The Problem with Pathogen-Selective Antibiotics

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In the battle with bacteria, humanity is outnumbered and outgunned. The ability of bacteria to quickly evolve and share antibiotic resistance strategies, combined with humanity's indiscriminate use of broad-spectrum antibiotics, has created a terrifying antibiotic resistance crisis: soon, even a simple scrape or a routine medical procedure may become life-threatening. Hope may lie in pathogen-selective antibiotics. That is, if we design "magic bullet" drugs that each target only one bacterial species, we can avoid the problems of cross-resistance and antibiotic overuse that have led to the

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current crisis. But that is difficult, both scientifically and economically. Current antibiotic incentives focus on antibiotics as a broad monolith and in general, inadequately incentivize the development of one-bug-per-drug therapies.

Here I identify two important respects in which pathogen-selective, "one-bug-per-drug," antibiotics differ from traditional, broad-spectrum drugs: conditional spillover benefits, and network-dependent social utility. These characteristics must be considered if we are to incentivize development of a pathogen-selective arsenal. Accordingly, I suggest that a comprehensive prize or bounty framework, targeted research grants, coupled or tolled exclusivity, or revised clinical trial standards may be useful tailored solutions. Last, I suggest that it might be more generally useful, in innovation scholarship, to think generally about incentive frameworks, not in terms of disease or symptom, but rather in terms of the contextual relationship between the drug, the doctor, the disease, and society.

I. Introduction

In 1906, only shortly after the acceptance of germ theory, German physician-scientist Paul Ehrlich articulated the idea of the "magic bullet."[1] Ehrlich had noticed that certain chemical dyes would accumulate selectively on certain kinds of cells.[2] This was, and still is, a useful laboratory technique for staining cells for microscopy.[3] But Ehrlich drew further inspiration. He envisioned the development of chemicals that would "seek out and specifically destroy invading microbes or tumor cells."[4] This idea—killing the infection and leaving other cells intact—was the magic bullet.[5] Ehrlich's insight led to the development of the first chemical treatment for syphilis.[6] And although most antibacterial drugs are not truly "magic bullets"—most of them kill *lots* of bacteria, friend or foe—the concept of chemotherapy,[7] which grew from the magic bullet concept, revolutionized medicine and ushered in the modern age of drug development.[8] For a while, it looked like we had beaten infectious disease,[9] and

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1 *Paul Ehrlich*, SCI. HIST. INST., https://www.sciencehistory.org/historical-profile/paul-ehrlich (last updated Dec. 5, 2017). *See generally* Klaus Strebhardt & Axel Ullrich, *Paul Ehrlich's Magic Bullet Concept: 100 Years of Progress*, 8 NATURE REVS. CANCER 473 (2008) (explaining the history of the "magic bullet"), and Robert S. Schwartz, *Paul Ehrlich's Magic Bullets*, 350 NEW ENG. J. MED. 1079 (2004) (describing the history of the "magic bullet").

2 Strebhardt & Ullrich, *supra* note 1 at 473.

3 *See id.* (describing the origins of chemotherapy to Ehrlich's staining techniques).

4 Schwartz, *supra* note 1, at 1079.

5 *Id.* at 1079.

6 *Id.* at 1080.

7 "Chemotherapy" is the use of chemical agents to treat disease generally and is not limited to cancer.

8 Strebhardt & Ullrich, *supra* note 1, at 473

9 Michael Specter, *The Risks of Viral Research*, NEW YORKER, (Dec. 26, 2014), https://www.newyorker.com/news/daily-comment/risks-viral-research (recounting the commonly shared account of the Surgeon General, in 1967, publicly declaring that "[i]t's time to close the books on infectious diseases [and] declare the war against pestilence won"); *but see* Michael Specter, *One of Science's Most Famous Quotes is False*, NEW YORKER (Jan. 5, 2015), https://www.newyorker.com/tech/annals-of-technology/william-stewart-science-erroneous-quote (noting in retrospect that the quote is almost certainly apocryphal).

the so-called Golden Age of antibiotic discovery began.[10]

But today, we have a terrifying antibiotic resistance crisis.[11] Recent news reports describe "nightmare bacteria."[12] In the United States alone, antibiotic-resistant bacteria account for two million infections annually, and at least 23,000 deaths, to the tune of $3–4 billion in added health care costs.[13] The corresponding toll in Europe is 25,000 deaths per year.[14] The problem impacts both high-income and low-income countries.[15] And it is worsening; by 2050, it is estimated, the toll is likely to be ten million annual deaths.[16]

To make matters worse, the crisis is of our own making, spurred by the kinds of drugs we use and the ways we use them.[17] Antibiotics tend to be broad-spectrum in their activity, targeting essential biological features shared by most bacteria.[18] This both wreaks collateral damage on our healthy gut microbiome and increases the spread of antibiotic resistance.[19] Resistance shows up surprisingly fast to new drugs:[20] clinically problematic resistance is typically observed within years and sometimes, even by the time the drug hits the market.[21] As for the harms of collateral damage, take, for instance, *Clostridium difficile*—an opportunistic pathogen most prevalent in patients whose gut microbiome has been weakened by the collateral damage induced by the administration of broad-spectrum antibiotics.[22] *C. difficile* infection and death

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10 Kate Gould, *Antibiotics: From Prehistory to the Present Day*, 71 J. ANTIMICROBIAL CHEMOTHERAPY 572, 573–75 (2016).

11 *See generally* Kathy Talkington et al., *The World is Running out of Antibiotics*, PEW CHARITABLE TRS. (Dec. 21, 2017), http://www.pewtrusts.org/en/research-and-analysis/analysis/2017/12/21/the-world-is-running-out-of-antibiotics (describing the emergence of "hard-to-treat bacteria" and the lack of new antibiotics to treat "drug-resistant bacterial infections").

12 Richard Harris, *Federal Efforts to Control Rare and Deadly Bacteria Working*, NPR (Apr. 3, 2018), https://www.npr.org/sections/health-shots/2018/04/03/599194350/federal-efforts-to-control-rare-and-deadly-bacteria-working (acknowledging "nightmare bacteria," where "[a]s many as half of patients with these infections die").

13 Evan Martens & Arnold L. Demain, *The Antibiotic Resistance Crisis, with a Focus on the United States*, 70 J. ANTIBIOTICS 520, 520–21 (2017).

14 *Id.* at 521.

15 *High Levels of Antibiotic Resistance Found Worldwide, New Data Shows*, WORLD HEALTH ORG. (Jan. 29, 2018), http://www.who.int/mediacentre/news/releases/2018/antibiotic-resistance-found/en/.

16 *Antibiotic Resistance: A Surprising Timeline*, INSTITUT PASTEUR (Nov. 30, 2017), https://www.pasteur.fr/en/press-area/press-documents/antibiotic-resistance-surprising-timeline.

17 *See generally* Eric D. Brown & Gerard D. Wright, *Antibacterial Drug Discovery in the Resistance Era*, 529 NATURE 336 (2016) (discussing the hurdles of modern antibacterial drug discovery); Martens & Demain, *supra* note 13, at 521–22.

18 Brown & Wright, *supra* note 17, at 342.

19 Martens & Demain, *supra* note 13, at 521, 525.

20 Oliver Denis et al., *The Problem of Resistance*, *in* ANTIBIOTIC AND CHEMOTHERAPY 24, 44 (Roger G. Finch et al. eds., 9th ed. 2010) ("Whatever the origins of resistance genes, there has clearly been a major increase in their prevalence during the past 60 years. This can be closely correlated with the use of antibiotics in humans and animals, and it is clear that resistance has eventually emerged to each new agent.").

21 *E.g.*, *About Antimicrobial Resistance*, CDC, https://www.cdc.gov/drugresistance/about.html (last updated Sept. 19, 2017).

22 Martens & Demain, *supra* note 13, at 521.

rates have increased by 400% from 2000 to 2013.[23]

What hope is there? Maybe we can actualize Ehrlich's "magic bullet" after all. Population-wide antibiotic resistance is driven largely by overuse, cross-resistance between drugs, and resistance transfer between bacterial species. Exceptionally *narrow*-spectrum antibiotics—i.e., pathogen-selective antibiotics—can avoid these problems by use in small populations, diversification of drug targets, and lack of inter-species resistance transfer. In short, the social value of an arsenal of pathogen-selective antibiotics is huge. But that arsenal is not here. Indeed, efforts to incentivize antibiotic development have seemingly ignored this option and have essentially treated all potential new antibiotics alike.

In this Note, I argue that antibiotics are *not* monolithic in their response to economic incentives and that pathogen-selective antibiotics exhibit certain economic features that compel development of a different set of incentives. In Part I, I briefly overview the history and nature of the antibiotic crisis. In Part II, I introduce the idea of pathogen-selective antibiotics and some of the practical obstacles to their development. In Part III, in considering why current antibiotic incentives don't work, I identify respects in which pathogen-selective antibiotics differ from traditional antibiotics—namely, conditional spillover benefits and network-dependent social utility. In Part IV, I propose solutions that take these differences into account and offer an observation that it might be more generally useful, in innovation scholarship, to think about incentive frameworks, not in terms of disease or symptom, but rather, in terms of the contextual relationship between the drug, the doctor, the disease, and society.

II. The Antibiotic Crisis

A. A Brief History of Antibiotics

The exploitation of antibiotics by society has been a relatively brief endeavor. Although throughout history there have been scattered examples of traditional antibacterial remedies that were, in retrospect, antibiotics, it wasn't until the 1940s that the modern idea of employing discrete chemicals to target bacteria based on biological mechanisms was employed as an earnest strategy.[24] Alexander Fleming famously discovered penicillin by serendipity in 1928 but was unable to attract enough attention to the idea to develop it into a medicine, despite its obvious public health value.[25] But, by the 1940s, advances in microbiology, chemistry, and engineering made such efforts possible.[26] The so-called Golden Age of antibiotic discovery dawned.[27]

The Golden Age saw society reaping Nature's bounty: an inordinately large percentage of antibiotics were discovered by systematically screening the extracts of

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[23] *Id.*
[24] *See generally* Gould, *supra* note 10 (describing the history of antibiotics).
[25] *See id.* at 572–73.
[26] *See id.* at 573.
[27] *See id.* at 573–75.

soil-dwelling microorganisms.[28] This strategy was immensely successful, and the 1940s–1960s saw development of almost every class of antibiotic that we use today.[29] But as drug companies began to simply find the same compounds—or those with the same mechanisms of action—again and again, it looked like the well had dried up.[30] Since then, most new antibiotics have been structural modifications of existing drugs.[31]

Indeed, new antibiotic classes have not been commercialized in many years,[32] although interest in genome mining has reinvigorated antibiotic discovery generally,[33] and several exciting new first-in-class compounds have been recently reported in the literature.[34] But resistance continues to grow apace.

As such, although antibiotic *resistance* continues to advance in bacterial populations, antibiotic *discovery* has slowed to a trickle. That is a problematic mismatch.

B. Resistance in a Nutshell

Thinking about antibiotic incentives benefits from understanding antibiotic resistance, which I review briefly here.

In simplified terms, antibiotics are molecules that kill bacteria by interfering with some important biological process(es) in the microorganism. This interaction of the antibiotic with the process is known, depending on the level of generality, as the "mechanism of action" or "mode of action."[35] All known antibiotics can be sorted

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28 *Id.* at 573.

29 Rustam I. Aminov, *A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future*, 1 FRONTIERS IN MICROBIOLOGY, Dec. 2010, art. 134, at 4.

30 *Id.* at 4; Jonathan I. Tietz & Douglas A. Mitchell, *Using Genomics for Natural Product Structure Elucidation*, 16 CURRENT TOPICS IN MEDICINAL CHEMISTRY 1645, 1645 (2016).

31 Aminov, *supra* note 29, at 3.

32 Tim Jinks, *Why is it So Difficult to Discover New Antibiotics?*, BBC (Oct. 27, 2017), http://www.bbc.com/news/health-41693229 ("No new classes of antibiotics have been invented for decades. In fact, all the antibiotics brought to the market in the past 30 years have been variations on existing drugs discovered by 1984.").

33 Tietz & Mitchell, *supra* note 30, at 1645–46.

34 *See generally*, Laura J.V. Piddock, *Teixobactin, The First of a New Class of Antibiotics Discovered by iChip Technology?*, 70 J. ANTIMICROBIAL CHEMOTHERAPY 2679 (2015) (discussing discovery of Teixobactin through genome mining); Losee L. Ling et al., *A New Antibiotic Kills Pathogens Without Detectable Resistance*, 517 NATURE 455 (2015) (discussing discovery of Teixobactin through genome mining); Bradley M. Hover et al., *Culture-Independent Discovery of the Malacidins as Calcium-Dependent Antibiotics with Activity Against Multidrug-Resistant Gram-Positive Pathogens*, 3 NATURE MICROBIOLOGY 415 (2018) (discussing discovery of Malacidins through genome mining); Wooseong Kim et al., *A New Class of Synthetic Retinoid Antibiotics Effective Against Bacterial Persisters*, 556 NATURE 103 (2018) (discussing discovery of the analogues of the synthetic retinoid CD437 through genome mining).

