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Kevin Outterson

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Kevin Outterson

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THE LEGAL ECOLOGY OF RESISTANCE: THE ROLE OF ANTIBIOTIC RESISTANCE IN PHARMACEUTICAL INNOVATION

Kevin Outterson[*]

ABSTRACT

Antibiotic effectiveness is a common pool resource that can be prematurely depleted through resistance. Some experts warn that we may face a global ecological collapse in antibiotic effectiveness.

Conventional wisdom argues for more intellectual property rights to speed the creation of new antibiotics. Recent theoretical literature suggests that conservation-based approaches may yield superior results. This Article describes a novel typology for organizing these emerging theories and provides an early empirical test of these models using proprietary data on the sales of vancomycin, an important hospital antibiotic for the last three decades.

The results challenge the assumptions in several models and will force a re-evaluation of the role of intellectual property rights in antibiotic resistance and conservation. In particular, insurance reimbursement may be a more effective policy lever than patent law to preserve antibiotic effectiveness.

I. THE TRAGEDY OF THE ANTIBIOTIC COMMONS

Antibiotics may be the greatest single medical success of the twentieth century. But this achievement rests on an insecure foundation. As antibiotics are used, they create evolutionary pressure that threatens their undoing through resistance.[1] In a post-antibiotic

[*] Associate Professor of Law, Boston University School of Law. My thanks to Dr. Marc Lipsitch of the Harvard School of Public Health for his assistance in the biology of resistance, and Aaron Kesselheim, M.D., at the Harvard Medical School, for our joint work relating to innovative coordination mechanisms for antimicrobial conservation.

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world,[2] some of the advances in health over the previous seventy-five years would be threatened.[3] The edifice of modern medicine assumes the efficacy of antibiotic therapies as a foundational tool.

Antibiotic effectiveness is correctly viewed as a valuable common pool resource[4] akin to verdant forests, productive fisheries, and a stable Greenland Ice Sheet. Common pools are prone to depletion and collapse through uncoordinated withdrawals. In the case of antibiotics, withdrawals occur as antibiotic resistance grows through use and misuse. We face a tragedy of the antibiotic commons as uncoordinated use and misuse of precious antibiotics may prematurely destroy these important drugs.[5]

September 2008; the Drug Policy Research Group at Harvard Medical School in October 2008; and at several meetings of the Drug Resistance Working Group at the Center for Global Development. This work is supported by research grants from The Robert Wood Johnson Foundation, Resources for the Future; the Boston University School of Law; the Ewing Marion Kauffman Foundation; and an in-kind grant from IMS Health.

[1] The relationships between use and resistance are not linear and are occasionally negatively correlated. Marc Lipsitch, *The Rise and Fall of Antimicrobial Resistance*, 9 TRENDS IN MICROBIOLOGY 438, 441-42 (2001).

[2] Per Nordberg, Dominique L. Monnet & Otto Cars, *Antibacterial Drug Resistance*, *in* WORLD HEALTH ORGANIZATION, PRIORITY MEDICINES FOR EUROPE AND THE WORLD: PUBLIC HEALTH APPROACHES TO INNOVATION ch. 6.1 (2004), *available at* http://archives.who.int/prioritymeds/report/index.htm; Richard P. Wenzel, *The Antibiotic Pipeline—Challenges, Costs, and Values*, 351 NEW ENG. J. MED. 523 (2004) ("Currently, the antibiotic era is threatened . . . .").

[3] Many commentators focus on the devastating return of infectious diseases in a post-antibiotic era. *See, e.g.*, RAMANAN LAXMINARAYAN ET AL., EXTENDING THE CURE: POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE 1-28, and sources cited therein (2007); William M. Sage & David A. Hyman, *Combating Antimicrobial Resistance: Regulatory Strategies and Institutional Capacity*, 84 TULANE L. REV. (forthcoming 2010), *available at* www.ssrn.com/abstract=1436154, at 3-4. But the majority of the decline in 20th-century infectious disease mortality in the United States occurred before the introduction of antibiotics. Gregory L. Armstrong, Laura A. Conn & Robert W. Pinner, *Trends in Infectious Disease Mortality in the United States During the 20th Century*, 281 J. AM. MED. ASS'N 61, 63 fig.1 (1999) (showing a decline in infectious disease mortality rates in the United States from about 800 per 100,000 persons in 1900 to less than 400 per 100,000 persons prior to 1935). Nevertheless, much of the current practice of medicine in U.S. hospitals and ambulatory surgical centers depends upon effective antibiotics and would undergo radical changes in a post-antibiotic era.

