[80] *See generally* David L. Pompliano, *GSK – A Major Pharmaceutical Company*, *Anti-Infective Research and Development – Problems, Challenges, and Solutions*, 7 LANCET INFECTIOUS DISEASES 71, 71 (2007) (describing the "short-term use of nearly all antibiotics").

chronic and lifestyle drugs because they are the financial top performers.[81] For example, Pfizer's Zithromax, one of the most profitable antibiotics while under patent, had only annual sales of $2 billion, whereas Pfizer's cholesterol drug Lipitor had annual sales of nearly $9 billion.[82] Eli Lilly's most recent financial results are also telling: their top selling drugs consisted of treatments for mental health disorders (including depression), diabetes, osteoporosis, and lifestyle issues.[83] Eli Lilly no longer engages in antibiotic research.

Antibiotic revenue streams are also likely to be lower because the drugs become less valuable as bacterial resistance grows. Moreover, conservation efforts designed to reduce the usage of antibiotics have the added consequence of reducing the pharmaceutical companies' incentives to invest in antibiotics in the first place.[84] This stems from the fact that conservation (and, for that matter, all efforts to reduce the incidence of infection) has the unavoidable effect of reducing the total amount of sales a drug company can expect to reap from their product.[85] This is especially so if the conservation efforts occur during the patent period, which is precisely when the medical community is more likely to conserve a novel therapy in order to preserve its

---

[81] Spellberg et. al., *Trends*, *supra* note 43, at 1279. The authors examined the publically disclosed descriptions of the research and development programs of the fifteen major pharmaceutical companies and the seven major biotechnology companies. They discovered that out of a total of 315 new molecular entities ("NME") undergoing development, only 5 (1.6%) of those could be classified as new antibacterial agents, whereas there were 67 (21%) NMEs related to cancer, 34 (10%) related to metabolic or endocrine diseases, and 33 (10%) related to inflammation or pain. *Id.* at 1281-82.

[82] Rubin, *supra* note 69, at 34.

[83] Results are for the first quarter of 2011. The following is a breakdown of their best selling drugs:

1. Zyprexa, an anti-psychotic, with sales of $1.28 billion.
2. Cymbalta, an antidepressant, with sales of $908.8 million
3. Cialis, an erectile dysfunction treatment, with sales of $434.4 million
4. Humulin, an insulin treatment, with sales of $289.8 million
5. Evista, an osteoporosis treatment, with sales of $266.1 million
6. Forteo, an osteoporosis treatment, with sales of $216.1 million

Drugmaker Eli Lilly's 1Q Sales Growth at a Glance, N.Y. TIMES, Apr. 18, 2011, *available at* http://www.nytimes.com/aponline/2011/04/18/business/AP-US-Earns-Eli-Lilly-Glance.html?_r=1&hp (last visited April 18, 2011).

[84] *See generally* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 642.

[85] *See id.*; Rubin, *supra* note 69, at 34 ("As usage is reduced to eliminate resistance, sales are also reduced, and antibiotics become relatively less profitable.").

effectiveness.[86] Kevin Outterson refers to this phenomenon as the "conservation dampens production" hypothesis, explaining that conservation works "at cross-purposes with incentives to produce novel antibiotics."[87] Of course, this hypothesis might not pose such a problem, as the end goal is better health outcomes, not just pharmaceutical innovation for its own sake.[88] If conservation alone were sufficient to solve the resistance problem, we could thus tolerate the resulting dampened incentives for antibiotic innovation. As discussed above in Part II, however, we cannot rely solely on demand-side conservation. We must also encourage supply-side research and development of new anti-infective drugs to augment the cache of antibiotic treatments as a critical component to a successful resistance strategy. Thus, unlike Kevin Outterson's proposition that antibiotics require fewer financial incentives than other drugs, I would argue that they need even more because of the effects of conservation initiatives on market demand.

Diminishing returns to research and development. Third, there is worry that the "low-hanging" fruit of antibiotic research have already been plucked, making the discovery of novel antibiotic drugs an even more difficult achievement.[89] Scientists have traditionally uncovered new antibiotics by evaluating natural products, like Alexander Fleming's broad mold, for their

[86] *See* Pompliano, *supra* note 80, at 71(noting that one of the aspects detracting from the commercial returns of antibiotics is the increasing "tendency by physicians to refrain from prescribing new antibiotics so as to keep them in reserve until older drugs fail."); *cf.* Tillotson, *supra* note 53, at 74 ("[F]ew practitioners are confident in using the newer agents – which are perceived to be more expensive – especially if the managed care organisations are unconvinced of the cost-benefit of such an approach.").

[87] Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 642. He further elaborates: "Antibiotic stewardship and rational use programs can be considered anti-marketing campaigns. Infection control efforts, if successful, reduce the spread of dangerous infections and reduce the need for antibiotic treatments." *Id.*

[88] *See id.* at 643 ("Remember that the goal is continued antibiotic effectiveness, not new drugs per se. If patients receive effective treatment, or better yet, avoid infection in the first place, then the social welfare goals have been met.").

[89] *See id.* at 644; *cf.* SHLAES, *supra* note 68, at 13 ("Our ability to discover new antibiotics is restrained by the more difficult science.").

inherent antibacterial properties and chemically modifying promising candidate molecules.[90] This natural products approach has been yielding fewer successes, however, which prompted scientists to turn their attention (and hopes) to high-technology approaches such as genomics and bioinformatics to help uncover new antibacterial targets.[91] Unfortunately, the medical community has been disappointed by the results.[92] One Glaxo-Smith-Kline researcher noted:

> A decade ago, the hope was that genomics would provide for drug discovery a trove of broadly useful bacterial targets. Although genomics has greatly informed bacterial pylogeny and physiology, it has not yet led to a marketed antibiotic. Nor has automated screening of bacterial targets against vast chemical libraries met early expectations: the 'hit' rate in these screens has been lower in than in therapeutic classes....[93]

The failure of these high technology approaches has led researchers to return to the more "traditional" methods of antibiotic research, but there is a remaining concern that the new drugs may not be as good as the old ones.[94] Even though they may be effective against certain bacteria, "most new antibiotics carry serious side effect risks, including adverse reactions, liver toxicity, and other serious risks of organ failure."[95] For example, vancomycin, the drug most often used to treat MRSA, carries with it the limitations of poor tissue penetration and the risks of potential liver toxicity.[96] If pharmaceutical companies take the view of those researchers who believe that "we have already harvested the low-hanging fruit of easily discoverable antibiotics,"[97] or, even more dismally, those researchers who believe that "the number of