35 "Mode of action" connotes more of the phenotypical changes associated with a drug; "mechanism of action" refers to the drug–target interaction itself. *See, e.g.*, Vicki L. Dellarco & Karl Baetcke, Editorial, *A Risk Assessment Perspective: Application of Mode of Action and Human Relevance Frameworks to the Analysis of Rodent Tumor Data*, 86 Toxicological Sciences 1, 1 (2005) (highlighting the differences associated with "mode of action" and "mechanism of action").

into a surprisingly small group of modes of action. Indeed, these basically consist of interfering with the cell wall, the ribosome, tRNA, nucleic acids, the cell membrane, or folate synthesis.[36] This is a short list, and these are common, widespread features among bacteria.[37]

Resistance emerges from the machinery of evolution.[38] When a given bacterium encounters an antibiotic, if it does not carry a mutation conferring some way to deal with the antibiotic (drug inactivation or destruction, altering its own metabolic pathway, avoiding drug accumulation, blocking the drug from binding to its cellular target, etc.[39]), it will likely die. But some bacteria may randomly harbor a mutation that gives them a selective survival advantage. These bacteria will reproduce, and their progeny may mutate further, gradually evolving an elaborate genetic countertactic to the antibiotic.

Resistance genes may be acquired either by mutation—that is, "mutational resistance" or "spontaneous mutation"—or from another organism by the transfer of genetic information—that is, "transferable resistance" or "horizontal gene transfer" (HGT).[40] HGT may be intra- or interspecies.[41] Moreover, resistant bacterial *populations* may be transferred between host individuals of the same species (e.g., patients to patients) or different species (e.g., livestock to humans). Resistant populations also reside in the environment.[42] Thus, so-called reservoirs of resistance include soil, sludge, wastewater, hospitals, and human and animal microbiota.[43] From each of these, antibiotic resistance may spread. Indeed, "many clinically relevant resistance genes are believed to have originated from nonpathogenic bacteria, highlighting the immense potential of HGT for these pathogens in overcoming human use of antibiotics."[44] Overall, resistance is not simply a matter of evolution of the

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36 *See generally* Ian Chopra, *Modes of Action*, *in* ANTIBIOTIC AND CHEMOTHERAPY 10 (Roger G. Finch et al. eds., 9th ed. 2010) (discussing the sites of action for antibacterial agents).

37 *See* Tucker Maxson & Douglas A. Mitchell, *Targeted Treatment for Bacterial Infections: Prospects for Pathogen-Specific Antibiotics Coupled with Rapid Diagnostics*, 72 TETRAHEDRON 3609, 3613 (2016) (showing that "the targets of current antibiotics are ubiquitous in the domain bacteria.").

38 *See generally* Jose M. Munita & Cesar A. Arias, *Mechanisms of Antibiotic Resistance*, *in* VIRULENCE MECHANISMS OF BACTERIAL PATHOGENS 481 (Indira T. Kudva et al. eds., 5th ed. 2016) (discussing antibiotic resistance as part of evolutionary change).

39 *See generally* Munita & Arias, *supra* note 38; Idan Yelin & Roy Kishony, *SnapShot: Antibiotic Resistance*, 172 CELL 1136 (2018), http://dx.doi.org/10.1016/j.cell.2018.02.018 (presenting a concise visual summary).

40 *E.g.*, Munita & Arias, *supra* note 38; Erdal Toprak et al., *Evolutionary Paths to Antibiotic Resistance Under Dynamically Sustained Drug Selection*, 44 NATURE GENETICS 101, 101 (2012); Denis et al., *supra* note 20. *See generally* Alita R. Burmeister, *Horizontal Gene Transfer*, EVOLUTION, MEDICINE & PUBLIC HEALTH 193 (2015) (defining horizontal gene transfer as the movement of genetic information between organisms).

41 James R. Brown, *Ancient Horizontal Gene Transfer*, 4 NATURE REVS. GENETICS 121, 121 (2013). Indeed, HGT is possible between not only species but *domains*. *Id.*

42 Christian J.H. von Wintersdorff, *Dissemination of Antimicrobial Resistance in Microbial Ecosystems Through Horizontal Gene Transfer*, 7 FRONTIERS IN MICROBIOLOGY, Feb. 2016, art. 173, at 1, 2–3.

43 *Id.*

44 *Id.* at 3.

bacteria within the patient taking a drug, but a "global phenomenon which is related to the interplay of several factors in different ecosystems."[45]

Resistance is not costless to a bacterium, however. Harboring a resistance gene often detrimentally impacts cell function in another way, and so the conventional wisdom is that resistance genes are only maintained if necessary.[46] In the absence of an antibiotic, resistant bacteria often grow more slowly than susceptible bacteria.[47] Put another way, a bacterium that is not susceptible to an antibiotic in the first place has no evolutionary incentive to gain resistance, whether by mutation or HGT.

The phenomenon of cross-resistance is the effect of resistance to one antibiotic on the same organism's resistance to a second antibiotic.[48] This is because the same biological pathway might be implicated in the mechanism of action in each drug, whether directly or indirectly. Thus, cross-resistance is not surprising given how similar the mechanisms of action of most new antibiotics are to previous antibiotics of the same class. However, this effect may occur even between antibiotic classes.[49]

In sum, the rate of overall antibiotic resistance of a given pathogen to a given drug is affected by three rates. First, the *intraspecies, same-drug resistance rate* (Table 1, yellow)—that is, (1) the rate of resistance within one bacterial population by spontaneous mutation, coupled with (2) the rate of resistance by HGT from another bacterium of the same species that has acquired resistance to the same drug. Second,

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45 Denis et al., *supra* note 20. Specifically:

> Antibiotic use is the driving force that promotes the selection, persistence and spread of resistant organisms. The phenomenon is common to hospitals, which have seen the emergence of a range of multidrug-resistant pathogens, to the community at large, where respiratory and gut pathogens have become resistant to often freely available antibiotics, and to animal husbandry, where the use of antibiotics for growth promotion and for mass therapy has promoted resistance in *Salmonella* and *Campylobacter*, and created a reservoir . . . that can be transmitted to humans.
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> In the community, where about 80–90% of human antibiotic consumption takes place, a large proportion of antibiotics is inappropriately prescribed . . . Globalization is stimulating international circulation of goods and people, and plays a role in accelerating the dissemination of pathogens, including resistant strains. . . .
>
> The hospital, particularly the intensive care unit, is a major breeding ground for antibiotic-resistant bacteria. Here, a high-density population of patients with compromised host defenses is exposed to a usage of antibiotics that is about 100 times more concentrated than in the community, and frequent contact with healthcare personnel creates ceaseless opportunities for cross-infection.

Id.

46 Munita & Arias, *supra* note 38.

47 *See, e.g.*, Viktória Lázár et al., *Genome-Wide Analysis Captures the Determinants of the Antibiotic Cross-Resistance Interaction Network*, 5 NATURE COMMUNICATIONS, art. 4352, June 8, 2014, at 4–5 (observing that "antibiotic resistance generally conferred a measurable fitness cost: at least 41% of the laboratory-evolved lines showed a significantly reduced growth in antibiotic-free medium compared to the wild-type").

48 Adam C. Palmer & Roy Kishony, *Understanding, Predicting and Manipulating the Genotypic Evolution of Antibiotic Resistance*, 14 NATURE REVS. GENETICS 243, 247 (2013). More specifically, "cross-resistance" is probably more correctly used to refer to multiple drugs in the same class with the same mechanism, whereas "co-resistance" describes the same phenomenon when it manifests cross-class. Denis et al., *supra* note 20. Yet the two are often used indiscriminately.

49 Lázár et al., *supra* note 47, at 8–9.

the *interspecies, same-drug resistance rate* (Table 1, green)—that is, the rate of resistance by HGT from another bacterial species that has acquired resistance to the same drug. Third, the *cross-drug resistance rate* (Table 1, blue)—that is, (1) the rate of resistance within one bacterial population by spontaneous mutation to *another* drug that confers a cross-resistance effect, coupled with (2) the rate of resistance by HGT from another bacterium of the same species that has acquired cross-resistance from another drug, further coupled with (3) the rate of resistance by HGT from another bacterial species that has acquired cross-resistance from another drug. Table 1 depicts these pathways. What is emphatically clear is that cross-resistance and HGT constitute major sources of antibiotic resistance.[50]

Table 1. Pathways of resistance acquisition

	Same-Drug	**Cross-Drug**
Intraspecies	Spontaneous mutation	Spontaneous mutation
	HGT	HGT
Interspecies	HGT	HGT

III. Pathogen-Selective ("One-Bug-Per-Drug") Antibiotics as a New Hope

A. The Promise of Pathogen-Selective Antibiotics

A potential solution to the antibiotic resistance crisis is the development of ultranarrow-spectrum antibiotics that selectively target a single pathogenic species; that is, pathogen-selective, "one-bug-per-drug" antibiotics.

So much of the antibiotic resistance crisis stems from the broad-spectrum nature of antibiotics.[51] Thus, the idea of more narrow-spectrum agents has been proposed recently in the literature.[52] Pathogen-specific antibiotics (PSAs)—therapies tailored

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[50] *See generally* Andrew C. Singer et al., *Review of Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators*, 7 FRONTIERS IN MICROBIOLOGY 1728 (2016) (discussing sources of antibiotic resistance with relation to environmental regulation); *see also supra* notes 40–45 and accompanying text.

[51] *See supra* notes 17–23 and accompanying text.

[52] *See, e.g.*, David J. Payne, *Desperately Seeking New Antibiotics*, 321 SCIENCE 1644, 1645 (2008) ("[R]ather than the traditional approach of seeking antibiotics that cover a broad set of pathogens, exploiting targets that are specific for only certain pathogens . . . may be a more productive strategy."); Katherine P. Lemon et al., *Microbiota-Targeted Therapies: An Ecological Perspective*, 4 SCIENCE TRANSLATIONAL MEDICINE 137 (2012) (highlighting the need for narrow-spectrum antibiotics with rapid companion diagnostics); *see also* Kendall Powell, *Narrowing in on Species-*

to a patient's exact illness—are expected to entail decreased collateral damage to the patient's healthy microbiome and significantly stall the rise of antibiotic resistance overall.[53]

Resistance may be forestalled by PSAs in two principal ways. First, there is a decreased risk of co-resistance, as effective PSAs will have narrow, specific targets unlikely to overlap. This stands in contrast with broad-spectrum drugs, which share a small pool of widely-distributed targets. Second, there is a decreased risk of interspecies HGT. This follows from the point that a non-susceptible species—one of the 800, say, in the human gut[54]—has no incentive to develop resistance to an antibiotic that won't kill it, given that resistance mechanisms impose fitness costs.[55] As such, four of the six resistance-pathway boxes presented in Table 1 (cell borders bolded) are likely hindered, and there is no categorical reason to suspect that in the other two categories (intraspecies mutational resistance and HGT), PSAs would be inferior to broad-spectrum antibiotics as far as resistance rates.

A third advantage is increased efficiency in antibiotic usage. That is, prophylactic use or over-prescription is not feasible under a precision antibiotic regime, which is necessarily tied to rapid companion diagnostics.[56] Rather, a patient presents with an infection, a diagnostic test rapidly identifies the precise pathogen and its antibiotic susceptibility, and the doctor prescribes the appropriate targeted therapy. This strategy lacks the heuristic, prophylactic guesswork of a typical shoot-first-and-ask-questions-later broad-spectrum approach wherein a doctor gives the most-likely-to-work broad-spectrum antibiotic while waiting for results of a laboratory culture test.[57] This is a rare alignment of antibiotic *conservation* goals with antibiotic *production* goals, in contrast to the existing anti-resistance strategies previously identified in the literature.[58]

Specific Antibiotics, NOVARTIS (May 19, 2015), https://www.novartis.com/stories/discovery/narrowing-species-specific-antibiotics (arguing for a new approach to combatting antibiotic resistance).

53 *See* Maxson & Mitchell, *supra* note 37, at 3611–12; Jianwei Yao et al., *A Pathogen-Selective Antibiotic Minimizes Disturbance to the Microbiome*, 60 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 4264, 4264 (2016) (showing that a pathogen-selective antibiotic decreases negative consequences to the microbiome).

54 Maxson & Mitchell, *supra* note 37, at 3616.

55 *See supra* text accompanying note 47.

56 *See infra* text accompanying notes 83–90 (discussing requirement for rapid, cheap diagnostics for PSA use).