[4] Several authors have written of antimicrobial effectiveness as a common pool resource. *See* LAXMINARAYAN ET AL., *supra* note 3; Eric Kades, *Preserving a Precious Resource: Rationalizing the Use of Antibiotics*, 99 NW. U. L. REV. 611 (2005); Kevin Outterson, Julie Balch Samora & Karen Keller-Cuda, *Will Longer Antimicrobial Patents Improve Global Public Health?*, 7 LANCET INFECTIOUS DISEASES 559 (2007) [hereinafter Outterson et al., *Antimicrobial Patents*]; Kevin Outterson, *The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Intellectual Property Law*, 67 U. PITT. L. REV. 67, 78-80 (2004) [hereinafter Outterson, *Vanishing Public Domain*]. Some consider antimicrobial effectiveness a public good. *See, e.g.*, RACHEL NUGENT ET AL., CENTER FOR GLOBAL DEVELOPMENT, PROTECTING DRUG EFFICACY AS A GLOBAL HEALTH GOOD: DRAFT REPORT OF THE DRUG RESISTANCE WORKING GROUP (Dec. 5, 2008) (on file with author); Sage & Hyman, *supra* note 3, at 8. But antibiotics themselves are not public goods: Consumption is rivalrous through resistance, and exclusion is possible through global intellectual property law.

[5] For a general introduction to the tragedy of the commons, see Randall R. Dipert,

This Article focuses on three important policy questions concerning resistance. The first is the tension between production of new antibiotics and conservation of existing drugs. At first blush, both seem to be laudable goals, but in many ways conservation and production work at cross purposes, and difficult choices must be made between them. For example, antibiotic conservation suppresses demand for antibiotics by controlling infectious diseases and curbing inappropriate use. Viewed from the perspective of new drugs, these programs undercut market incentives by dampening future demand. This is known as the "conservation dampens production" hypothesis, as discussed at length below.[6] But from the perspective of public health, infection control is an unqualified success when infections are prevented. Another important hypothesis, "patent holder conservation,"[7] posits that patent holders will be careful stewards of antibiotics, promoting conservation through patent law. This Article explores these concepts and suggests that greater emphasis should be placed on conservation, but not necessarily through patent law.

The second question is the relationship between resistance and innovation. The conventional wisdom assumes that resistance is a problem in antibiotic innovation, but this Article argues that resistance may actually stimulate innovation rather than retard it.[8] Resistance makes highly effective antibiotics obsolete over time, which clears the competitive field before a new drug enters the market. This process of creative destruction may favor innovation.

The final question evaluates the policy levers employed in the battle against antibiotic resistance. This Article questions the current reliance on patent law to solve antibiotic resistance problems. For example, the Infectious Diseases Society of America (IDSA) correctly identifies the need for effective antibiotic therapies, but has mistakenly called for significant changes in patent law to remedy the problem, including patent extensions and wildcard patent extensions[9] for

Sidestepping the Tragedy of the Commons, *in* THE COMMONS: ITS TRAGEDIES AND OTHER FOLLIES 27 (Tibor R. Machan ed., 2001); Garrett Hardin, *The Tragedy of the Commons*, 162 SCIENCE 1243 (1968).

6 *See infra* Part II.C.

7 *See id.*

8 This is the "resistance stimulates innovation" hypothesis, discussed *infra* Parts II.C and III.C.

9 A wildcard patent extension grants additional years of patent life on any drug of a company's choice if the company achieves some socially desirable goal—in this case, development of a novel antibiotic. Wildcard patent extensions have generated sharp academic exchanges in recent years. *See* Jorn Sonderholm, *Wild-Card Patent Extensions as a Means to Incentivize Research and Development of Antibiotics*, 37 J.L. MED. & ETHICS 240 (2009) (supporting wildcard patent extensions); Amy Kapczynski, *Commentary: Innovation Policy for a New Era*, 37 J.L. MED. & ETHICS 264 (2009) (critiquing Sonderholm); Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 561-62 (finding wildcard patent extensions to be inefficient, unfair, and possibly unconstitutional); Brad Spellberg, *Antibiotic Resistance and*

antibiotics.[10] Patent law mechanisms are ill-suited to address this problem, in part because pharmaceutical prices in the United States are not really set by the market.[11] To the extent that market-based pricing is an important element of the patent system,[12] its absence in pharmaceuticals is quite troubling. If the primary market signals are muddled or broken, additional patent-based programs should not be rolled out before the reimbursement system is fixed.[13]