---

[90] *See* Fox, *supra* note 68, at 1526; Schulman, *supra* note 14, at 225 ("Many successful antibiotics were discovered by observing how other organisms, such as fungi, inhibit the growth of bacteria.").
[91] *See* Fox, *supra* note 68, at 1526.
[92] *Id.*
[93] Pompliano, *supra* note 80, at 72.
[94] *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 643-45 ("If a new drug is not better and entails unknown safety risks, then innovation results in an even greater social welfare loss.")
[95] *Id.* at 644.
[96] *Id.* at 644 n.149.
[97] Outterson, *Vanishing Public Domain*, *supra* note 18, at 77; *see also* BAD BUGS, *supra* note 11, at 17 (nothing that "'the discovery of new antibiotics is not as easy as was once believed.'") (citation omitted).

possible antibiotic targets is *finite*,"[98] then without additional incentives, these companies will abandon their antibiotic programs under the belief that such investments will only yield progressively diminished returns.[99]

Institutional competence favoring large pharmaceutical companies over small biotechnology companies. Fourth, while large pharmaceutical companies have been shedding their antibiotic research and development programs, we have seen an influx of smaller pharmaceutical companies and biotechnology companies enter the space.[100] This trend is in large part a product of the industry consolidation itself, as larger pharmaceutical companies began to (1) spin-off small groups to focus exclusively on anti-infectives[101] and (2) to sell off the chemical compounds in their antibiotic portfolio in an effort to wind down their investments. Indeed, "there is a small window during which discarded discovery research programs may be continued in meaningful new products."[102]

The story of Cubist Pharmaceutical's daptomycin offers one such glimpse into what a successful transition of a compound from a large pharmaceutical company to a smaller biotech looks like.[103] In 2003, Cubist received approval in the United States for daptomycin (brand

---

[98] Outterson, *Vanishing Public Domain*, *supra* note 18, at 77.
[99] Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 644-45.
[100] *See* Fox, *supra* note 68, at 1521 ("[T]here are signs of renewed energy and progress, much of it emanating from an odd assortment of several dozen biotech companies, many of them in the United States but also in Europe and Asia."); Frank Tally & Praveen Tipirneni, *Cubist – A Small Pharmaceutical Company Focusing on Hospital Infections*, *Anti-Infective Research and Development – Problems, Challenges, and Solutions*, 7 LANCET INFECTIOUS DISEASES 72, 72 (2007).
[101] *See* Tillotson, *supra* note 53, at 77. Examples of this include Roche's offshoot Basilea Pharmaceutica (Basel), Sanofi-Aventis' 2004 spinout of Novexel, and Peninsula's spinoff of Cerexa. Fox, *supra* note 68, at 1524. To be sure, those large pharmaceutical companies that remained in the antibiotic space tended to acquire smaller pharmaceutical companies whose pipelines looked promising, including Pfizer's acquisition of Vicuron Pharmaceuticals in 2005 for $1.9 billion, and Johnson & Johnson's acquisition of Peninsula Pharmaceuticals for $245 million. *See* Fox, *supra* note 68, at 1524.
[102] Roger Echols, *The Biotech Company View*, 24 NATURE BIOTECH. 1519, 1519 (2006).
[103] Cubist Pharmaceuticals, Inc. employs more than 600 people and had 2010 net revenues of $636.4 million. See Cubist Pharmaceuticals, About Cubist, http://cubist.com/about/. By contrast, Eli Lilly is the tenth largest pharmaceutical company in the world, with close to 40,000 employees and 2010 net revenues of over $23 billion. Eli Lilly, About Us: Facts at a Glance, http://www.lilly.com/about/facts/#financials.

name Cubicin), the first antibiotic in the new class of lipopetides.[104] Daptomycin is active against MRSA as well as other types of gram-positive bacteria, though it requires intravenous treatment.[105] As a testament to the drug's success, Cubist reported that daptomycin "has had the fastest and most impressive sales growth of any intravenous launched in recent history."[106] Daptomycin, however, was initially discovered by Eli Lilly, which eventually discontinued its work on the compound in 1991 due to its high levels of toxicity.[107] Cubist then in-licensed the compound in 1997, with the view towards meeting the demand for an antibiotic other than vancomycin that could treat those patients infected with MRSA.[108] Cubist spent the next several years re-developing the drug to solve the dosing and toxicity issues and putting it through clinical trials, eventually working cooperatively with the FDA to get the drug approved.[109] Those who look to small pharmaceuticals to fill the gap left by "big pharma" in the antibiotic space point to this example as illustrative of how "small pharmaceutical companies can take a nascent product from early development through to commercialization."[110]

There are some in the medical community, however, who are concerned about the ability of small pharmaceuticals and biotechnology companies to take over where large pharmaceutical companies left off. First, they note that antibiotic development has mainly been the work of "big pharma." As such, the research and development programs of the world's fifteen largest pharmaceutical companies account for 93% of the antibiotics approved by the FDA from 1980 to

[104] *See* Tally & Tipirneni, *supra* note 100, at 72.
[105] *Id.*
[106] Outterson et. al., *Antimicrobial Patents*, *supra* note 61, at 560.
[107] Tally & Tipirneni, *supra* note 100, at 72.
[108] *Id.* at 72-73.
[109] *Id.* at 73. The solution to daptomycin's toxicity problems lay in changing the drug to a once-daily dosing, a surprising discovery that led to a new patent issued to Cubist, as this finding was considered both "novel and counterintuitive." These changes in the drug's dosing were "masterminded" by Cubist researcher Francis Talley. Talley passed away in October 2006, only a few months after the FDA approved daptomycin for additional uses, including against MRSA. It was initially approved in 2003 for treating skin infections. *See* Fox, *supra* note 68, at 1526.
[110] Tally & Tipirneni, *supra* note 100, at 73. Jeffrey Fox discusses other examples of smaller companies that have in-licensed late-stage antibiotic compounds from larger pharmaceutical companies. Fox, *supra* note 68, at 1526.