57 *Id.*

58 *Cf.* Kevin Outterson, *The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation*, 31 CARDOZO L. REV. 613, 619–21 (2010) [hereinafter Outterson, *Legal Ecology*] (drawing dichotomy between conservation and production). Although not discussing PSAs, Outterson implicitly shows that they serve conservation aims:

> Some [conservation/property] models look to patent law to solve antibiotic conservation problems. An obvious solution would be to patent technologies that promote antibiotic conservation, such as rapid diagnostic tests that would permit a physician to specifically diagnose an infection in the office. The physician could then prescribe the appropriate antibiotic for the specific infection, or, if the infection was not bacterial, avoid an unnecessary prescription altogether.

Id. at 625.

Combined, these advantages indicate the potential of a strategy with huge social value.

There are numerous proof-of-concept examples of such strategies, even if few are yet to arrive to market.[59] Some represent basic science; others have advanced to clinical trials.[60] Tucker Maxson and Douglas Mitchell provide a helpful review of the current technology.[61] Such molecules might be otherwise conventional-looking drugs that simply target enzymes, cellular components, or metabolic pathways unique to a given pathogen or based on differences between that target in a pathogen and in other bacteria.[62] Or a molecule might interfere with signaling systems,[63] which tend to be inherently species-specific. Alternatively, one could depart the traditional drug space in search of more complex molecules. Antibody–drug conjugates, for instance,[64] exploit the highly discriminating nature of antibodies to imbue otherwise-indiscriminate drugs with selectivity. Peptide drugs, too, can exhibit increased selectivity by virtue of their size and complexity.[65] Another strategy is to target so-called *virulence factors*—i.e., typically species-specific biological features, like toxins, that a pathogen uses to infect a host.[66] Because virulence factors are not essential for microbial growth but instead affect their ability to infect or harm a host, interfering with them might forestall antibiotic resistance (and disarm the pathogen).[67] Or, vaccine or bacteriophage therapy might be employed.[68] And the rapid development of genome-editing technologies like CRISPR-Cas9 suggest that individual genes could be targeted.[69] Alternatively, a therapy might selectively inactivate broad-spectrum antibiotics in the gut (protecting the microbiome) while leaving them active otherwise (targeting an infection).[70] Suffice it to say, advances in

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59 Fidaxomicin is the closest thing to a true PSA on the market; it kills *C. difficile* with a 10–100-fold selectivity factor over other bacteria and was specifically designed to have minimal effects on the gut microbiome. *See* Maxson & Mitchell, *supra* note 37, at 3613.

60 *E.g.*, *Synthetic Biologics Initiates SYN-004 Phase 2b Proof-of-Concept Clinical Trial*, SYNTHETIC BIOLOGICS (Sept. 28, 2015), https://www.syntheticbiologics.com/news-media/press-releases/detail/183/synthetic-biologics-initiates-syn-004-phase-2b (microbiome-protecting strategy); *Case Study: CAL02*, AMR INDUS. ALLIANCE, https://www.amrindustryalliance.org/case-study/cal02/ (last visited Apr. 7, 2018) (antivirulence strategy).

61 *See generally* Maxson & Mitchell, *supra* note 37 (describing recent and future developments of narrow-spectrum antibiotics).

62 Maxson & Mitchell, *supra* note 37, at 3613; *e.g.*, Yao et al., *supra* note 53.

63 Maxson & Mitchell, *supra* note 37, at 3613.

64 *See, e.g.*, Sanjeev Mariathasan & Man-Wah Tan, *Antibody–Antibiotic Conjugates: A Novel Therapeutic Platform Against Bacterial Infections*, 23 TRENDS IN MOLECULAR MEDICINE 135 (2017); Sophie M. Lehar et al., *Novel Antibody–Antibiotic Conjugate Eliminates Intracellular* S. aureus, 527 NATURE 323 (2015).

65 Maxson & Mitchell, *supra* note 37, at 3614.

66 *Id.* at 3615; Seth W. Dickey et al., *Different Drugs for Bad Bugs: Antivirulence Strategies in the Age of Antibiotic Resistance*, 16 NATURE REVS. DRUG DISCOVERY 457, 457 (2017).

67 Maxson & Mitchell, *supra* note 37, at 3615.

68 *Id.*

69 *Id.* at 3615–16; *see also* ELIGO BIOSCIENCE, http://eligo.bio/ (last visited Apr. 5, 2018) (touting "[n]ext-gen biotherapeutics for bacteria-associated diseases & precision microbiome engineering").

70 *E.g.*, *Synthetic Biologics Initiates SYN-004 Phase 2b Proof-of-Concept Clinical Trial*, SYNTHETIC BIOLOGICS (Sept. 28, 2015), https://www.syntheticbiologics.com/news-media/press-

chemistry, molecular biology, synthetic biology, and bioinformatics have unlocked a large toolbox with which to pursue pathogen-selective strategies.

B. Obstacles to Implementation

Several challenges stand in the way of the development and deployment of PSAs. Many of these obstacles are scientific or technological.

One is simply that finding unique targets for antibiotics is hard. We've seemingly already exploited many of the essential pathways of bacteria.[71] There's a limited menu of options from which to pick, as reflected, for instance, by the slowed discovery pipeline.[72] In the field of broad-spectrum antibiotics, for example, a new class of antibiotics (i.e., a fundamentally different *way* of killing bacteria) has not been introduced to the market in years.[73] This problem might be attenuated with PSAs; with only a single species targeted, the requirement that a given target be present in numerous disparate species is absent.[74] And advances in genomics have shown that we are far from completely understanding the workings of bacteria—so new targets likely remain undiscovered.[75] Thus, the new-targets problem might be less significant for narrower-spectrum agents. However, advances in basic science are essential for this aim.

Another obstacle, of course, is the number of drugs that might be needed. There are about 1,400 human pathogens.[76] The number of known *bacterial* pathogens is probably closer to 500[77]—many pathogens are viruses, protozoa, fungi, helminths, etc.[78]—but with fewer than 200 commercialized antibiotics in history,[79] even this

releases/detail/183/synthetic-biologics-initiates-syn-004-phase-2b.

71 Kevin Outterson, *The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Intellectual Property Law*, 67 U. PITT. L. REV. 67, 69, 77 (2005) [hereinafter Outterson, *Vanishing Public Domain*] (speculating that "the easiest biological targets may have already been found" and pointing out that "[i]f the number of possible antibiotic targets is finite, then resistance will eventually master them all").

72 *See* Alexandra Flemming, *Antibacterials: Resistance-Guided Discovery of New Antibiotics*, 12 NATURE REVS. DRUG DISCOVERY 826, 826 (2013) ("Natural product screening . . . has been one of the most fruitful sources of antimicrobials. However, the 'low-hanging fruit' appear to have been picked.").

73 Jinks, *supra* note 32. The only two new classes of antibiotics in the last thirty years are oxazolidinones—e.g., linezolid—and cyclic lipopeptides—e.g., daptomycin. Sandeep Kumar Gupta & Roopa P. Nayak, *Dry Antibiotic Pipeline: Regulatory Bottlenecks and Regulatory Reforms*, 5 J. PHARMACOLOGY & PHARMACOTHERAPEUTICS 4, 4 (2014).

74 Maxson & Mitchell, *supra* note 37, at 3611.

75 *See, e.g.*, Fredrick M. Mobegi et al., *From Microbial Gene Essentiality to Novel Antimicrobial Drug Targets*, 15 BMC GENOMICS 958 (2014) (using genomic techniques to "identif[y] 249 potential drug targets, 67 of which are acknowledged targets for 75 FDA-approved antimicrobial drugs").

76 Editorial, *Microbiology by the Numbers*, 9 NATURE REVS. MICROBIOLOGY 628, 628 (2011).

77 Mark E.J. Woolhouse & Sonya Gowtage-Sequeria, *Host Range and Emerging and Reemerging Pathogens*, 11 EMERGING INFECTIOUS DISEASES 1842, 1843 (2005).

78 *Microbiology by the Numbers*, *supra* note 76.

79 David J. Newman & Gordon M. Cragg, *Natural Products as Sources of New Drugs from 1981 to 2014*, 79 J. NAT. PRODUCTS 629, 636–38 (2016) (for instance, there were only 141 antibacterial drugs approved worldwide between 1981 and 2014).

might seem a daunting number. But reality would probably accommodate a smaller number of PSAs. The ideal, of course, would be one (or more!) PSA per single human bacterial pathogen, with each PSA having perfect selectivity, free of target overlap. That one-to-one, comprehensive PSA model helps to conceptually understand the benefits of PSAs, but it is not a necessary predicate to a successful PSA arsenal in real life. (Indeed, consider that nearly every drug we use is a compromise, as evidenced by off-label uses and side effects.) It is unclear what a working PSA system would look like, but there are strategic options. For instance, we might target with only the most common or most deadly pathogens. Or we might target pathogens that frequently co-occur, where the risks of resistance arising from broad-spectrum drugs are highest. Broad-spectrum drugs could be left available for rare or emergent infections. This follows from the fact that pathogens are heterogeneously distributed: Certain bacteria are more burdensome than others.[80] And certain bacteria are more able to acquire resistance than others.[81] It is also not absolutely required that a PSA kill only one bacterium: The benefits of narrow-spectrum agents exist along a continuum, and narrower-spectrum drugs in general would capture these in part. Balancing is thus required in light of well-informed public health research and microbiology. It is perhaps conceivable that a PSA strategy could be implemented with relatively narrow-spectrum antibiotics targeting only the ten most dangerous bacteria.[82]

Third, rapid, precise, and practical diagnostics are needed.[83] Today, a doctor most often knows or suspects a patient has *an* infection well before knowing *which* infection.[84] Say a patient presents with the symptoms of an infection. We have the technology to know what the infectious pathogen is—but not cheap, and not fast. The gold standard is still swabbing and culturing on a petri dish followed by microscopy and antibiotic susceptibility testing,[85] a process that typically requires 24 to 72

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80 *See, e.g.*, NATIONAL CENTER FOR EMERGING AND ZOONOTIC INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL & PREVENTION, ESTIMATED ANNUAL NUMBER OF HOSPITALIZATIONS AND DEATHS CAUSED BY 31 PATHOGENS TRANSMITTED COMMONLY BY FOOD, UNITED STATES, CS228412 (2011), https://www.cdc.gov/foodborneburden/PDFs/scallan-estimated-hospitalizations-deaths-foodborne-pathogens.pdf (tabulates 31 pathogens and the estimated number of hospitalizations and deaths they caused).

81 *See, e.g.*, J.L. Martinez & F. Baquero, *Mutation Frequencies and Antibiotic Resistance*, 44 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1771 (2000) (explains the factors that contribute to the mutation rate of antibiotic-resistant bacteria).

82 *See 10 Most Dangerous Antibiotic-Resistant Bacteria*, LONGITUDE PRIZE (Aug. 26, 2014), https://longitudeprize.org/blog-post/10-most-dangerous-antibiotic-resistant-bacteria (describes the ten most antibiotic-resistant bacteria, the illnesses they cause, and their antibiotic resistance).

83 Lemon et al., *supra* note 52, at 5; Maxson & Mitchell, *supra* note 37, at 3616–17 (describing the need for advanced diagnostics fulfilling the requirements of speed, accuracy, and sensitivity); Payne, *supra* note 52, at 1645 ("[T]his approach will succeed only . . . with the availability of diagnostics that can very rapidly and accurately identify the specific infecting pathogen . . . .")

84 *See* Lemon et al., *supra* note 52, at 5.

85 *See, e.g.*, Kevin B. Laupland & Louis Valiquette, *The Changing Culture of the Microbiology Laboratory*, 24 CAN. J. INFECTIOUS DISEASES & MED. MICROBIOLOGY 125, 125 (2013) ("Generally speaking, when cultures are positive they represent a 'gold standard' diagnosis.").

hours,[86] and even weeks for certain infectious agents.[87] But a critically ill patient may not have the luxury of waiting three days (or even hours[88]); as such, using broad-spectrum antibiotics guided by statistical, heuristic guesswork remains not only common but necessary. In such cases, any collateral damage or antibiotic resistance is an inevitable side-effect (but better than death). And by the time that a culture test comes back, the damage of the broad-spectrum antibiotic has been done and switching to the PSA makes little sense.[89] However, recent developments in FDA, health, and patent law have thrown up significant obstacles that likely disincentives diagnostics development in general.[90]

However, other obstacles are economic. There are certain general economic truths about antibiotics; because these have been discussed abundantly in the literature,[91] I apply them here only briefly. First, we're used to low prices—antibiotics are often offered for free,[92] and there's plenty of low-cost generics.[93] Market uptake is limited; new antibiotics tend merely to be non- inferior to existing antibiotics,[94] and because of lack of uptake there's a threefold-higher withdrawal rate than for other drugs.[95] Government support is generally stagnant. [96] Fears of hoarding new antibiotics as "last resort" drugs may scare off drug companies[97] (and in counterpoint, fears of initial overuse to make up for the costs of clinical trials is a competing

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86 *See* Lemon et al., *supra* note 52, at 5.