Insurance reimbursement is a powerful tool that is not well deployed to promote continued antibiotic effectiveness. As discussed *infra* Part III.C, reimbursement has created both helpful and perverse financial incentives. The former improves access to drugs through third party reimbursement; the latter hinders conservation and allows hospitals and physicians to receive additional payments for out-of-control infections and unnecessary prescriptions. Private incentives and social goals are seriously mismatched. But perhaps it is easier to fix the reimbursement system than to implement effective patent-based solutions. If so, our policy focus should be on reimbursement rather than patents.

This Article proceeds as follows. Part II maps the theoretical terrain surrounding the tragedy of the antibiotic commons, with an emphasis on organizing existing approaches into a new typology, found in Table 1.[14] The goal of this exercise is to place existing work into six theoretical categories and to identify missing elements in the current literature. Seven key hypotheses from the most relevant theories are then collected and summarized in Table 2.[15] For example, one hypothesis is called "patent holder waste" because it posits that an antibiotic patent holder, facing imminent expiration of its patent, may be inclined to waste the asset (from society's viewpoint) through overzealous marketing before the patent enters the public domain. The patent holder waste hypothesis, if proven, offers patent law as a possible antibiotic conservation tool: With a longer patent, the drug company

Antibiotic Development, 8 LANCET INFECTIOUS DISEASES 211-12 (2008) [hereinafter Spellberg, *Antibiotic Resistance*] (critiquing Outterson et al.); Kevin Outterson, *Antibiotic Resistance and Antibiotic Development—Author's Reply*, 8 LANCET INFECTIOUS DISEASES 212-14 (2008) [hereinafter Outterson, *Antibiotic Resistance*] (responding to Spellberg's critique); B. Spellberg et al., *Societal Costs Versus Savings from Wild-Card Patent Extension Legislation to Spur Critically Needed Antibiotic Development*, 35 INFECTION 167 (2007) [hereinafter Spellberg et al., *Societal Costs Versus Savings*] (supporting wildcard patent extensions for antibiotics).

10 INFECTIOUS DISEASES SOC'Y OF AM., BAD BUGS, NO DRUGS: AS ANTIBIOTIC DISCOVERY STAGNATES . . . A PUBLIC HEALTH CRISIS BREWS 22-26 (2004) [hereinafter BAD BUGS]. This report was a call to action from the leading infectious diseases society in the United States.

11 *See infra* Part III.C.

12 *See infra* Part III.C.

13 Arti K. Rai, *Building a Better Innovation System: Combining Facially Neutral Patent Standards with Therapeutics Regulation*, 45 HOUS. L. REV. 1037, 1056-57 (2008).

14 *See infra* Part II.B tbl.1.

15 *See infra* Part II.C tbl.2.

could manage the antibiotic more in keeping with society's long-term interests. This Article casts some doubt on the validity of the patent holder waste hypothesis, as well as several other proffered hypotheses.

Since context matters, Part III is more practical in orientation, exploring the institutional and legal structures in the U.S. market that directly affect continued antibiotic effectiveness, including the central role of reimbursement (in Part III.C). This Part also draws heavily upon the biomedical evidence on resistance, since resistance involves biologically complex systems with many heterogeneous elements. To adequately understand and model resistance, understanding both the biological and legal ecology is vital.

Part IV is the case study on vancomycin, using proprietary sales and volume data for this important antibiotic over the past few decades. Vancomycin sales and patent data are evaluated with respect to two of the most important conditions related to antibiotic resistance: *Clostridium difficile*-associated disease (CDAD) and methicillin-resistant *Staphylococcus aureus* (MRSA). The data are placed in the context of U.S. markets for antibiotics, including the relevant patents and insurance reimbursement systems.