2003.[111] Even now, the smaller biotech companies have been able to enter the space because they could in-license compounds that were discovered yet discarded by the large pharmaceutical programs. Critics remain skeptical that these small companies can independently discover novel therapies when the current pipeline of abandoned compounds runs dry.[112] These worries are driven in part by the immense amount of capital required to discover novel antibacterial molecules,[113] let alone the capital required to undergo clinical testing necessary for approval. The high cost of testing and marketing explains why, traditionally, biotech companies have handed off promising medical compounds to large pharmaceutical companies to pay for the clinical testing and marketing phase of the drug's development. What we are seeing now is the reverse of this trend, whereby smaller companies have taken over the drug at the end of development and into the testing phase.[114]

To that end, the circumstances of the daptomycin transition were such that Cubist needed relatively low capital outlays for the drug's testing and marketing. Because daptomycin was an intravenous antibiotic, it could only be administered in a hospital setting, and "[t]ypically, trial sizes [for acute indications in a hospital setting] are smaller than those in an outpatient setting, in the range of several thousand patients."[115] Comparatively, for a broad-spectrum drug available on an out-patient basis (e.g., pill form), "much larger trials and safety databases are necessary; it is much more difficult for small companies to afford and to implement such operations."[116] The hospital-setting indication also helped Cubist save on marketing costs, because "the prescribing

[111] *See* Spellberg et. al., *Trends*, *supra* note 43, at 1281.
[112] *See* Echols, *supra* note 102, at 1519 ("Ultimately, however, the big pharma pipeline of discarded programs will also dry up and it is unclear whether biotech will be capable of independently discovering novel antibiotic classes and bringing them to market.").
[113] *See* Fox, *supra* note 68, at 1526.
[114] *See* Joseph Gottfried, *History Repeating? Avoiding a Return to the Pre-Antibiotic Age* 49 (2005), in Peter Barton Hutt, ed., FOOD AND DRUG LAW: AN ELECTRONIC BOOK OF STUDENT PAPERS.
[115] Tally & Tipirneni, *supra* note 100, at 73.
[116] *Id.*

bodies in hospitals can be targeted in a much more specific way than practitioners in the community, meaning that a large and expensive marketing team is not necessary."[117] Thus, it seems that antibiotics for hospital-based acute infections may be well-suited to the small pharmaceutical or the biotechnology company cost structure.[118] We will not, however, be able to solely rely on niche antibiotics to overcome the resistance problem and sustain society's innovation needs, especially when those antibiotics are only available in a hospital setting. The medical community acknowledges the need for more broad-spectrum antibiotics and antibiotics available in an oral formulation, precisely those drugs that are better suited for the R&D programs of a large scale pharmaceutical company.[119]

B. Antibiotic Market Externalities

The growing problem of antibiotic resistance is also exacerbated by certain externalities associated with antibiotic usage. According to Paul Rubin, "an externality is said to exist when one person's behavior has effects – positive or negative – on another person and those effects are not priced into the market."[120] Because of this mispricing of the activity, "externalities lead to non-optimal behavior."[121] If an activity is associated with a positive externality, then "private agents will not do enough of the activity because an agent does not obtain all the benefits of the action."[122] Conversely, if an activity is associated with a negative externality, then private agents will engage in too much of the activity because they are not forced to bear the entire cost of the

---

[117] *Id.*
[118] *See* Fox, *supra* note 68, at 1525 ("Clinical and commercial success with a drug that targets a single pathogen 'would reopen a lot of rooms worth revisiting with target-based approaches and might be very attractive for smaller companies,'....'There are a lot of challenges, including the need for a clean safety profile....But if successful, it would open a new world.'").
[119] *See id.* at 1524 (noting the need for orally available drugs to treat gram-positive bacteria, whereas most of the newer drugs are only given intravenously); *id*. (noting that there appears to be more of a demand for extended-spectrum drugs rather than single pathogen drugs). To be sure, broad-spectrum antibiotics also pose a significant resistance risk, as they apply selective pressure on a broader array of bacteria to mutate in order to avoid susceptibility. *See* Gould, *supra* note 25, at S3; MacDougall & Polk, *supra* note 4, at 651.
[120] Rubin, *supra* note 69, at 34.
[121] *Id.*
[122] *Id.*

action.[123] Antibiotics face certain notable externalities, suggesting that their current market pricing is not accurately reflective of the true cost of antibiotic use.

Public health externality (positive). The most traditional reason to encourage antibiotic usage is that public health is improved as more people take antibiotics to cure their infections. Because one person's taking an antibiotic also prevents someone else from contracting the same infection, the public benefits from that person's usage.[124] In this way, the market price of antibiotics can be considered too expensive, because it does not take into account the public health benefits arising out of an individual dosage. Thus, this account would lead us to subsidize antibiotic usage to adequately price in the public benefit. Efforts to encourage antibiotic usage may take the shape of expanding access to antibacterial drugs, especially to poorer populations; educating patients of the importance of finishing the schedule of treatment; and prescribing broad-spectrum antibiotics "to enhance the likelihood of therapeutic success."[125] As Paul Rubin notes, the public health externality "is the ultimate theoretical reason for public health interventions and for the existence of the CDC."[126]

Conservation externality (negative). As discussed more thoroughly above, as antibiotics are conserved and thus used less frequently, the incentives for antibiotic development diminish in turn as expected profitability is reduced.[127] However, conservation is designed to prevent the largest externality of antibiotic usage – antibiotic resistance.

Resistance externality (negative). Antibiotic resistance is the most threatening externality of antibiotic usage. As antibiotic usage increases, the exposure to the antibiotic puts pressure on

[123] *Id.*
[124] *Id.* at 34-35.
[125] Cars & Nordberg, *supra* note 3, at 3 (in the context of noting that usage of broad-spectrum antibiotics is one of the contributing factors of resistance because it "increases the rate of selection of resistant bacteria.").
[126] Rubin, *supra* note 69, at 35.
[127] *See id.*

bacteria to develop resistance. This suggests that antibiotics are in fact *too cheap*, as the current pricing does not take into account the true cost of antibiotic usage. The under-pricing of antibiotics is consistent with the account that antibiotics are grossly overused and misused;[128] neither patients nor their doctors have to pay for the resistance externalities imposed on others, so they are not incentivized to invest in proper information-gathering at the prescription stage. Such information-gathering would include patient education as well as incentives for developing and using diagnostic tests to determine whether a patient's infection is bacterial or viral in nature.[129] This would work towards curbing the misuse of antibiotics, as nearly 40% of antibiotic consumption in the community "is considered based on incorrect indications, mostly viral infections"[130] Similarly, sensitivity testing could be used to determine whether the patient can be given "narrow-spectrum or weaker drugs" as opposed to the powerful broad-spectrum antibiotics, which are associated with a higher resistance externality.[131]

Currently, these sorts of tests only impose costs on the patient, both in the form of delayed care and added expense; the patient is not rewarded for undertaking this initial assessment.[132] If the use of antibiotics were accurately priced to take into account the potential resistance effects, however, then individuals would be discouraged from inappropriate overuse of antibiotics, and cost-benefit analysis would incentivize them to spend more resources in pre-prescription research.[133]