87 Laupland & Valiquette, *supra* note 85, at 125.

88 *E.g.*, Anand Kumar et al., *Duration of Hypotension Before Initiation of Effective Antimicrobial Therapy Is the Critical Determinant of Survival in Human Septic Shock*, 34 CRITICAL CARE MED. 1589, 1589 (2006) ("Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock.").

89 Maxson & Mitchell, *supra* note 37, at 3616.

90 Rachel E. Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. DAVIS L. REV. 1881, 1881 (2016); Doran Satanove, Note, *The Challenging Economics of the Companion Diagnostics Industry: A Compelling Case for Invigorated Patent Protection*, 6 NYU J. INTELL. PROP. & ENT. L. 142, 173 (2016); *cf.* Rebecca S. Eisenberg, *Diagnostics Need Not Apply*, 21 B.U. J. SCI. & TECH. L. 256, 286 (2015) ("One can only hope that . . . the exclusion of diagnostics from patent-eligibility will do more to enhance future innovation than it does to suppress it."). *But see* Martin Madaus, *Changes in the Diagnostics Industry Demand Agility, Innovation*, STAT (May 16, 2017), https://www.statnews.com/2017/05/16/diagnostics-industry-innovation/ ("The industry is also rapidly developing innovative immunoassays that diagnose diseases faster, giving clinicians more time to intervene with new and effective therapies that can change the course of disease.").

91 *See, e.g.*, *infra* notes 92–101 (collecting sources).

92 *E.g.*, Tara Parker-Pope, *Are Free Antibiotics Good for You?*, N.Y. TIMES: WELL (Mar. 5, 2009, 7:03 AM), https://well.blogs.nytimes.com/2009/03/05/are-free-antibiotics-good-for-you/.

93 Kevin Outterson et al., *Repairing the Broken Market for Antibiotic Innovation*, 34 HEALTH AFF. 277, 278 (2015) [hereinafter Outterson et al., *Broken Market*].

94 That is, they don't necessarily work better than known drugs, but they're not *worse*.

95 Outterson et al., *Broken Market*, *supra* note 93, at 278.

96 *Id.* at 278–79.

97 *See, e.g.*, Ezekiel J. Emanuel, Opinion, *How to Develop New Antibiotics*, N.Y. TIMES (Feb. 24, 2015), https://www.nytimes.com/2015/02/24/opinion/how-to-develop-new-antibiotics.html ("Furthermore, any new antibiotics that might be developed to fight these drug-resistant bacteria are likely to be used very sparingly under highly controlled circumstances, to slow the development of resistant bacteria and extend their usefulness.").

concern for public health advocates[98]). Success rates from lead to approval are lower for antibiotics than other drugs.[99] And the return on investment is generally quite low—antibiotics are really not very profitable, especially compared to other drugs;[100] they're also used for comparatively shorter time periods than so-called lifestyle drugs.[101]

Also, many possible PSAs may have already been screened by pharmaceutical companies and discarded because they lacked *broad*-spectrum activity;[102] even if they were re-screened for narrow-spectrum activity, the novelty requirement of patent law would likely frustrate their development.[103] In addition, pathogen-selective antibiotics exhibit certain unique economic features that change the calculus, as discussed below.

IV. Why Current Incentives Miss the Mark

Much attention has been devoted to the antibiotic resistance crisis, as evidenced by the scientific literature, the legal literature, and numerous examples of ongoing efforts to incentivize antibiotic development. Indeed, some of these efforts look highly promising vis-à-vis their stated aims. But they are inadequate for development of a "one-bug-per-drug" strategic arsenal. I argue here that this is because antibiotics are not a monolith.[104] Rather, pathogen-selective antibiotics exhibit certain economic features that distinguish them. I then survey a few of the most promising antibiotic incentive efforts and illustrate why these don't align with these features.

A. What's Different About Pathogen-Selective Antibiotics?

Not all antibiotics are alike, economically speaking. Rather, pathogen-selective

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98 *See* Katrina Megget, *Fixing the Broken Antibiotics Business Model*, CHEMISTRYWORLD (Jan. 13, 2016), https://www.chemistryworld.com/news/fixing-the-broken-antibiotics-business-model/9337.article.

99 *See, e.g.*, INFECTIOUS DISEASE SOC'Y OF AM., STATEMENT PROMOTING ANTI-INFECTIVE DEVELOPMENT AND ANTIMICROBIAL STEWARDSHIP THROUGH THE U.S. FOOD AND DRUG ADMINISTRATION PRESCRIPTION DRUG USER FEE ACT (PDUFA) REAUTHORIZATION BEFORE THE HOUSE COMMITTEE ON ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH 17 (Mar. 8, 2012), http://emerald.tufts.edu/med/apua/index_363_626155726.pdf ("One company reports that over a 10 year period, it took 72 lead candidate antibiotic compounds in the early discovery phase to yield one FDA-approved product; other drug categories only took 15 leads to yield an FDA approval.").

100 Kimberly Sciarretta et al., *Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations from the Transatlantic Task Force on Antimicrobial Resistance*, 63 CLINICAL INFECTIOUS DISEASES 1470, 1470 (2016) ("For antibacterial drugs, the [net present value] is estimated to be approximately ~$42.61 million . . . . This contrasts to neurological or musculoskeletal drugs, where NPVs range between $720 million . . . to in excess of $1.15 billion . . . ."); Outterson et al., *Broken Market*, *supra* note 93, at 279.

101 *See* Matthew Thompson, *Antibiotic Crisis Grows While Drug Companies Make Lifestyle Meds*, CONVERSATION (Nov. 21, 2011), https://theconversation.com/antibiotic-crisis-grows-while-drug-companies-make-lifestyle-meds-4373.

102 *See* Maxson & Mitchell, *supra* note 37, at 3611.

103 *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEXAS L. REV. 503, 517–31, 545–56 (2009).

104 That is, not all kinds of antibiotics are economically similar.

antibiotics, as a class of goods, exhibit certain properties that make them likely to respond to a different set of innovation incentives than classical broad-spectrum antibiotics. Encouragingly, reduced exhaustibility and rivalry in here in PSAs. But pathogen-selective antibiotics also exhibit conditional spillover benefits and network-dependent social utility. These two properties combine to lower the appropriability of the value of pathogen-selective antibiotics. In particular, these properties suggest that there is a threshold condition—a critical mass—of number of deployed PSAs and companion diagnostics before which research, development, and commercialization will likely be deterred.

1. Reduced Exhaustibility and Rivalry

Pathogen-specific antibiotics harbor great potential for a reduced rivalry or exhaustibility problem compared to broad-spectrum drugs, for which these traits are problematic.

Antibiotics in general have a twofold problem with rivalry (or exhaustibility). As tangible goods, they are rivalrous in the ordinary sense that only one person can consume any one pill.[105] However, they are also rivalrous in the sense that use by one person reduces the utility of the good to another.[106] Because of the spread of antibiotic resistance, more a particular antibiotic is used by a population, the less valuable it becomes to that population.[107] In a sense, this phenomenon is at the heart of the resistance crisis.

PSAs are arguably less rivalrous than broad-spectrum antibiotics. Specifically, because the ideal PSA only exhibits selective pressure on the targeted pathogen, inter-species resistance spread is avoided.[108] This avoids the problem of cross-resistance (wherein resistance to one antibiotic confers resistance to another antibiotic with a very similar target) as well as the use of other bacterial species as resistance reservoirs.

However, there is an underlying empirical premise here—that the rate of resistance to a PSA is comparable to or less than that of a broad-spectrum antibiotic. If a PSA's mechanism of action is based on targeting a highly specific but highly nonessential or easily mutated feature of a given pathogen, the rate of resistance might be expected to be very high. This might be the case with antibody–drug conjugates where the antibody targets a relatively nonessential external feature of a bacterial cell. In that case, the rivalry problem could actually be aggravated compared to common broad-spectrum antibiotics that target less easily mutated bacterial features. That is, if the rate of resistance within a single species is high enough, the antibiotic will

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[105] *See generally* Alan Devlin, *The Misunderstood Function of Disclosure in Patent Law*, 23 HARV. J.L. & TECH. 401, 413–14 (2010).

[106] *See* Outterson, *Legal Ecology*, *supra* note 58, at 626 ("Antibiotics depart from the general case because antibiotic innovation is potentially exhaustible (rivalrous). Antibiotic innovation is exhaustible when use creates resistance and resistance degrades utility.").

[107] *See* Outterson, *Vanishing Public Domain*, *supra* note 71, at 76–77 (discussing "Exhaustible Pharmaceutical Knowledge").

[108] *See supra* Section II.A.

become useless quite quickly anyway, despite avoiding the problem of resistance spreading between species.

Thus, to truly take advantage of the benefits of reduced rivalry, ideal PSAs would feature low resistance rates. That's easy enough to say, and perhaps seemingly self-evident, but it highlights why PSAs are likely to be inherently costlier per unit than broad-spectrum drugs. One current strategy to avoid resistance entails building more complex molecules that can simultaneously target multiple features of a given bacterium.[109] Another involves the discovery and targeting of novel features of a bacterium that are unique but nonetheless essential.[110] The resulting compounds have tended to be, and are thus likely to continue to be, biologics or of similar structural complexity. A third strategy, however, would entail a multi-drug "cocktail," as has been done to forestall resistance that would otherwise rapidly arise against tuberculosis drugs.[111]

2. Conditional Spillover Benefits

Pathogen-selective antibiotics exhibit diminished negative externalities[112] and increased positive externalities (that is, spillover benefits to society)[113] compared to traditional broad-spectrum antibiotics. For instance, PSAs inflict less collateral damage to a patient's healthy microbiome, and they reduce rates of cross-species and cross-drug antibiotic resistance. However, these spillover benefits are conditional: They require reduced use of competing goods—namely, broad-spectrum antibiotics.

Compared to broad-spectrum drugs, pathogen-selective antibiotics have fewer negative externalities associated with their use. Broad-spectrum antibiotics inflict externalities[114] through two mechanisms.

First, broad-spectrum antibiotics inflict collateral damage in a patient. To the extent that the patient's own microbiome is weakened and opportunistic infections occur, this is a negative externality, as the costs of additional treatments are—by

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[109] The multiple-mechanism strategy is how the lantibiotic nisin, for instance, evades resistance. Sakshi Khosa et al., *Structural Basis of Lantibiotic Recognition by the Nisin Resistance Protein from* Streptococcus agalactiae, 6 SCIENTIFIC REPORTS 18679, at *1 (2016) ("Due to their multiple modes of action, hardly any resistance against lantibiotics [like nisin] has developed over the past decades").

[110] For example, plantazolicin targets unique features of the *Bacillus anthracis* membrane. Katie J. Molohon et al., *Plantazolicin Is an Ultranarrow-Spectrum Antibiotic That Targets the* Bacillus anthracis *Membrane*, 2 ACS INFECTIOUS DISEASES 207, 207 (2016).

[111] *See* Maxson & Mitchell, *supra* note 37, at 3613. Such a combination, although technically comprising more than one pharmaceutical agent, could nonetheless be classified as a pathogen-selective antibiotic given the appropriate selectivity profile.

[112] Externalities entail costs or benefits not borne or captured by the parties to a transaction. *E.g.*, Outterson, *Vanishing Public Domain*, *supra* note 71, at 80.

[113] *See generally* Brett M. Frischmann & Mark A. Lemley, Essay, *Spillovers*, 107 COLUM. L. REV. 257 (2007) ("[S]pillovers aren't always bad . . . ."); Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1587–88 (2003).

[114] *E.g.*, Constantinos I. Michaelidis et al., *The Hidden Societal Cost of Antibiotic Resistance per Antibiotic Prescribed in the United States: An Exploratory Analysis*, 16 BMC INFECTIOUS DISEASES 655 (2016) (estimating that externalities of ambulatory antibiotic prescriptions alone would raise antibiotic costs by 65% if integrated into actual cost of goods).

virtue of the health insurance system—not only borne by the patient but also heavily by third parties. *Clostridium difficile*, the most prominent opportunistic pathogen in such cases, likely imposes a significant economic *annual* burden of more than $796 million to society, at least $547 million of which is borne by third-party payers.[115]

Second, broad-spectrum antibiotics contribute to the spread of antibiotic resistance. To the extent that an antibiotic's utility is exhausted through its use, this leads to externalities in the form of waste and decreased access, among others.[116] Again, the costs of decreased efficacy of the drug are largely borne by third parties, such as future patients. Moreover, to the extent that broad-spectrum drugs promote cross-resistance, the harms of decreased efficacy vis-à-vis the *other drugs* are borne by not only other patients but other drug developers.