The case study challenges several key hypotheses from Table 2.[16] For example, the "resistance stimulates innovation" hypothesis is found to be supported, upending conventional wisdom. Resistance appears to have an overall positive effect on antibiotic production, at least from the public health perspective. On the other hand, the vancomycin case study does not support the "patent holder waste" hypothesis, since limited patent terms do not appear to have encouraged vancomycin waste. The evaluation of the seven hypotheses in light of the case study is found in Table 3.[17]

This Article also challenges the assumption that intellectual property law is the key policy lever for antibiotic markets. The language of intellectual property has been an important framing tool,[18] but other market structures are equally or more important for antibiotics, especially insurance reimbursement. If we repair the broken reimbursement system for antibiotics, patent changes may not be necessary at all.

The stakes are huge for getting these policies right; the Infectious Diseases Society of America warns that the alternative may be a global ecological collapse in antibiotic effectiveness.[19]

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16 *Id.*

17 *See infra* Part IV.C tbl.3.

18 Amy Kapczynski, *The Access to Knowledge Mobilization and the New Politics of Intellectual Property*, 117 YALE L.J. 804 (2008).

19 *See* BAD BUGS, *supra* note 10.

II. LEGAL RESPONSES TO COMMON POOL DEPLETION PROBLEMS

Tragedies of the commons can be addressed through law. Three legal mechanisms have been used in other contexts: private coordination through property law, public coordination through regulation, and private coordination through contract.

A. *Property, Regulation, and Contract*

The first mechanism is privatization—enclosure of the commons—through property rights.[20] The archetype is the overgrazed common pasture facing ecological collapse. The common pasture first becomes private property, and then the new owner manages the resource with property law. The consolidated owner or firm, it is hoped, manages the property for long-term sustainability. The "patent holder conservation" hypothesis is an application of this narrative, substituting public domain antibiotics for common pastureland.[21] We will call this approach "property."

The second legal mechanism is public coordination through regulation. The federal and state regulation of air pollution is a prime example. The atmosphere itself is not easily privatized, and the number of polluters is too large for private coordination, so regulation is a likely tool.[22] We will call this approach "regulation."

The final legal mechanism is private coordination through contract. When transaction costs are low enough, contract can be used for private coordination, often in conjunction with property law.[23] In addition, groups can sometimes manage common resources through informal mechanisms to prevent uncoordinated use and withdrawals.[24] With due regard for the potential for informal coordination, we will nevertheless call this approach "contract."

When property, regulation, and contract tools are all plausible options, the ideal policy surely depends on the context. For some

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[20] For a critical view, see James Boyle, *The Second Enclosure Movement and the Construction of the Public Domain*, 66 LAW & CONTEMP. PROBS. 33 (2003).

[21] *See infra* Part II.C.

[22] If one focuses solely on downwind property owners, and their number is small, pollution externalities could be resolved in contract. *See* Ronald H. Coase, *The Problem of Social Cost*, 3 J.L. & ECON. 1 (1960). When the number of parties and transaction costs grow, contract evolves into either the firm or social contract (i.e., regulation).

[23] *Id.*

[24] *See generally* ROBERT C. ELLICKSON, ORDER WITHOUT LAW: HOW NEIGHBORS SETTLE DISPUTES (1994); ELINOR OSTROM, GOVERNING THE COMMONS: THE EVOLUTION OF INSTITUTIONS FOR COLLECTIVE ACTION (1990).

common pools such as pastureland, property rights may be an effective primary regime. For the Greenland Ice Sheet, direct property rights are an unlikely path to success. Even if we were willing and able to privatize the Greenland Ice Sheet, most of the damages and benefits would not easily be internalized to the owner. The owner would find it difficult to collect fees from the low-lying regions of the world threatened by a rise in sea levels and would find it equally difficult to influence the behaviors of billions of people partially responsible for climate change in order to protect the integrity of the common pool resource. This problem appears to be a candidate for global regulation. Nevertheless, property rights and contract may still play a prominent part. Property rights might slow global climate change through property-based contract schemes like carbon "cap and trade" programs.[25]

In some contexts, mixed approaches dominate. Many forests are a mix of public and private ownership, but even privately owned forests are sometimes regulated for various public benefits. Multiple companies may own and tap large pools of underground oil, but legal regulation can attempt to protect the joint oil pool when private contract falls short.[26] Other examples could be offered, but in each one the ideal mix of property rights, regulation, and contract is likely to vary considerably according to the context. As Coase noted:

> [D]irect governmental regulation will not necessarily give better results than leaving the problem to be solved by the market or the firm. But equally there is no reason why, on occasion, such governmental administrative regulation should not lead to an improvement in economic efficiency. This would seem particularly likely when, as is normally the case with the smoke nuisance, a large number of people are involved and in which therefore the costs of handling the problem through the market or the firm may be high.[27]

We will return to context in Part III.