---

[128] *See* Sage & Hyman, *supra* note 1, at 791.
[129] *See* Kades, *supra* note 2, at 639; *cf.* Rubinstein & Zhanel, *supra* note 34, at 70 (noting the need for investment in methods to "augment innate immunity" such that one's chances of contracting a resistant infection are lessened).
[130] Cars & Nordberg, *supra* note 3, at 3; *see also* Kades, *supra* note 2, at 617 ("Some estimate that half of all antibiotic prescriptions are written for patients who will experience no benefit from the medication.").
[131] Sage & Hyman, *supra* note 1, at 791.
[132] *See* Kades, *supra* note 2, at 639.
[133] For example, prescriptions for antibiotics could uniformly cost more when no pre-prescription research is undertaken. Pre-prescription research would include an analysis to determine whether the ailment is bacterial or viral in nature and a sensitivity analysis to determine the necessity of using broad-spectrum drugs. *See id.* ("The higher prices for antibiotics resulting from Pigovian taxation would also create greater incentives for using various

Admittedly, there are many practical limitations to this line of reasoning. First, the task of accurately pricing in the externality effect of antibiotic resistance would be a challenge in itself.[134] A second complicating factor is the tension between the individual and community interest within the resistance externality. There are times when the two are aligned: when an individual takes an antibiotic, that person risks having some bacteria in his own body develop resistance to that drug, such that it will become "more difficult for [him] to overcome future infections."[135] This private cost is aligned with the cost to the community of that person spreading the resistant bacteria to others. However, there are times when the interests diverge: when "a strong antibiotic may indeed be preferable for the treatment of each particular infected patient, even if it results in adverse consequences for future patients."[136] These cases require us to weigh the health interests of the individual against the health interests of society, a task that implicates a larger normative debate about the primacy of liberty versus community interests in medical decision-making. As William Sage and David Hyman explain, "liberty is one of the founding principles of the United States, and it has independent ethical and constitutional importance."[137] A government measure that would subordinate the interest of the individual in receiving the antibiotic to the interests of the community in preserving antibiotic effectiveness would be viewed as a terrible "incursion on liberty" by such supporters. The same measure would more likely "resonate with supporters of communitarian conceptions of government, who

---

tests to determine if an infection is bacterial, and if so, whether the bug is resistant to any antibiotics."). Kades notes that while there are some "new [diagnostic] tests on the horizon that yield results much more rapidly," "such progress...appears to be the exception rather than the rule." *Id.* at 639.

[134] *See id.* at 627 (discussing problems of remedying externalities associated with antibiotic use).

[135] Rubin, *supra* note 69, at 35 (though, Rubin characterizes this as a private cost, not an externality).

[136] Sage and Hyman, *supra* note 1, at 791-92.

[137] *Id.* at 796.

view the proper regulation of common resource pools as a politically important commitment, as well as one that produces a long-term efficiency gain."[138]

Balancing Act. The public health externality and the resistance externality are squarely at odds with each other. The former suggests that antibiotics should be subsidized, while the latter suggests that antibiotics should be taxed.[139] To reconcile these competing propositions, we would have to undertake a comprehensive netting analysis to determine which externality effect is more powerful, and by how much. It seems, though, that an effective antibiotic usage policy need not be so unvarying that it could not distinguish between circumstances where different externalities may dominate. For example, there may be some situations in which the immediate public health externality outweighs a future resistance externality.[140] It thus seems that an optimal antibiotic usage policy would want to encourage the drug's use in cases where the public health benefits are high and the resistance externalities are low and, conversely, to discourage use when the resistance externalities are high and the public health externalities are low (such as when the patient has a virus, not a bacterial infection).[141] I submit that there are ways to distinguish between these circumstances and tailor the market prices accordingly.[142]

Antibiotic usage, however, constitutes only a portion of the larger policy question concerning antibiotic resistance. It would thus be a mistake to conflate the externality discussion with the decline in research and development discussion: externalities suggest that consumers are

---

[138] *Id.*

[139] I use the word "tax" not in the formal sense of the term, but only to suggest that the prevailing market price of antibiotics is too low and should be increased in order to take into account the effects of the negative resistance externality. Imposing a tax is one classic way to address activities associated with negative externalities. *See* Kades, *supra* note 2, at 638 (discussing Pigovian taxation in the context of antibiotics).

[140] Such an example might occur when there is high potential for an infectious disease outbreak and the risk of resistance is low.

[141] *See* Kades, *supra* note 2, at 628 ("[A]ny solution must somehow discourage some present low-value use to preserve the potency of antibiotics for future high-value use.").

[142] *See infra* notes 194-202 and accompanying text for a discussion on price discrimination as a method to tailor market prices.

being mispriced in the market, while the R&D question suggests that pharmaceutical companies lack the financial incentives to invest in antibiotic programs at a socially optimal level. Both explain why we have suboptimal outcomes in the antibiotic market, but each has a different temporal focus. The R&D issue concerns the suboptimal incentives for the producer, while the externality issue concerns the suboptimal incentives for the patient-user. While these two questions are obviously related, they require distinct policy treatment.[143] Many scholars advocate that a comprehensive antibiotic policy should "disassociate" the financial incentives for pharmaceutical companies to engage in research and development from the market signals conveyed to consumers.[144] In agreement, this paper argues that antibiotic resistance should be addressed by separately considering the financial incentives to engage in antibiotic innovation from the market-based incentives to prescribe or consume antibiotics.

IV. SHAPING AN EFFECTIVE ANTIBIOTIC RESISTANCE POLICY

Developing an effective antibiotic resistance policy is complicated because many of the policy levers to achieve this goal work at cross purposes. Conservation is necessary to reduce resistance, but conservation also reduces the incentives to engage in antibiotic innovation by lowering the net present value of the market. Moreover, the more we prolong the effectiveness of one antibiotic, the less we incentivize pharmaceutical companies to develop replacement drugs.[145] In a perfect market, resistance, conservation and innovation would all exist in equilibrium, and we would continually have a sufficient supply of new antibiotics to treat

[143] They are related in the sense that a pharmaceutical company's decision to enter the antibiotic space will depend on the demand they expect from consumers (i.e., patients and doctors).
[144] *See* Amy Kapczynski, *Commentary: Innovation Policy for a New Era*, 37 J.L. MED. & ETHICS 264, 265 (2009); James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV., 1519, 1528 (2007) (in the context of advocating a prize-based system to stimulate investments rather than a patent-based system).
[145] *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 642-43.

pathogens that developed resistance to older drugs. This is not, unfortunately, an accurate description of our current world.

In order to overcome the problem of antibiotic resistance, we need both conservation and innovation. The debate right now seems to take a "winner takes all approach," with one side arguing that because innovation has not worked, we need to emphasize conservation, and the other side arguing the reverse.[146] This paper argues that both conservation and innovation are necessary to deal with the growing rate of antibiotic resistance; and, if conservation has the effect of reducing incentives to innovate, then we need to compensate for that reduction and incentivize pharmaceutical companies even more than we would have without that dampening effect. The remainder of this section reviews the current policy options to achieve the twin goals of encouraging antibiotic innovation and discouraging inappropriate antibiotic usage and suggests those that appear most promising.