Pathogen-selective antibiotics are different. As discussed previously, the theory is that cross-drug and interspecies resistance transmission rates should be substantially lowered.[117] There is some empirical support: for instance, ionophores—a class of antibiotics used in cattle feed but not in humans—seem not to increase antibiotic resistance rates in human populations.[118] The implication for this is that as a society we should be comfortable paying more for PSAs than for broad-spectrum drugs: doing so will help counteract the otherwise unfavorable market pressures caused by the decreased target populations and will still represent a net less-expensive therapy for healthcare payers.[119]

These above attenuated negative externalities and increased spillover benefits, however, are conditional: They require the reduced use of broad-spectrum antibiotics on a societal level to be fully appreciated.

Take the phenomenon of reduced collateral damage. A single PSA for a particular pathogen can have this benefit to a single patient. But suppose the patient develops a *second* disease for which a broad-spectrum antibiotic is the standard of treatment. Then, the microbiome is damaged, and the benefit of the previously taken PSA is nullified.

Take also the phenomenon of reduced cross-drug and cross-species antibiotic resistance. Again, a single PSA can have this benefit for a patient. A drug perfectly selective for *Acinetobacter baumannii* is unlikely to select for resistance in *Staphylococcus aureus*. But that is of little value, given that the drug only kills *A. baumannii* in the first place. As long as broad-spectrum drugs are still used for *S.*

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115 S.M. McGlone et al., *The Economic Burden of* Clostridium difficile, 19 CLINICAL MICROBIOLOGY & INFECTION 282, 282 (2011).

116 Outterson, *Vanishing Public Domain*, *supra* note 71, at 80–102.

117 *See supra* Section II.A.

118 *See, e.g.*, James B. Russel & Adam J. Houlihan, *Ionophore Resistance of Ruminal Bacteria and Its Potential Impact on Human Health*, 27 FEMS MICROBIOLOGY REVS. 65 (2003) (reviewing evidence and concluding that "use of ionophores in animal feed is not likely to have a significant impact on the transfer of antibiotic resistance from animals to man").

119 *But see* Dana Goldman & Anupam Jena, *Value-Based Drug Pricing Makes Sense, but Is Difficult to Pull Off*, STAT (June 8, 2017), https://www.statnews.com/2017/06/08/value-based-drug-pricing/.

aureus, the use of those drugs in *other* species continues to pose a risk. Put another way, society only benefits from an antibiotic selective for Pathogen X to the extent that using other broad-spectrum drugs for Pathogen X indirectly caused problematic drug resistance in Pathogen Y. If the same class of broad-spectrum drugs are still used for Pathogen Z that were problematically used for Pathogen X, Pathogen Y is still at risk of troublesome resistance.

3. Network-Dependent Social Utility

Pathogen-selective antibiotics are also different because their social utility depends on the existence of a twofold network of technologies—that is, a set of *other* PSAs and a set of paired diagnostics—that are interdependent. That is, regardless of the individual value of a PSA to a given patient, the social value is dependent on broader patterns of PSA or broad-spectrum antibiotic use and the availability of companion diagnostics.

The network effect is the idea that a good's utility may change based on the usage of a like good by others or the existence of compatible goods.[120] A good may have no consumer value in isolation but may be valuable when other, complementary goods are available.[121] Take, for instance, diabetic test strips.[122] These are only valuable when a compatible blood glucose meter exists.[123] And by extension, both the meter and the test strips are only really useful if medicines like insulin are first available for diabetics to correct irregularities in blood glucose.[124]

It is not uncommon to be prescribed an antibiotic in the absence of diagnosis of a specific infection, or an infection at all.[125] This is possible because as a probabilistic matter, a broad-spectrum antibiotic is likely to be useful to a given patient—such drugs kill many things. Upfront diagnostics *might* help, but they're not necessary. This is not so for pathogen-selective drugs. PSAs require a critical mass of other effective PSAs to be useful as a viable general strategy that displaces broad-spectrum drugs.[126] Contrast this with broad-spectrum drugs: a new broad-spectrum drug is actually *more valuable* as other antibiotics fade in effectiveness.[127] Further, pathogen-

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[120] *See generally* Mark A. Lemley & David McGowan, *Legal Implications of Network Economic Effects*, 86 CALIF. L. REV. 479, 483–84 (1998); Michael L. Katz & Carl Shapiro, *Systems Competition and Network Effects*, 8 J. ECON. PERSPECTIVES, no. 2, Spring 1994, at 93 [hereinafter Katz & Shapiro, *Systems Competition*]; Michael L. Katz & Carl Shapiro, *Technology Adoption in the Presence of Network Externalities*, 94 J. POLIT. ECON. 822 (1986) [hereinafter Katz & Shapiro, *Technology Adoption*]; Michael L. Katz & Carl Shapiro, *Network Externalities, Competition, and Compatibility*, 75 AM. ECON. REV. 424, 424 (1985).

[121] *See* Katz & Shapiro, *Systems Competition*, *supra* note 120, at 93.

[122] *See generally* Kenneth S. Polonsky, *The Past 200 Years in Diabetes*, 367 NEW ENG. J. MED. 1332 (2012).

[123] *See generally id.*

[124] *See generally id.*

[125] *See, e.g.*, F. Christiaan K. Dolk et al., *Antibiotics in Primary Care in England: Which Antibiotics Are Prescribed and for Which Conditions?*, 73 J. ANTIMICROB. CHEMOTHER. ii2, ii2 (2018) ("[I]n almost one-third of all prescriptions no clinical justification was documented.").

[126] *See supra* Section II.B.

[127] *See* Outterson, *Legal Ecology*, *supra* note 58, at 630–31.

selective antibiotics require effective diagnostics. Indeed, although a PSA might be equally effective as a broad-spectrum antibiotic in treating a patient's infection, that only matters if the doctor *knows* what the infection is.

Each PSA in isolation is thus of low social value. Without a paired diagnostic, it is unlikely to be deployed in the clinic.[128] And without a need for a low-cost diagnostic for a *specific* pathogen (as opposed to low-cost diagnostics for antibiotic susceptibility), that diagnostic is unlikely to be developed, given the costly regulatory burdens and lack of patent incentives in diagnostics generally.[129] And without a reduction in broad-spectrum antibiotic use, an isolated PSA's social benefits of decreased interspecies HGT and attenuated cross-drug resistance are likely to be frustrated.[130] First movers are also penalized in that their patent- and FDA-based market exclusivity times are undercut by the lag between the first such drugs and their market-wide deployment, presumably only once many such drugs have been made.[131]

Accordingly, the dual network-dependence of pathogen-selective antibiotics presents what is arguably a unique economic challenge among drugs. An incentive mechanism should account for this challenge by coordinating innovation efforts[132]—both PSA–PSA and PSA–diagnostic—and reducing the first-mover disadvantage.

4. The Tipping Point

Pathogen-selective antibiotics are different because the appropriability to the drug developer of their social value is hindered by the fact that most of the social benefit that accrues by their use is not enjoyed by the patient or the payer. This is due in part to the so-called "tipping point"—a critical mass before which it does not make economic sense to develop a PSA.

That is, consider the following hypothetical involving two drugs for the same disease: Drug B is broad-spectrum, treating all Gram-negative bacteria, and Drug N treats only a single Gram-negative pathogen. Assume that Drug B and Drug N are otherwise equivalent in terms of same-drug mutational resistance rate and intraspecies HGT.[133] Further, assume that Drug B and Drug N have equal efficacy against the pathogen in question, and the patient will be cured in one week with either. Assume that there are no differences in toxicity between the two. In that scenario, the patient still might prefer Drug N because of decreased cross-resistance rates and collateral damage to the patient's own gut microbiome. But the drug company would

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[128] *See supra* Section II.B.

[129] *See supra* Section II.B.

[130] Akin, for instance, to drying up a lake with a paper towel.

[131] This is an economic disadvantage to the extent that if there is no reason for payers to opt for PSAs over broad-spectrum drugs—i.e., before the "tipping point"—the exclusivity clock will run out while very little revenue flows in. If later movers introduce drugs after the tipping point, they will benefit from a comparative advantage versus the first movers.

[132] *Cf.* Katz & Shapiro, *Systems Competition*, *supra* note 120, at 101–03 (noting that the control of product systems like hardware/software networks—essentially vertical integration—by large firms helps capture network externalities).

[133] *See supra* Section I.B, including Table 1.

have a strong preference for Drug B: the broader spectrum would mean a larger market, and cross-resistance (which will impact *other* company's drugs) would be economically irrelevant. A physician hedging their bets or uncertain about their diagnostics might prefer Drug B, too—after all, maybe a different, undetected infection also plagues the patient. And to the extent that a larger market for Drug B enables a lower price, the patient (or the payer) might prefer Drug B, any risk of collateral damage notwithstanding.

In the above situation, Drug N would still be superior from a social-good perspective. But most of the benefits—lack of cross-resistance and attenuated interspecies HGT—would accrue to those outside the drug company–patient transactional relationship. In contrast, broad-spectrum antibiotics generally lack these positive externalities, and so a much larger fraction of their social value may be captured by the manufacturer.

That is to say, there is a tipping point. If most societal antibiotic usage consists of broad-spectrum, resistance-prone drugs, the social benefits of each pathogen-specific antibiotic are exceedingly small. The value of attenuated negative externalities and enhanced spillovers are negligible. Thus, even properly conceived incentive programs designed to appropriate social value will find little to appropriate. But there exists a theoretical critical mass—a tipping point at which enough PSAs (and paired diagnostics) are available that broad-spectrum drugs can be used more sparingly and strategically, and the value of PSAs can be appreciated and captured.

So, what then, does a pathway to PSAs look like? As discussed earlier, we probably do not need *perfectly* selective antibiotics, and we do not necessarily need one for *each* of the more than 500 bacterial pathogens which plague humanity.[134] Certain bacteria are more problematic than others in the ecosystem of antibiotic resistance (or, the "resistome").[135] It would be feasible to target first the bacteria that inflict the highest direct burden (i.e., those for which current therapies are least effective, those with the highest morbidity rates) and indirect burden (i.e., those which are most likely to contribute to resistance reservoirs).[136] These are the bacteria for which the biggest societal gains are to be had, and they are likely to suffer least from the conditional-benefit problems detailed above. Developing PSAs first for "key" pathogens would thus both reduce the rates of broad-spectrum antibiotic use where it matters most and would prime the development of PSAs for less critical infectious agents.

B. Current Approaches to Antibiotics Incentives

Current approaches to antibiotic incentives are promising and creative, but they are aimed—by and large—at broad-spectrum solutions. Such efforts have been extensively reviewed, and so here I consider them only briefly. Two are

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134 *See supra* notes 76–82 and accompanying text.

135 *See* Gerard D. Wright, *The Antibiotic Resistome: The Nexus of Chemical and Genetic Diversity*, 5 NATURE REVS. MICROBIOLOGY 175 (2007).

136 *See supra* note 82 and accompanying text.

representative: CARB-X and the GAIN Act.

CARB-X,[137] a so-called "public–private partnership for preclinical antibacterial research,"[138] is probably the most prominent antibiotics-incentivization effort today. The organization touts its mission as "[a]ccelerat[ing] a diverse portfolio of at least 20 high-quality antibacterial products towards clinical development leveraging $455 million in BARDA funds with matching funds from Wellcome Trust."[139] In addition to antibiotics, the scope of CARB-X includes vaccines, diagnostics, and devices.[140] Merely incremental drug advances are disfavored.[141]

CARB-X works by providing funding to preclinical applied research (but not basic science), particularly startup companies spun off from universities.[142]

CARB-X is exciting and promising because of the immense range of creativity that its sponsored projects embody.[143] But CARB-X's scope is oriented at specific drug-resistant bacteria (those prioritized by the CDC and WHO) without regard to selectivity.[144] As such, the larger-market economics of broad-spectrum therapies still nudge companies operating in the framework to adopt a broader-spectrum approach, all other things being equal.

The Generating Antibiotic Incentives Now (GAIN) Act, signed into law as part of the Food & Drug Administration Safety & Innovation Act of 2012,[145] represents the most recent legislative effort specifically focused on antibiotic incentives. The GAIN Act provides five extra years of market exclusivity for drugs targeting "qualifying pathogens"—those with the "potential to pose a serious threat to public health."[146] This exclusivity is additive to other special FDA exclusivity periods.[147] "Qualifying pathogens" include the usual suspects: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and the ESKAPE pathogens are specifically included, but others may be added to the list.[148] Considerations for inclusion include "impact on the public health due to drug-resistant organisms in humans," "the rate of growth of drug-resistant organisms in

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137 CARB-X, http://www.carb-x.org/ (last visited Apr. 7, 2018).