B. *A Legal Typology of Resistance*

Like the collapse of global fisheries,[28] we may be experiencing an ecological crisis through biological resistance.[29] Legal institutions must

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[25] *U.S. State Governments Join International Carbon Action Partnership on Global Cap-and-Trade Carbon Markets*, 102 AM. J. INT'L L. 162 (John R. Crook ed., 2008) (describing the use of cap-and-trade carbon markets to reduce global carbon emissions). Bill Sage and David Hyman have discussed this concept for antibiotics as well. Sage & Hyman, *supra* note 3, at 16.

[26] *See, e.g.*, EUGENE KUNTZ ET AL., LAW OF OIL AND GAS (2009).

[27] Coase, *supra* note 22, at 18. Coase also notes a third option: doing nothing at all when the costs of regulation exceed the costs of the underlying problem.

[28] *Plenty More Fish in the Sea?*, ECONOMIST, Jan. 3, 2009, Special Report, at 10.

evolve to confront this crisis, with the goal being continued antibiotic effectiveness. The conventional prescriptions in the policy literature are familiar: (1) public health regulation to dampen demand and conserve existing antibiotics (conservation or demand-side tools);[30] and (2) incentives to create new antibiotics, typically through intellectual property rights and government grants (production or supply-side tools).[31]

Conservation/Production are a related dyad for antibiotic common pools, similar to the Property/Regulation/Contract coordination discussion immediately above. Mapping these elements onto a simple grid creates the following Table 1. This approach organizes existing tools into six sectors. Any particular sector should not be mistaken as the ultimate objective. The policy goal is not more drug patents (Sector 2), better conservation programs (Sector 3), or more efficient insurance reimbursement (Sector 5), but the continued availability of effective antibiotic treatments when needed.

[29] *See* BAD BUGS, *supra* note 10.

[30] For a classic book length introduction, see STUART B. LEVY, THE ANTIBIOTIC PARADOX: HOW THE MISUSE OF ANTIBIOTICS DESTROYS THEIR CURATIVE POWERS (2d ed. 2002); *see also* DEPT. OF COMMUNICABLE DISEASE SURVEILLANCE & RESPONSE, WORLD HEALTH ORGANIZATION, WHO GLOBAL STRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE (2001). For a recent review, see Aaron S. Kesselheim & Kevin Outterson, *Fighting Antibiotic Resistance—Innovative Strategies to Promote Continued Antibiotic Effectiveness*, 29 HEALTH AFF. (forthcoming 2010).

[31] *See, e.g.*, F.M. Scherer, *The Pharmaceutical Industry—Prices and Progress*, 351 NEW ENG. J. MED. 927 (2004) (presenting an authoritative overview on the relationship between patented drug prices and R&D). Otto Cars and colleagues advocate both approaches in concert. Otto Cars et al., *Meeting the Challenge of Antibiotic Resistance*, 337 BRIT. MED. J. 726 (2008).

Table 1. Legal Approaches to Continued Antibiotic Effectiveness

	Conservation	**Production**
Property	1. Patents as conservation tools to privately constrain demand.	2. Patents as incentives to bring new antibiotics to market.
Regulation	3. Public health infection control and regulatory antibiotic stewardship programs regulate demand for antibiotics.	4. FDA regulations could be relaxed to speed approval of new antibiotics. Tax subsidies support antibiotic research and development.
Contract	5. Insurance reimbursement could be deployed as a conservation tool.	6. Prizes, grants, and generous reimbursement could support antibiotic research and development.