A. Developing Incentives for Optimal Antibiotic Innovation

Traditionally, the government has employed intellectual property law to stimulate the research and development of new drugs through the patent system, which grants pharmaceutical companies a temporary monopoly over their discovery through exclusive marketing rights.[147] Many scholars recognize that the current patent system is not sufficiently promoting optimal levels of investment in antibiotic research and development programs, but they vary dramatically

[146] *Compare* Gould, *supra* note 25, at S4 (arguing that because financial incentives have not yet worked, "we have no alternative but to use antibiotics more wisely") *and* Spellberg, *Antibiotic Resistance and Antibiotic Development*, 8 LANCET INFECTIOUS DISEASES 211, 211 (2008) (arguing that certain other authors "favor antibiotic preservation efforts in lieu of creating incentives for antibiotic development.") *with* Kades, *supra* note 2, at 661 ("[I]t appears that the only way to 'escape' from the exhaustibility of antibiotics is to invent new ones continually.").

[147] As Kades notes, "[t]he usual justification for rewarding inventors with monopoly rights, called patents, is 'a practical utilitarianism: reward the creator of a useful thing, and society will get more useful things...this mode of thought...is the core of all patent systems.'" Kades, *supra* note 2, at 644 (quoting ROBERT P. MERGES & JOHN F. DUFFY, PATENT LAW & POLICY: CASES & MATERIALS 2 (3d ed. 2002)).

in terms of their suggested approaches.[148] The main debate is between those who advocate for increased patent protection to stimulate antibiotic innovation and those who advocate for abandoning the patent system entirely in favor of a cash-based prize system.[149]

Wild Card Patent Extensions. Those scholars who favor continued reliance on the patent system to increase innovation incentives often support the use of wild-card patent extensions to spur research and development. A wild-card patent extension "is the name commonly attributed to the idea that a pharmaceutical company that introduces a new and effective antibiotic on the market should be allowed to get an extension on its patent-rights for one of its other products."[150] The IDSA recommended that Congress enact legislation to establish such a system, whereby any pharmaceutical company that receives FDA approval for an antibiotic that targets a high priority pathogen receive a patent extension of six months to two years on any drug that it sells.[151]

Supporters of this idea argue that it will provide the necessary incentives for pharmaceutical companies to engage in antibiotic research programs because it dramatically increases the profitability of developing a successful antibiotic, and it does so through the market without "requiring upfront public financing."[152] They also argue that despite the increased costs

---

[148] The range of measures designed to make antibiotic R&D more attractive to pharmaceutical companies include "wildcard patent extensions, patent extensions, advance-market commitments, cash prizes, increased funding for public antimicrobial research and various sorts of tax credits...." Jorn Sonderholm, *Wild-Card Patent Extensions as a Means to Incentive Research and Development of Antibiotics*, 37 J.L. MED. & ETHICS 240, 240 (2009).

[149] *Compare id.* at 241-44 *and* Spellberg et. al., *Societal Costs versus Savings from Wild-Card Patent Extension Legislation to Spur Critically Needed Antibiotic Development*, 35 INFECTION 167, 171-72 (2007) [hereinafter Spellberg et. al., *Societal Costs versus Savings*] (both advocating for wild-card patent extensions) *with* Kapczynski, *supra* note 144 *and* Outterson et. al., *Antimicrobial Patents*, *supra* note 61, at 562 (both rejecting wild-card patents as an effective way to incentivize R&D).

[150] Sonderholm, *supra* note 148, at 241.

[151] BAD BUGS, *supra* note 11, at 24; *see also* Spellberg et. al., *Societal Costs versus Savings*, *supra* note 149, at 167-68. Some scholars even advocate for a system of tradable wild-card extensions, such that a pharmaceutical company that develops an antibiotic targeting a high priority pathogen could sell its wild-card patent extension to another firm with a more profitable drug on the market. Through this system, all pharmaceutical companies would be incentivized to engage in antibiotic research, not just those companies that have a current blockbuster drug on the market. *See* Sonderholm, *supra* note 148, at 241.

[152] Sonderholm, *supra* note 148, at 241. For example, a six-month extension of Pfizer's blockbuster drug Lipitor would have resulted in protected sales of an additional $3.1 billion if sales remained constant throughout the patent period. *Id.* Lipitor's patent expired in 2010. *Id.*

that would result from a patent extension on a top-selling drug, the wild-card patent system would ultimately be a cost-effective measure once the savings from the costs associated with resistant infections are taken into account.[153]

In contrast, wild-card detractors take issue with many of these arguments, questioning "the fairness, efficiency, and cost-effectiveness of wildcard patents and patent extensions."[154] They argue that the costs of a wild-card system would be staggering. For example, Kevin Outterson suggests that implementing a wild-card patent scheme would "require spending in the range of $8.7 billion to $11.9 billion per delivered antimicrobial drug, greatly exceeding the industry's [current] estimates of $800 million per new molecule by an order of magnitude."[155] They argue that these funds could be better deployed in other ways to help address the resistance problem.[156] This concern for the efficiency of the wild-card patent system is grounded in a larger concern for the efficiency of the patent system in general to stimulate optimal levels of research and development. As James Love and Tim Hubbard ask: "[H]ow much R&D do we get for the [patent] price premium?"[157] They go on to estimate that "[c]onsumers pay eight or nine dollars in higher prices to stimulate one dollar in R&D spending," arguing that "the patent system (as currently implemented) is a very expensive way to stimulate R&D."[158] Further perpetuating this patent system would only serve to continue the inefficient incentivizing of research programs, and it would unfairly do so at the expense of those patients who are in need of the blockbuster drug that would now continue to sell at monopoly prices via the wild-card

---

[153] *See* Spellberg et. al., *Societal Costs versus Savings*, *supra* note 149, at 170 (arguing that a wild-card patent extension program would take 10 years after approval of a qualifying antibiotic to become cost-neutral).
[154] Kevin Outterson, *Author's Reply*, 8 LANCET INFECTIOUS DISEASES 212, 212 (2008) [hereinafter Outterson, *Reply*].
[155] Outterson et. al., *Antimicrobial Patents*, *supra* note 61, at 561.
[156] Outterson, *Reply*, *supra* note 154, at 212-13.
[157] Love & Hubbard, *supra* note 144, at 1523.
[158] *Id.*

extension.[159] Perhaps more fundamentally, those who reject the use of wild-card patents argue that the system is not necessarily a logical one. To that end, Amy Kapczynski notes that wild-card patent supporters do not provide a rational explanation as to why the "right measure of reward" for antibiotic innovation is "the market for a term extension for Lipitor," "rather than, for example, the market for a term extension for a software patent or a copyright in a film[.]"[160] Rather, these scholars advocate approaches that are more transparent and linked to antibiotic demand itself, either through direct financing from the government,[161] prize systems,[162] or through raising the prices of antibiotics themselves.[163]