138 Kevin Outterson et al., *Accelerating Global Innovation to Address Antibacterial Resistance: Introducing CARB-X*, 15 NATURE REVS. DRUG DISCOVERY 589, 589 (2016) [hereinafter Outterson, *CARB-X*].

139 CARB-X, http://relreview.org/carbx/about (last visited Apr. 7, 2018).

140 Outterson, *CARB-X*, *supra* note 138, at 590.

141 *Id.* at 590.

142 Asher Mullard, *Antibiotics Funding Splurge Gets Mixed Reception*, NATURE (July 28, 2016), https://www.nature.com/news/antibiotics-funding-splurge-gets-mixed-reception-1.20341.

143 *See Powered by CARB-X Portfolio*, CARB-X, http://www.carb-x.org/portfolio/gallery/ (last visited Apr. 7, 2017).

144 *About CARB-X*, CARB-X, http://www.carb-x.org/about/overview/ (last visited Apr. 7, 2017).

145 Food & Drug Administration Safety & Innovation Act of 2012, Pub. L. No. 112-144, Title VIII, §§ 801–806, 126 Stat. 993, 1077–82.

146 *Id.* § 801, 126 Stat. 1077–79 (codified at 21 U.S.C. § 505E).

147 Food & Drug Administration Safety & Innovation Act of 2012, Pub. L. No. 112-144, Title VIII, § 801, 126 Stat. 993, 1077–79.

148 *Id.*

humans," "the increase in resistance rates in humans," and "the morbidity and mortality in humans."[149] Thus, under the logic of PSAs—that their development will slow resistance rates—many target organisms could be included on the qualifying-pathogens list. Yet the five-year exclusivity is awarded regardless of how broad or narrow the resulting spectrum is, providing no specific incentive for PSAs over broader drugs, and the baseline economics favor broad-spectrum antibiotics.

The GAIN Act also provides for priority review and fast-track approval for such antibiotics,[150] directs a reconsideration of clinical trial standards for antibiotics generally,[151] and directs the HHS Secretary to consult with the FDA and CDC and submit a report to Congress a report on recommended antibiotic incentives.[152] Again, these do not specifically address PSAs.

Interestingly, PSAs *do* appear in the final section of the GAIN Act, which directs the HHS Secretary to (not later than June 30, 2013), publish draft guidance that "provides advice on approaches for the development of antibacterial drugs that target a more limited spectrum of pathogens."[153] While this in itself is not an incentive, it does signal increasing attention to the prospect of PSAs generally. The FDA promulgated draft guidance under this section in July 2013[154] and final guidance in August 2017.[155] The guidance document does note that the FDA is contemplating a "streamlined development program[]" for "serious bacterial disease in patients with unmet medical need."[156] But because the criterion here is "unmet medical need" rather than, say, "single-species activity spectrum," such a program would fall short for PSAs—a fully effective PSA arsenal would likely need PSAs not only for bacterial infections with no cures at all, but ones with current cures that may simply become ineffective in the future. The guidance document, however, suggests that the FDA is hesitant to encompass such drugs within its envisioned streamlined pathway.[157] Encouragingly, the FDA recommends the "codevelopment of a rapid diagnostic test for use in clinical practice"[158]—but that recommendation does not

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149 *Id.*

150 *Id.* §§ 802, 803, 126 Stat. 1079.

151 *Id.* § 804, 126 Stat. 1080.

152 *Id.* § 805, 126 Stat. 1080–81.

153 *Id.* § 806, 126 Stat. 1082.

154 Draft Guidance for Industry on Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases; Availability, 78 Fed. Reg. 39,737 (July 2, 2013).

155 CTR. FOR DRUG EVALUATION AND RESEARCH, FOOD & DRUG ADMIN., ANTIBACTERIAL THERAPIES FOR PATIENTS WITH AN UNMET MEDICAL NEED FOR THE TREATMENT OF SERIOUS BACTERIAL DISEASES: GUIDANCE FOR INDUSTRY (August 2017), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf.

156 *Id.* at 3.

157 *See id.* at 4. The FDA notes that "a drug that treats a single species (or a few species) of bacteria is a *possible* candidate for a streamlined development program," but cautions that "[w]hen the single species is an *infrequent cause of infection*, sponsors should discuss possible development approaches with the FDA." *Id.* (emphasis added).

158 *Id.* The guidance notes:

The clinical trial for a candidate antibacterial drug may provide an opportunity to contribute to the

come hand-in-hand with an incentive and does not seem to be a suggested *requirement* for a streamlined program. Notably, the 21st Century Cures Act also established a limited population pathway for antibacterial drugs, which could provide an eased regulatory pathway for some, but not all, PSAs.[159]

Briefly, most antibiotic incentive mechanisms seem to largely rely on either exclusivity, profit-volume delinkage, or market-based mechanisms aimed at antibiotics broadly without regard to their therapeutic selectivity.[160] Indeed, a recent review of worldwide proposals for economic incentives for antibacterial drug development shows a consensus for delinkage of drug reimbursement from sales volume, combined with a variety of globally coordinated push and pull mechanisms.[161] But pathogen selectivity is not mentioned.[162] Further, some initiatives, such as BARDA's Broad Spectrum Antimicrobials program, seem to by their nature (and title, even) preclude narrow-spectrum drugs.[163]

Indeed, a PSA-enabling incentive framework needs to include measures or requirements specifically directed to the narrowness of the spectrum of the given antibiotic. Otherwise, all things being equal, the prospect of a broader market available for a broader-spectrum drug seems to inherently disincentivize a narrow-spectrum alternative. That is, a drug for one of the infamous "ESKAPE pathogens"[164]

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development and evaluation of a new diagnostic test. Sponsors are encouraged to discuss these approaches with the Division of Anti-Infective Products and the appropriate review division in the Center for Devices and Radiological Health.

The development and use of rapid detection methods should be helpful in identifying patients with the particular pathogen for drugs that have a narrow spectrum of activity (e.g., drugs active against a single species or a few species within a genus).

Id. at 14.

159 *See infra* Section IV.A.4.

160 *See* Outterson, *Legal Ecology*, *supra* note 58, at 622 ("[M]ost of the relevant legal scholarship has focused on IP solutions . . . such as drug patents."). Outterson has since proposed three specific reforms: "increased incentives for antibiotic research and development, surveillance, and stewardship; greater targeting of incentives to high-priority public health needs, including reimbursement that is delinked from volume of drug use; and enhanced global collaboration, including a global treaty." Outterson et al., *Broken Market*, *supra* note 93, at 277. Of these, the surveillance incentives and reimbursement delinkage could *help* development of PSAs, but they still tend to favor broad-spectrum drugs, all else being equal.

161 Kimberly Sciarretta et al., *Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations from the Transatlantic Task Force on Antimicrobial Resistance*, 63 CLINICAL INFECTIOUS DISEASES 1470 (2016). Proposed mechanisms are diverse and include data coordination, open funding for investigator-initiated research, tax credits for research and development, tradeable vouchers, extensions of market exclusivity, higher reimbursement or pricing, payment at the point of regulatory approval, restricted marketing, stewardship programs, educational campaigns, and taxes on human antimicrobial use, among others. *See id.* Again, while some of these could be useful for PSAs, none categorically favor them.

162 *See id.*

163 *See* Kelly Servick, *BARDA Broadens Pharma Funding to Fight Superbugs*, SCIENCE (Sept. 17, 2015, 4:00 PM), http://www.sciencemag.org/news/2015/09/barda-broadens-pharma-funding-fight-superbugs. *See generally* John K. Billington, *The ABCs of the US Broad Spectrum Antimicrobials Program: Antibiotics, Biosecurity, and Congress*, 13 HEALTH SECURITY 349 (2015).

164 The ESKAPE pathogens are a small group of particularly burdensome bacteria, often highly prioritized by public health agencies and biomedical researchers. *See generally* Louis B. Rice,

might be valuable, but to the drug company, a drug for *all* the ESKAPE pathogens is even more valuable. The same "general economic truths" that make companies wary of antibiotics in the first place[165] distort innovator firm preferences in favor of broader spectrum agents, and common strategies relying on exclusivity and market mechanisms are unlikely to remedy this innovation distortion.[166]

As such, the dearth of PSAs on the market is not surprising.

V. Where Do We Go from Here?

How, then, can the development of pathogen-selective antibiotics be incentivized? Here I propose four ideas. I then consider what the case of pathogen-selective antibiotics might illustrate about incentive frameworks more generally.

A. Proposed Solutions to Incentivize Pathogen-Selective Antibiotics

As a general matter, a solution to the PSA problem must addresses both conditional spillover benefits and network-dependent social utility, as identified earlier.[167] There are countless possibilities. But four key approaches in particular may be useful approaches to incentivize development of PSAs: comprehensive prize or partnership frameworks, targeted research grants, coupled or tolled exclusivity, and revised clinical trial standards.

1. Comprehensive Prize or Partnership Framework

A unifying principle underlying the problems with PSAs is the lack of a centralized coordinating body that can both assess and prioritize solutions based on social need. As such, a prize-based framework may offer a solution.

Numerous famous prizes have been used to induce technology development.[168] Prizes are an attractive ex post way to compensate companies who successfully develop a given technology; for instance, in 2004 the X Prize Foundation awarded $10 million for a successful private spaceflight.[169] They have become increasingly popular.[170] Additionally, such prizes often also entail considerable prestige that, interestingly, may lead the net monetary investment in a project to far exceed the value of the prize itself.[171] In the PSA context, then, the government (or a resource-

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Federal Funding for the Study of Antimicrobial Resistance in Nosocomial Pathogens: No ESKAPE, 197 J. INFECTIOUS DISEASES 1079 (2008) (coining term).

165 *See supra* discussion accompanying notes 92–103.

166 *Cf.* Rachel E. Sachs, *Prizing Insurance: Prescription Drug Insurance as Innovation Incentive*, 30 HARV. J.L. & TECH. 153, 160–71 (2016) [hereinafter Sachs, *Prizing Insurance*] (considering "innovation distortions" associated with exclusivity and market mechanisms).

167 *See supra* sections III.A.1–2.

168 *See generally* Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents–Prizes Debate*, 92 TEXAS. L. REV. 303, 317–19 (2013) (discussing examples, including the Longitude Prize and the X Prize).

169 *Id.* at 317.

170 *See id.* at 317–18.

171 *E.g.*, Vijay V. Vaitheeswaran, *The Rise of the Prize*, FREAKONOMICS (Mar. 14, 2012, 11:29 AM), http://freakonomics.com/2012/03/14/the-rise-of-the-prize/.

laden nonprofit foundation) could award prizes for the development of a particular PSA–diagnostic pair. As such, the prize administrator could determine at the outset the most appropriate pathogens, in terms of social burden, for a PSA strategy and could adjust the prize amount of each one based on the anticipated scientific and market difficulties in each. (Interestingly, the current iteration of the Longitude Prize is a £10 million reward for whoever developed a point-of-care diagnostic test to enable antibiotic conservation.[172])

However, a government-funded prize has a pragmatic drawback: it would entail a large and politically unpopular budgetary drain. Drug development is expensive and risky,[173] and so effective prize amounts would likely need to be large. Moreover, the number of PSAs needed to make the overall strategy effective might exacerbate the budgetary concerns. And where consumers are generated by need, not by brand goodwill, the prestige of a prize may have less sway than, say, in the software industry.[174] And some contend that the government is not really any better than the market at assessing demand.[175] Of course, the above considerations are worth weighing against the enormous financial burden of the current and future antibiotic resistance crisis.

An alternative mechanism might be a public–private partnership. Such organizations capitalize on the unique strengths of public institutions (i.e., delinkage of profits from funding; derisking) and private institutions (i.e., commercialization expertise; infrastructure and resources). This approach would also be likely less of a budgetary drain, relying more on private capital investment. Notably, public–private partnerships have been touted as a viable mechanism for innovation where there exists a combination of an unmet social need and certain barriers to a solely private market solution.[176] Such partnerships also offer an opportunity for companies to derive some possible use out of their own intellectual property that would otherwise not be exploited.[177] Antibiotics-focused partnerships include ND4BB[178] and CARB-

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[172] *The Challenge: Reduce the Use of Antibiotics*, LONGITUDE PRIZE, https://longitudeprize.org/challenge (last visited Apr. 7, 2018).

[173] *See* Lisa Larrimore Ouellette, *Patentable Subject Matter and Nonpatent Innovation Incentives*, 5 U.C. IRVINE L. REV. 1115, 1140 (2015).

[174] On the other hand, public fixation on big-name figures in pharma—like Martin Shkreli—and diagnostics—like Elizabeth Holmes—as well as fervor around the entry of certain brands, like Apple, into the health care field, suggests that the biomedical industry is not *immune* from the influences of brand.