Patent Extensions. Another patent-related proposal to incentivize antibiotic research and development is to extend the patent life of a qualifying antimicrobial drug.[164] Patent extensions of this sort are already available for pediatric drugs and orphan drugs.[165] For example, the Best Pharmaceuticals for Children Act[166] provides an additional six months of market exclusivity for qualifying drugs, along with priority review status with the FDA for pediatric supplements to a drug application.[167] The Orphan Drug Act[168] provides similar incentives to develop drugs that lack a large consumer demand, including an additional seven years of market exclusivity, tax

[159] Outterson et. al., *Antimicrobial Patents*, *supra* note 61, at 562. He argues that "[w]ildcard patents are essentially a hidden tax on heart disease, depression, and other common ailments to fund antimicrobial research and development." *Id.* (citations omitted). Outterson further suggests that "[d]irect financing would be more transparent and efficient, especially since the projected cost per drug exceeds the industry's average research and development costs by a factor of ten or more." *Id.*
[160] Kapczynski, *supra* note 144, at 265.
[161] *See* Schulman, *supra* note 14, at 255.
[162] *See generally* Love & Hubbard, *supra* note 144; Kapczynski, *supra* note 144.
[163] For instance, Kevin Outterson recommends that we rely on market forces, noting that the market can tolerate increased prices for antibiotics to such an extent that pharmaceutical companies will be incentivized to re-engage in R&D. He argues that this be done principally through reimbursement rates and increased prices for antibiotic treatments. *See* Outterson, *Reply*, *supra* note 154, at 213.
[164] *See* BAD BUGS, *supra* note 11, at 24.
[165] Orphan diseases or conditions are those that "affect fewer than 200,000 individuals in the United States," or diseases or conditions that "provide no reasonable expectation that the sales of the drug will recover the costs of development." *Id.* at 23.
[166] Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in various sections of 21 U.S.C. and 42 U.S.C.).
[167] *See* BAD BUGS, *supra* note 11, at 23.
[168] Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. § 360aa-ee (1998)).

incentives of up to fifty percent for clinical research, and research grants.[169] Supporters of this approach also argue that extending the patent term will provide the additional benefit of promoting antibiotic stewardship, as the pharmaceutical company will feel less compelled to engage in wasteful marketing of the drug during the early years of the patent term.[170]

Those who disagree with proposals to extend the life of the antibiotic patent in order to stimulate R&D investment argue that longer patent terms are a "financially inefficient...innovation mechanism."[171] They employ arguments similar to those used in the wild-card patent context to cast doubt on the patent system's ability to efficiently incentivize R&D. They point out that only 17.5% of the incremental revenue a company receives through patent rents (or the higher prices a company is able to charge during the patent term) is directed towards research and development. Given current revenue figures, Kevin Outterson argues that patent extensions would only result in $910 million in additional R&D, a figure that industry estimates suggest would only produce "one new antimicrobial drug...developed per year, after a delay of more than a decade" spent in research, development and clinical testing.[172]

---

[169] *See* BAD BUGS, *supra* note 11, at 23.

[170] Eric Kades is one of the more extreme proponents of this position. He argues that an unlimited patent term would be socially optimal for antibiotic conservation, because otherwise a limited-term patent holder of an exhaustible resource would deplete the entire supply of that resource. Kades, *supra* note 2, at 651. He argues that a risk-averse society would prefer "an exhaustible resource monopoly without any time constraint" in order to "stretch out the useful life of the resource" and accept the higher prices associated with an unlimited patent term. *Id.* at 652.

Kevin Outterson takes issue with many of Kades' arguments, instead proposing that patent terms are an ineffective way to address antibiotic conservation. First, Outterson notes that bacteria do not develop exclusive resistance to a particular patented antibiotic, but rather to the class of antibiotics of which that drug is a part. *See* Outterson, *Vanishing Public Domain*, *supra* note 18, at 94 ("[T]he biology of resistance pays no attention to...patent doctrines...Resistance may develop against a particular mode of action rather than to a specific patented molecule."). For a patent-based conservation strategy to be at all workable, there would need to be coordination among all of the patent-holders and generic producers within a class. To do this, competition laws would need to be relaxed to permit this type of cooperation, or the patent system itself would need to be overhauled such that patents were granted on a class-wide basis. There are a host of problems associated with these approaches, and it would be unclear whether they would actually produce optimal conservation results. *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 671-73.

[171] Outterson et. al., *Antimicrobial Patents*, *supra* note 61, at 562.

[172] *Id.*

Another criticism of using patent extensions to promote innovation concerns the relatively marginal effect that a patent extension has on the antibiotic's net present value, a figure which is comprised of the discounted value of the drug's projected future revenue streams. The more distant in the future a revenue stream is, the less it is valued at "time zero," or the time at which the pharmaceutical company has to decide whether to invest in developing an antibiotic as opposed to another type of drug. The prospect of additional revenue streams in twenty years (i.e., the effect of a patent extension) will do little to incentivize the pharmaceutical company to act at the crucial moment when they are deciding how to allocate their R&D resources.[173] As Kevin Outterson explains, "for a best-selling antibiotic, even a substantial extension to the patent term would increase the net present value of cash flows by a modest amount."[174]

Prize Systems. Advocates of prize systems offer an alternative approach to the patent system as a means to stimulate investment in pharmaceutical research and development. James Love and Tim Hubbard aptly explain this view:

> The current [patent-based] system of financing research and development...for new medicines is deeply flawed by the impact of high prices on access to medicine, the wasteful spending on marketing and R&D for medically unimportant products, and the lack of investment in areas of greatest public interest and need.[175]

They argue that prizes remedy these pitfalls associated with our reliance on patent systems to generate research and development. Instead of granting pharmaceutical companies temporary monopolies over their drug discoveries, under a prize system the government would award

---

[173] Assume an antibiotic has $200 million in annual revenues during the patent term. This is a reasonable assumption, given that vancomycin had $203.7 million in sales in 2007 and $232.8 million in 2008. *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 662. Given a 5% discount rate, a cash flow of $200 million in Year 21 would only be worth $71,790 today. This amount is not going to increase the profitability profile of antibiotics such that it becomes equivalent to the other potential blockbuster drugs in which the pharmaceutical company could choose to invest. Wild-card patent systems seem to address this concern, but also come with their own criticisms. My calculation was performed with Microsoft Excel. Any errors are my own.

[174] *Id.* at 645.

[175] Love & Hubbard, *supra* note 144, at 1520.

innovators with a large monetary payment that would be "tied to the actual impact of the invention on the improvements in health care outcomes...."[176] Pharmaceutical companies would take the cash prizes in exchange for the ability to charge monopoly prices; the new drugs would then immediately enter the public domain at cost pricing.[177] Although prize systems have often been suggested in the context of trying to improve the development of drugs to combat diseases that mainly afflict poor populations (and thus those drugs that would be overlooked by companies relying on monopoly pricing to generate returns),[178] there has been an increased amount of attention on prizes as a viable policy option to reform the business model for the way we create medicine in this country.[179] Prizes de-link the innovation incentive of payment from the market signal of pricing. Thus, companies would be incentivized to pursue those drugs that are the most medically important as determined by the size of the potential prize,[180] rather than those drugs with the largest market potential, such as me-too drugs following on the heels of blockbuster medications that may have a large market demand but do little to advance medically important objectives. The use of prize systems thus has particular resonance in the antibiotic space, as the commercial market for antibiotics is not profitable enough to independently

[176] *Id.*
[177] *See* Kades, *supra* note 2, at 646.
[178] *See generally* Love & Hubbard, *supra* note 144, at 1527.
[179] See *id.* at 1521 n.2 and citations therein for a complete list of scholarship. Prizes are often suggested as a superior way to incentivize the production of "knowledge goods," which are costly to create and "non-rival" in use. *Id.* at 1528. Prize systems have become a politically feasible option, as in 2005 then Representative Bernie Sanders introduced in the 109th Congress H.R. 417 – a piece of legislation entitled the Medical Innovation Prize Fund Act – which proposed supplementing our current patent system with a prize system. See *id.* at 1532-34, for further discussion on the mechanics of this particular piece of legislation. As William Sage and David Hyman note, the Food and Drug Administration Amendments Act of 2007 offers a non-monetary prize of tradable "'priority review vouchers' for expedited FDA review of unrelated products [to] companies that develop therapies for neglected (less profitable) diseases." Sage & Hyman, *supra* note 1, at 810-11.
[180] The standard by which the medical importance of a given drug is determined would be set by the operator of the prize fund – namely the government. Some examples include tying the prize reward to the drug's impact on an individual's quality adjusted life years. *See* Love & Hubbard, *supra* note 144, at 1531.

incentivize pharmaceutical companies to engage in optimal levels of research and development.[181]

The main drawback of a prize-system approach is its complete sidestepping of the market to determine the value of medical innovation. As Amy Kapczynski notes, "the ability to disassociate incentives from the market is both the promise and the peril of a prize scheme."[182] Many are reluctant to "abandon a system of prices determined by actual market transactions as the method of determining the value of a knowledge good" in favor of a system of prices set by the government.[183] Other critics of prize funds in the specific context of antibiotics argue that cost-based pricing of antibacterial drugs will lead to excessive use, which will in turn speed up resistance rates.[184] Also, given the current budget climate in Washington D.C., it seems that there is little political will to increase the federal budget to create the prize fund.[185]

Recommendations. After much consideration, this author believes that we need a more nuanced set of policies to incentivize antibiotic innovation than an exclusive reliance on the patent system, which in operation works to be a relatively blunt mechanism to achieve the specific goal of increasing investment of antibiotic research and development. To encourage investment in antibiotic development, we should offer pharmaceutical companies monetary incentives that they can take advantage of in the near term, as opposed to patent extensions in the

[181] See *supra* Part III.A for further discussion.
[182] Kapczynski, *supra* note 144, at 265.
[183] Love & Hubbard, *supra* note 144, at 1528. Proponents of prize systems offer several responses to this criticism, as there has been much literature on the appropriate design of prize funds. For instance, Michael Kremer proposed a patent buyout system to purchase patent rights based on values set by an auction. *See* Michael Kremer, *Patent Buyouts: A Mechanism for Encouraging Innovation*, 113 Q.J. ECON. 1137 (1998). For further analysis on patent design systems, see generally Michael Abramowicz, *Perfecting Patent Prizes*, 56 VAND. L. REV. 115 (2003).
[184] *See* Kades, *supra* note 2, at 646-47 (noting that because antibiotics are an exhaustible resource, "[p]rices in excess of cost, though perhaps not as high as monopoly prices, are positively desirable.").
[185] The size of the fund would not be insubstantial; H.R. 417 initially proposed a prize budget set at 0.5 percent of United States GDP. *See* Love & Hubbard, *supra* note 144, at 1532. Although Senator Sanders re-introduced a version of H.R. 417 in the Senate in 2007, no further progress seems to have been made on the bill.

form of continued marketing exclusivity that will not take effect for another twenty years.[186] These monetary incentives should be related to the value the medical community places on developing new antibiotics, as opposed to wild-card patent extensions whose price tag could vary dramatically depending on which top-selling drug the pharmaceutical company elects to be extended. As Amy Kapczynski appropriately notes, "[i]t is easy to see why [wild-card patents] would be attractive to leading pharmaceutical companies, but far less clear why it makes sense from the perspective of innovation economics."[187]

Examples of such near-term monetary incentives could include tax credits for research and development, or perhaps more importantly, direct funding from the government with levels tied to certain research programs. This funding could take the form of prizes, direct government grants, government funding of clinical trials for promising candidate antibiotics, or, more aggressively, a government buyout of the patent itself.[188] Given that the complete dismantling of the patent system seems like a political unlikelihood, we should find ways to work within the current framework to incentivize antibiotic innovation. Examples of working within our current patent framework could include providing a guaranteed market (or advance purchase commitments) by the government or offering higher reimbursement rates by insurance companies.[189]

---

[186] As many other commentators have noted, the task of antibiotic research and development should be left to large pharmaceutical companies, rather than the government or smaller biotechnology companies. Although the government is often engaged in basic research, it is a "relatively inefficient drug developer and marketer." Kades, *supra* note 2, at 654. It is notable that "'no government has successfully discovered and developed an antibiotic, and it is unlikely that any public body would have the resources or technical ability to do this.'" Sonderholm, *supra* note 148, at 241 (citation omitted).

[187] Kapczynski, *supra* note 144, at 265.

[188] *See id.* at 266; Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 677 (discussing the possibility of government buyout or the development of a Strategic Antibiotic Reserve).

[189] *See* Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 645-55 (discussing the use of insurance reimbursement as a policy lever).

Antibiotics present a special challenge because we need to incentivize innovation at the same time that we want to incentivize delayed usage of newly developed drugs in order to preserve their effectiveness. Accordingly, the signals for innovation and the signals for market use should be de-linked in order to achieve an optimal antibiotic resistance policy.[190] The following section thus briefly explores this second set of policy considerations – namely, how to encourage appropriate antibiotic usage and conservation through such market signals.