[175] *See, e.g.*, Ouellette, *supra* note 173, at 1140–41 (noting this in the context of software).

[176] *See* Liza S. Vertinsky, *Patents, Partnerships, and the Pre-Competitive Collaboration Myth in Pharmaceutical Innovation*, 48 U.C. DAVIS L. REV. 1509, 1530–37 (2015) (describing the benefits traditionally ascribed to public–private partnerships).

[177] For example, some companies share libraries of patented compounds with research institutions under material transfer agreements. *See, e.g.*, Stefan Knapp et al., Commentary, *A Public-Private Partnership to Unlock the Untargeted Kinome*, 9 NATURE CHEMICAL BIOLOGY 3 (2013) (proposing "a large-scale public-private partnership as a new approach that offers economies of scale, minimized redundancy and sharing of risk and cost").

[178] ND4BB, http://www.nd4bb.eu/ (last visited Apr. 7, 2018).

X.[179]

Although public–private partnerships have been criticized as ignoring market realities and not actually promoting increased information-sharing,[180] this approach—like a prize framework—would benefit from a centralized body that could assess social value and coordinate research efforts. The envisioned partnership would function much like the prize system described above. Additionally, the partnership could adjust incentive mechanisms (targets, funding amounts, etc.) in a more quick, dynamic fashion than could a traditional grant or regulatory program bound by procedural rules. Further, the attachment of the partnership's *brand*, so to speak, to the individual drugs might offer a signal of confidence to investors, promoting further investment and development.[181]

Such a partnership could also require contractual commitments to information-sharing, for instance, between the participating institutions.[182] This spillover benefit (e.g., one firm's data about the efficacy of a discarded compound against a pathogen pursued by a second company in the partnership) would serve efficiency aims. Moreover, a partnership offers the ability for integrated healthcare systems or healthcare payers (like insurers) to get involved.[183] These organizations are often massive institutions that control not only significant medical infrastructure (e.g., networks of doctors and hospitals) but also have large quantities of data on the burdens of particular diseases in patients.[184] Healthcare payers also stand to perhaps benefit from the most—in terms of cost-savings—from the development of a PSA arsenal, reducing appropriability concerns.

On the other hand, a public–private partnership model has a certain anticompetitive flavor that a prize model lacks.[185] Under the contract-based partnership model, participating institutions would seem to be segmenting the market among themselves—"you take *Klebsiella*; I'll take *Enterococcus*"—and reducing competition within each particular pathogen. A prize model, in contrast, by its entirely ex post nature would *encourage* competition within each pathogen. To the extent that such competition is deemed socially wasteful, however, and to the extent that the inherently unfavorable economics of PSAs mean that there wouldn't be any

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179 CARB-X, http://www.carb-x.org/ (last visited Apr. 7, 2018).

180 *See* Vertinsky, *supra* note 176 (criticizing the model).

181 Investors often care about the brand and trademark rights associated with particular patents or inventions. The use of institutional trademarks, for instance, is often included in a license agreement with a university's technology transfer office. For example, the microphone startup Vesper notes on its website that its technology was "invented by . . . founders at the University of Michigan." *About*, VESPER, http://vespermems.com/about/ (last visited Apr. 7, 2018).

182 *Cf.* Jacob S. Sherkow, *Cancer's IP*, 96 N.C. L. REV. 297 (2018) (arguing that data-sharing is essential for success of public–private partnerships in cancer).

183 *See generally* Rebecca S. Eisenberg & W. Nicholson Price, II, *Promoting Healthcare Innovation on the Demand Side*, 4 J.L. & BIOSCIENCES 3 (2017) (arguing that healthcare payers are in a prime position to play a role in the innovation landscape).

184 *See id.* at 5.

185 *See generally* Jorge L. Contreras & Liza S. Vertinsky, *Pre-Competition*, 95 N.C. L. REV. 67 (2016) (examining so-called pre-competitive collaboration in pharmaceuticals through an antitrust lens).

real competition, anyway, in the absence of the partnership, these concerns are likely minimal.

The prize framework and the public–private partnership solution address appropriability vis-à-vis network-based social utility. Regarding appropriability, the centralization of decision-making and the separation of the funding decisionmaker from the health care payer mean that the prize administrator or the partnership governance can more accurately, at a bird's-eye level, assess social need and benefit, as well as account for positive externalities inherent in PSAs. Regarding network-based social utility, a coordinating body is better poised than an individual or single firm to determine when the threshold of social utility has been crossed, or to anticipate when that will occur.

2. Targeted Research Grants

Government-funded basic research provides a rich body of fundamental science, and spillover benefits, that are critical for drug development.[186] Recent attention in the literature has highlighted the value of basic research grants in incentivizing the downstream development of applied technologies.[187] Given that our knowledge of mechanisms to selectively target bacteria is limited, increased grant support in this area would likely benefit. (Indeed, a criticism by Kim Lewis of public–partnerships aimed at development, such as CARB-X, is that development is fruitless without a sufficient supply of underlying basic scientific knowledge, and that current market-oriented efforts inadequately address that concern.)[188]

Government grants do address antibiotics research in general—for instance, the National Institute of Allergy and Infectious Diseases, an arm of the NIH, administers a program aimed at addressing antibiotic resistance generally.[189] A relatively small portion of this research is specifically focused on pathogen-selective antibiotics.[190] However, the increasing trend of funding for alternatives to traditional antibiotics forecasts future opportunities for such projects.[191]

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[186] *See, e.g.*, Megan Thielking, *NIH Funding Contributed to 210 Approved Drugs in Recent Years, Study Says*, Stat (Feb. 12, 2018), https://www.statnews.com/2018/02/12/nih-funding-drug-development/ ("Federally funded studies contributed to the science that underlies every one of the 210 new drugs approved between 2010 and 2016.") (discussing Ekaterina Galkina Cleary et al., Contribution of NIH funding to new drug approvals 2010–2016 PNAS (2018), https://www.pnas.org/content/115/10/2329 (last visited Apr 7, 2018)).

[187] *E.g.*, W. Nicholson Price II, *Grants*, 34 BERKELEY TECH. L.J. 1 (2019).

[188] *See* Mullard, *supra* note 142.

[189] *Antimicrobial (Drug) Resistance*, NIH: NAT'L INST. OF ALLERGY & INFECTIOUS DISEASES, https://www.niaid.nih.gov/research/antimicrobial-resistance (last updated July 11, 2016).

[190] Indeed, there appear to be only a handful of active NIH grants aimed at pathogen-selective antibiotic discovery, as evidenced by a search of the NIH database. *See Research Portfolio Online Reporting Tools (RePORT)*, NIH, https://report.nih.gov/ (last visited Apr. 7, 2018).

[191] *See, e.g.*, New Release, *New NIH Awards Will Support Development of Therapeutic Alternatives to Traditional Antibiotics*, NIH: NAT'L INST. OF ALLERGY & INFECTIOUS DISEASES (Jan. 11, 2016), https://www.niaid.nih.gov/news-events/new-nih-awards-will-support-development-therapeutic-alternatives-traditional-antibiotics (including, in particular, (1) an Avidbiotics Corporation project for development of bacteriocins that specifically target *Clostridium difficile*; (2) a Brigham and

The recent increase in funding to governmental research agencies[192] suggests that such an approach may be politically feasible, and support for biomedical research is generally bipartisan.[193] This would also address both the network-linkage aspect of the threshold social utility problem (providing simultaneous support for diagnostics research and basic microbiology in individual bacteria species, for instance) and the appropriability problem (delinking downstream profits from utility; enabling centralized federal government to set priorities holistically). The aphorism goes that "a rising tide lifts all boats." Funding basic science rather than specific innovator firms in an area with high scientific uncertainty is consistent with this philosophy; innovator firms benefit from spillover knowledge, and the disclosure incentives inherent in scientific research minimize problems of trade secrecy and inefficient research overlap between firms.[194] Additionally, even basic science funding often leads to patenting and to commercialization of related inventions.[195]

3. Coupled or Tolled Exclusivity

The network-dependence and conditional spillover problems mean that exclusivity for one particular technology is an inadequate incentive: by the time it is useful, exclusivity is likely gone. However, where two technologies are interdependent, their exclusivity might be coupled to incentivize their co-development, simultaneously bolstering the technology network and increasing appropriability.

As discussed above, intellectual property protection for diagnostics has eroded, potentially disincentivizing innovation in the area.[196] Moreover, antibiotics—

Women's Hospital project for development of RNA-enriched, cell type–specific exosomes; (3) an IUPUI project for development of *Staphylococcus aureus*–specific antivirulence agents; (4) a Texas A&M project for development of bacteriophages specific to *Klebsiella pneumoniae*; and (5) a University of Wisconsin-Madison project for development of a CRISPR strategy specific for *Clostridium difficile*).

192 *See* Marina Koren, *Congress Ignores Trump's Priorities for Science Funding*, THE ATLANTIC (Mar. 23, 2018), https://www.theatlantic.com/science/archive/2018/03/trump-science-budget/556229/ ("[T]otal federal spending on research and development will 'reach its highest point ever in inflation-adjusted dollars' . . . .").

193 *See, e.g.*, Robert Pear, *Plan to Cut Funding for Biomedical Research Hits Opposition in Congress*, N.Y. TIMES (Apr. 3, 2017), https://www.nytimes.com/2017/04/03/us/politics/trump-medical-research-funding-nih.html; Katrina vanden Heuvel, *Why Slashing the NIH Budget Is Indefensible*, WASH. POST (Apr. 18, 2017), https://www.washingtonpost.com/opinions/why-slashing-the-nih-budget-is-indefensible/2017/04/18/727f16cc-2383-11e7-b503-9d616bd5a305_story.html.

194 In contrast, private funding—even of public researchers—tends to decrease disclosure incentives. *See, e.g.*, Dirk Czarnitzki, Christoph Grimpe & Andrew A. Toole, *Delay and Secrecy: Does Industry Sponsorship Jeopardize Disclosure of Academic Research?*, 24 INDUSTRIAL & CORPORATE CHANGE 251 (2015) (reporting data suggesting that "industry sponsorship jeopardizes public disclosure of academic research").

195 Danielle Li, Pierre Azoulay & Bhaven N. Sampat, *The Applied Value of Public Investments in Biomedical Research*, 356 SCIENCE 78 (2017) ("About 10% of grants are directly cited by patents . . . and 30% of grants are cited in research articles that are then cited in patents. . . . We also find no systematic relationship between the 'basic' versus 'applied' research focus of a grant and its propensity to be cited by a patent.").

196 *See supra* note 90.

especially repurposed drugs[197] or natural compounds[198]—face patentability challenges. And the probable delay between the invention of the first PSA therapies and the maturation of a broad PSA arsenal means that much of the exclusivity period for the initial PSAs will be wasted.

One possible solution would be to leverage the FDA's patent-like exclusivity regime[199] and award additional exclusivity time where a PSA is submitted for approval with a companion diagnostic. This could not only incentivize development of the PSA vis-à-vis increased exclusivity but also function as indirect exclusivity for the diagnostic.

Another option would be to toll the exclusivity period until the FDA makes a determination that societal use of the PSA is necessary or proper. This would be appealing to drug developers in one sense—exclusivity wouldn't end prematurely—but it would also entail an initial no-revenue period in which competitors could use the information disclosed in the company's patents to invent around the product before it is even marketed. Instead, the government might offer a yearly payment to the company while the exclusivity is tolled and the antibiotic held on reserve—a rent or license option of sorts.[200]

However, these options would require legislative action,[201] and the tolled-exclusivity-plus-rent option might be politically unpopular, viewed as a handout to pharma. Intriguingly, however, a similar approach has been recently considered. The year before the GAIN Act was introduced in the Senate and eventually signed into law,[202] a similar act by the same name had been introduced in the House.[203] The House version contained a provision giving an additional six-month exclusivity period to "qualified infectious disease products for which a companion diagnostic test is

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197 *See* Roin, *supra* note 103.

198 *See* Erika Check-Hayden, *Biotech Reels over Patent Ruling*, 511 NATURE 7508 (2014).

199 *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 359–64 (2007) (describing FDA pharmaceutical exclusivity regime as "pseudo-patents"),

200 This is analogous to the concept of the Advance Market Commitment, which guaranteed suppliers of a pneumococcal vaccine a subsidy per vaccine dose sold. *See* Hemel & Ouellette, *supra* note 168, at 318–19.

201 Tolled exclusivity is not unknown. For example: Under the Hatch–Waxman framework designed to increase access to generic drugs, there is a statutorily mandated 30-month automatic stay against the FDA's approval of a challenger generic submitted under the ANDA Paragraph IV framework. *See generally* Allen M. Sokal & Bart A. Gerstenblith, *The Hatch-Waxman Act: Encouraging Innovation and Generic Drug Competition*, 10 CURRENT TOPICS IN MEDICINAL CHEMISTRY 1950 (2010). This is 30 more months of exclusivity, even if the underlying drug patent ends up being invalid. This exclusivity period may be tolled by delays caused by citizen petitions. *See* Erika Lietzan, Julia Post, *The Law of 180-Day Exclusivity*, 71 FOOD & DRUG L.J. 327, 370 (2016); 21 U.S.C. § 355(q)(1)(G) (2017 Supp.). Pediatric exclusivity, too, can be tolled if it overlaps with ANDA 180-day exclusivity. David E. Korn, Erika Lietzan & Shaw W. Scott, *A New History and Discussion of 180-Day Exclusivity*, 64 FOOD & DRUG L.J. 335, 362 (2009).

202 Food & Drug Administration Safety & Innovation Act of 2012, Pub. L. No. 112-144, Title VIII, §§ 801–806, 126 Stat. 993, 1077–82.

203 GAIN Act, H.R. 2182, 112th Cong. (2011).

cleared and approved."[204] Another provision would have created a study on "incentives for qualified infectious disease biological products."[205] Neither provision was in the Senate-originating version eventually passed into law.

Notably, coupled exclusivity by itself is almost certainly inadequate, as altering the length of exclusivity does not alter the underlying market mechanisms that distort innovation in the first place.[206] But combined with one or more of the other approaches discussed here, it could help solve the appropriability problem and would address threshold social utility as well.

4. Revised Clinical Trial Standards

Commentators have widely noted a perception that the FDA regulatory process itself poses a barrier for antibiotic development.[207] Regardless of whether FDA approval standards should be weakened for antibiotics generally,[208] it seems clear that a change is warranted for pathogen-selective antibiotics in particular.

New antibiotic clinical trials are frequently performed under a standard of noninferiority, rather than superiority, to current therapies.[209] This is in part because of the difficulty of demonstrating therapeutic superiority where an alternate treatment currently exists, and in part because the motivation behind developing a new antibiotic might be related to a side effect rather than its efficacy against the target pathogen. Recent FDA guidance has addressed the noninferiority standard in the antibiotic context.[210] Selection of a noninferiority trial is an ethical consideration—if another therapy exists for an infection, using a placebo, no-treatment control, or low-dose control is unreasonable.[211] A noninferiority study measures the so-called *NI margin*—i.e., how much worse the drug is than the standard of care—and considers

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204 *Id.* § 4.

205 *Id.* § 7.

206 *See* Sachs, *Prizing Insurance*, *supra* note 166, at 161–68 (describing innovation distortions created by duration and scope of IP rights); *id.* at 172–75 (arguing that in the context of drugs, "[patent and FDA exclusivity] interventions are likely to be more effective at the margins, where return-on-investment calculations are roughly comparable[, and] lengthening patent rights or exclusivity periods simply does not create a market where none exists").

207 *E.g.*, Gupta & Nayak, *supra* note 73; Maxson & Mitchell, *supra* note 37, at 3610; Outterson, *Legal Ecology*, *supra* note 58, at 631–32 (describing the "excessive regulation dampens production hypothesis"); Cecilia H. Burke & Geoffrey M. Levitt, *A Manufacturer's Perspective: Recent Challenges in Antibiotic Drug Approval*, 2 UPDATE: FOOD & DRUG L. REG. & EDUC. 12 (2008). *But see* Aaron S. Kesselheim & Kevin Outterson, *Improving Antibiotic Markets for Long Term Sustainability*, 11 YALE J. HEALTH POL'Y, L. & ETHICS 101, 121 (2011) ("While these claims about clinical study designs are plausible, they are not universally accepted.").

208 *See, e.g.*, Kesselheim & Outterson, *supra* note 207, at 121 (noting relatively high rate of post-approval withdrawals of antibiotics from the market due to safety concerns).

209 Maxson & Mitchell, *supra* note 37, at 3610. *See generally* FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., NON-INFERIORITY CLINICAL TRIALS TO ESTABLISH EFFECTIVENESS: GUIDANCE FOR INDUSTRY (Nov. 2016), https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf [hereinafter FDA NON-INFERIORITY GUIDANCE].

210 FDA NON-INFERIORITY GUIDANCE, *supra* note 209.

211 *Id.* at 7.

this margin against the risks and benefits of the drug.[212] This makes sense on the level of the individual patient—and for drugs without significant externalities, it is logical. But where the social value of a drug predominantly accrues to society generally—e.g., in the form of decreased antibiotic resistance—noninferiority presents a roadblock to certain drugs.[213] It also fails to consider the decreasing utility of the standard of care over time.[214]

One solution might be to relax the acceptable NI margin if the FDA makes a finding that the standard of care is likely to be diminished in utility over time. This would allow prioritization of public health–prioritized drugs and allow foresight in drug development. But it would also presumably shift the burden to physicians to avoid prescribing an inferior drug to their own patient, relying on the physician's duty to the patient. This seemingly presents the same ethical problem as that underlying the noninferiority trial design generally.

Alternatively, a solution might be a *threshold-based conditional approval*. In this situation, clinical trials would establish safety and would also establish an FDA-determined "efficacy threshold"—i.e., a determined efficacy level at which the reference standard of care would be considered equivalent to the new drug. Approval for marketing would be tolled until a finding that the threshold had been reached in the clinic. This approach could also be paired with an exclusivity period that began at the conditional approval but was similarly tolled, such that the clock would not begin to run until the efficacy threshold was triggered.

A third solution entails broadening the consideration of what noninferiority means. That is, trials could take into account collateral damage to the patient's microbiome as well as resistance rates (including cross-resistance) and rates of HGT.[215]

The dependence of pathogen-selective antibiotics on rapid diagnostics poses another challenge: clinical trial study design. If the idea is to diagnose an infection within minutes and then administer the drug so that prophylactically administered broad-spectrum antibiotics can be avoided, then the inherently slow recruitment of clinical trial subjects is exceptionally burdensome. This perhaps weighs in favor of a

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[212] *Id.* at 8.

[213] *See* John H. Rex et al., *Progress in the Fight Against Multidrug-Resistant Bacteria 2005–2016: Modern Noninferiority Trial Designs Enable Antibiotic Development in Advance of Epidemic Bacterial Resistance*, 65 CLINICAL INFECTIOUS DISEASES 141, 141 (2017) ("The frustratingly circular nature of this paradoxical problem is made more confusing because active-control trials (including superiority trials) of new antibiotics are so easily designed on paper.").

[214] *Id.* at 144 ("One additional prominent concern has been the theoretical risk of 'biocreep,' wherein use of successively less efficacious comparator agents results in a sequential degradation of the acceptable efficacy of a new antibiotic.").

[215] This is consistent with the ideas behind noninferiority trials. *See, e.g.*, Mark J. DiNubile, *Noninferior Antibiotics: When is "Not Bad" "Good Enough"?*, 3 OPEN F. INFECTIOUS DISEASES, May 2016, no. 3, at 2 ("Noninferiority trials primarily aim to establish that at worst a clinically acceptable decrement in efficacy between a standard and experimental therapy could exist. Any tradeoff in efficacy might potentially be compensated by decreased toxicity, more convenience, lower cost, and/or a broader (or narrower) spectrum of activity.").

more flexible regulatory model, perhaps based more on postmarket surveillance.[216]

Current legislative trajectory is perhaps encouraging on this front. The 21st Century Cures Act[217] in 2016 introduced changes to the FDA approval process that apply to antibiotics.[218] Such changes include limited-population approval for drugs that treat certain serious infections accompanied by circumscribed drug labeling (the so-called "Limited Population Antibacterial Drug" pathway).[219] The Act also provides for the use of observational data (so-called "real-world evidence"), biomarkers, and surrogate markers of efficacy in identifying treatments whose effectiveness has decreased.[220] However, many have voiced concerns that the Act really just lowers safety standards without concomitant gains in meeting public health needs.[221]

Regardless of the precise approach, any revised clinical trial standards must take into account the likely diminishing utility of existing therapies.

Of course, revised clinical trial standards are unlikely to be a sufficient independent incentive for antibiotic development, as this approach directly addresses neither the appropriability nor the network-dependence problems. However, it is an important predicate for the success of the other interventions noted above. Without such a change, so-called anticipatory drug development[222] will be impossible, as clinical development would require waiting until existing broad-spectrum drugs have become ineffective enough to be useful.

B. Rethinking Disease-Specific Incentive Frameworks

The case of pathogen-selective antibiotics suggests something about innovation policy more broadly. Kevin Outterson has noted that the literature often does not treat antibiotics separately from other drugs, underestimating the complexity of their legal

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216 *Cf.* W. Nicholson Price II, *Regulating Black-Box Medicine*, 116 MICH. L. REV. 421, 462–65 (2017).

217 21st Century Cures Act, Pub. L. No. 114-255 (2016).

218 Statement, *Pew Applauds Provisions of 21st Century Cures Act*, PEW CHARITABLE TRUSTS (Dec. 7, 2016), http://www.pewtrusts.org/en/about/news-room/statements/2016/12/07/pew-applauds-provisions-of-21st-century-cures-act.

219 Editorial, *A Better Pathways to Approval of 21st Century Cures?*, 17 LANCET INFECTIOUS DISEASES 117 (2017).

220 *Id.*

221 *See, e.g.*, Rachel Sachs, *What is the Right Number of Unsafe, Ineffective Drugs for the FDA to Approve?*, HARV. LAW: BILL OF HEALTH (Dec. 5, 2016), http://blogs.harvard.edu/billofhealth/2016/12/05/what-is-the-right-number-of-unsafe-ineffective-drugs-for-the-fda-to-approve/; Ameet Sarpatwari & Michael Sinha, HEALTH AFF. BLOG (Nov. 30, 2016), https://www.healthaffairs.org/do/10.1377/hblog20161130.057730/full/. *But see* Derek Lowe, *The Politics of the 21st Century Cures Act*, IN THE PIPELINE (Dec. 9, 2016), http://blogs.sciencemag.org/pipeline/archives/2016/12/09/the-politics-of-the-21st-century-cures-act ("In all the horrified talk – and some of the horror would be justified – it's worth remembering that the FDA's mandate to consider efficacy and safety is not up to the desires of any one commissioner or administration. It's part of the legislation establishing the entire agency. If you want to change that, you have a lot more shovel work to do.").

222 Rex et al., *supra* note 213, at 141.

ecology.[223] And as Amy Kapczynski and Talha Syed observe, a key difficulty in some areas of innovation is that appropriability by the inventor of social value varies with the kind of good.[224] The case of pathogen-selective antibiotics suggests that this is true even *within* a kind of good. Indeed, a broad-spectrum antibiotic and a pathogen-selective antibiotic, set side-by-side on a desk or a chalkboard, might look like nearly indistinguishable permutations of carbon and other elements. Both are compositions of matter made and distributed under an identical manufacturing and regulatory framework. Both might even be primarily directed at the same medical indication. Yet the most effective innovation lever for each differs strikingly.

As such, the above suggests that it might be more useful to think generally about incentive frameworks not in terms of disease or symptom[225] (e.g., Alzheimer's, infectious disease, cancer, depression, etc.) but rather in terms of the contextual relationship between the drug, the doctor, the disease, and society (e.g., precision vs. prophylactic, phenotypic vs. genomic, broad-spectrum vs. narrow-spectrum, etc.).[226] There is some irony in this recommendation coming in the context of a Note focused very squarely on a very particular public health burden. But the analysis above might apply to the development of therapies in areas of high network-dependence, such as precision oncology, epidemiological prevention, or theranostics.

VI. Conclusion

Pathogen-selective antibiotics offer hope in the fight against antibiotic-resistance superbugs, promising reduced collateral damage and resistance rates. But current antibiotic incentives focus on antibiotics as a broad monolith and are generally inadequate for incentivizing the development of one-bug-per-drug therapies. In some respects, pathogen-selective antibiotics are special: namely, via conditional spillover benefits and network-dependent social utility. These characteristics must be considered if we are to incentivize development of a pathogen-selective arsenal. Accordingly, I suggest that a comprehensive prize or bounty framework, targeted research grants, coupled or tolled exclusivity, or revised clinical trial standards may be useful tailored solutions.

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223 Outterson, *Legal Ecology*, *supra* note 58, at 623.

224 *See generally* Amy Kapczysnki & Talha Syed, Essay, *The Continuum of Excludability and the Limits of Patents*, 122 YALE L.J. 1900 (2013).

225 *E.g.*, Outterson, *Legal Ecology*, *supra* note 58 (looking at antibiotics).

226 *E.g.*, W. Nicholson Price II, *Black-Box Medicine*, 28 HARV. J.L. & TECH. 419 (2015) (examining phenomenon of black-box medicine by examining relationship between data sources, doctors, and regulatory bodies, in the absence of any particular disease indication).