B. Developing Incentives for Optimal Antibiotic Usage

Conservation (i.e., regulating antibiotic usage) is a necessary approach to achieve an overall reduction in antibiotic resistance, especially since we cannot guarantee the efficacy of and speed at which new antibiotics are developed pursuant to increased investments in antimicrobial research and development.[191] Industry estimates suggest that it takes nearly ten years for a new drug to reach the market from its day of discovery, which means that even if the new financial incentives to increase antibiotic R&D expenditure were put into effect today, we would likely have to wait until 2021 for a new drug to be available.[192] In the interim, conservation has to be a key approach in the effort to preserve antibiotic effectiveness. There is already an extensive legal and medical literature on the topic of antibiotic conservation; this paper does not seek to summarize all of the potential policy options here.[193] Rather, this section will review the use a market-based strategy to alter consumer use of antibiotics.

Price Discrimination. Antibiotics are both too cheap and too expensive, depending on the patient at issue. If the negative resistance externality outweighs the individual benefit and

---

[190] This is advocated by prize system proponents. I offer it not to justify prize systems per se, but to show that incentivizing innovation through market pricing does not make sense when you want the market and innovation to act in ways that are at odds with each other.

[191] See *supra* notes 89-99 and accompanying text for discussion of the potential difficulties of finding new and effective antibiotics.

[192] *See* BAD BUGS, *supra* note 11, at 3.

[193] *See generally* Gould, *supra* note 25; MacDougall & Polk, *supra* note 4; Sage & Hyman, *supra* note 1, at 799-822.

positive public health externality from the use of the antibiotic, then that antibiotic is priced too cheaply for that particular patient; she will thus engage in excessive antibiotic use because she is not required to pay the full cost of treatment. Conversely, when the reverse situation holds with a presented patient, then that same antibiotic would be priced too high. This author believes that the medical industry should be able to discriminate between these two users in price to make each bear her true cost of taking the course of antibiotic treatment.

Commentators have acknowledged that market prices do have the ability to affect patient behavior. Namely, a patient is more likely to engage in overuse or misuse of antibiotics if the drug costs less than the benefit (physical or psychological) they receive from obtaining the prescription.[194] As William Sage and David Hyman describe:

> [M]aking healthcare more affordable might actually increase antibiotic overuse. Stated bluntly, a patient who receives an "unnecessary" prescription for an antibiotic is more likely to have it filled if it costs $4 at Wal-Mart (or is free at a Giant supermarket) than if it costs $25 at the local drugstore.[195]

Many in the medical community have expressed concern over reduced-price antibiotic prescription programs for this reason.[196]

What would price discrimination look like in the antibiotic market? The traditional account of price discrimination provides that a firm maximizes gains from trade with its customers when it is able to price its product according to each customer's willingness to pay (i.e., according to where the customer falls on the demand curve).[197] Thus, price is based on how much the individual values the product at issue. Eric Kades offers that price discrimination as applied to antibiotics would entail a patent holder charging lower prices for low-value uses of its

---

[194] *See* Sage & Hyman, *supra* note 1, at 805-06 (noting that consumers may misperceive risks).
[195] *Id.* at 805.
[196] *See* Alliance for Prudent Use of Antibiotics Consumer Fact Sheet on Free or Discounted Antibiotic Promotions (Feb. 9, 2009), http://www.tufts.edu/med/apua/Patients/consumerfactsheetfreeantibiotics2-09-09.pdf.
[197] *See* Kades, *supra* note 2, at 647 (usually price discrimination is discussed in the context of monopoly firms).

drug (e.g., mild infections treatable by many antibiotics) and higher prices for high-value uses of the drug (e.g., serious infections only susceptible to the patent holder's antibiotic).[198] This proposal tracks the traditional account's emphasis on pricing the product according to the individual's willingness to pay for it.

This author, however, believes that if preservation of antibiotic effectiveness is the end-goal, the critical measure should not be the individual's subjective willingness to pay, but the individual's objective need for the drug, adjusted to take into account the positive public health externality and negative resistance externality.[199] This model would suggest an opposite outcome from the one Kades predicted: low-value uses of antibiotics, as measured by an objective test, should cost more, and high-value uses of antibiotics should cost less.[200] Such a paradigm makes sense if the goal is to discourage unnecessary or low-value antibiotic use and encourage (or at least remain neutral to) necessary or high-value use.[201] Admittedly, determining between these two types of uses would be a difficult task, and enforcement might prove to be an issue as well. These challenges, although real, should not deter policymakers from devising a market-signal approach to antibiotic conservation based on directing consumer behavior towards only those socially valuable uses of antibiotics.[202]

---

[198] *Id.*

[199] For example, the price of the antibiotic could vary depending on whether the prescribing doctors performed tests to determine whether the infection was bacterial or viral or whether the prescribing doctor believes that the infection will clear up on its own without the use of antibiotics. Similarly, broad-spectrum antibiotics could be more expensive if tests were not done to assess whether the infection is susceptible to a narrow-spectrum drug. *See* Sage & Hyman, *supra* note 1, at 805-06 (discussing the problem of overprescribing "big-gun" broad-spectrum antibiotics).

[200] This is consistent with a strategy to impose a Pigovian tax on antibiotic use when it is associated with negative externalities. *See* Sage & Hyman, *supra* note 1, at 806-07.

[201] *Cf.* Schulman, *supra* note 14, at 237 ("If a pharmaceutical company developed an antibiotic that was effective against [high-priority resistant bacteria], it would be most beneficial from a public health perspective to 'save' the antibiotic for these infections and not to use it on bacteria that can be effectively treated by other antibiotics.").

[202] Commentators have noted problems with relying on market signals in the pharmaceutical market, largely because of the presence of market intermediaries, such as health insurance companies or hospitals, which bear the brunt of the cost; the individual patient bears only a small portion of the actual cost of the product. *See id.* at 805; see also Outterson, *Legal Ecology of Resistance*, *supra* note 28, at 645-55, for an interesting discussion on the role of

CONCLUSION

Antibiotic resistance poses a serious threat to public health. In order to properly counter such resistance, we need to financially incentivize development of antibiotics and to use the drugs we currently have in a more rationed manner. Because conservation and antibiotic production work at cross-purposes, it is essential to understand how they interact in order to develop appropriate resistance-reduction strategies. Given the current standoff in Congress over the fiscal budget, it does not seem likely that the government will be able to fund antibiotic programs without the assistance of the private market. Thus, we need to re-enlist the major pharmaceutical companies into the antibiotic space by providing them with the promise of a sufficient monetary reward for successful new therapies. Moreover, the implementation of a market-signal based conservation program would be a step towards altering consumer behavior to more accurately reflect the true cost of antibiotic usage.

---

insurance reimbursement as an important policy lever. I do not argue with these observations; rather, I would try to work within the ways that consumers (and doctors) are charged for antibiotic use to raise or reduce the costs they face.