This typology can help identify policy gaps among the six sectors. For example, it is often assumed that antibiotic production incentives are largely property-based, rooted in intellectual property law to foster the introduction of new antibiotics,[32] but the production column of Table 1 identifies other options, including modifying U.S. Food and Drug Administration (FDA) regulations and creating prizes and grants for new antibiotics. Conversely, antibiotic conservation programs are generally described as regulatory approaches, without sufficient discussion of possible property-based and contract-based conservation tools.[33] The conservation column of Table 1 identifies some alternative approaches, including insurance reimbursement as a contract-based tool.

More fundamentally, it is important to view production and conservation as separate but interrelated realms and to focus appropriate attention on both. Our energy policy once suffered from a singular focus on production and neglected conservation. Today, a broader consensus supports government intervention in favor of both production and conservation.[34] Politicians and economists debate their relative importance but generally support incentives for both as complimentary strategies. For antibiotic policy, a similar consensus has yet to translate into effective action. Sector 3 public health programs, such as hospital infection control and rational use of antibiotics, are commonly

32 *See, e.g.*, BAD BUGS, *supra* note 10.

33 *See, e.g.*, LEVY, *supra* note 30.

34 *See, e.g.*, American Clean Energy and Security Act of 2009, H.R. 2454, 111th Cong. (2009).

applauded, but the structure of our health care system funnels remarkably little money to them. As a result, policy options in Sectors 3 and 5, such as reimbursement for conservation, are starved for cash.[35] The U.S. health care system spends most of the relevant financial resources in Sector 2, to the detriment of the other policy options.

In a similar fashion, most of the relevant legal scholarship has focused on IP solutions in Sector 2, such as drug patents.[36] Patents are particularly valuable for the pharmaceutical industry.[37] Patents and intellectual property law allow pharmaceutical companies to earn excess profits from health insurance companies, government health programs, and consumers. Patent-based drug companies can charge higher prices during periods of marketing exclusivity,[38] which in turn support investments in research and development (R&D). Patents may also

35 Otto Cars et al., *Meeting the Challenge of Antibiotic Resistance*, 337 BRITISH MED. J. 726, 726 (2008) ("However, sufficient financial and human resources to implement the strategy were never provided."); *see also* NUGENT ET AL., *supra* note 4, at 35-38; Richard S. Saver, *In Tepid Defense of Population Health: Physicians and Antibiotic Resistance*, 34 AM. J.L. & MED. 431 (2008) (emphasizing physician demand-side conservation issues).

36 For an overview, see COMM'N ON INTELLECTUAL PROP. RIGHTS, INNOVATION & PUB. HEALTH, WORLD HEALTH ORG., PUBLIC HEALTH: INNOVATION AND INTELLECTUAL PROPERTY RIGHTS 22 (2006), *available at* http://www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf [hereinafter WHO CIPIH Report]. For an introduction to the legal literature, see Frederick M. Abbott & Jerome H. Reichman, *The Doha Round's Public Health Legacy: Strategies for the Production and Diffusion of Patented Medicines Under the Amended TRIPS Provisions*, 10 J. INT'L ECON. L. 921 (2007); Mark A. Lemley, *Ex Ante Verses Ex Post Justifications for Intellectual Property*, 71 U. CHI. L. REV. 129 (2004). For an introduction to the economic literature, see Kenneth W. Dam, *The Economic Underpinnings of Patent Law*, 23 J. LEGAL STUD. 247, 247-48 (1994); Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265, 276-77 (1977); F.M. Scherer, *Nordhaus' Theory of Optimal Patent Life: A Geometric Reinterpretation*, 62 AM. ECON. REV. 422, 427 (1972).

37 JAMES BESSEN & MICHAEL JAMES MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS AND LAWYERS PUT INNOVATORS AT RISK 14 (2008).

38 In addition to patents, drug company products may enjoy additional periods of marketing exclusivity based on regulatory standards. In the United States, the FDA often manages these additional periods of exclusivity. *See, e.g.*, 21 U.S.C. § 355 (2006) (establishing general five-year period of data exclusivity); The Orphan Drug Act, 21 U.S.C. § 360cc(a)(2) (2006) (granting seven years of data exclusivity for qualifying orphan products); U.S. FDA, DEPT. HEALTH & HUMAN SERV., THE PEDIATRIC EXCLUSIVITY PROVISION: JANUARY 2001 STATUS REPORT TO CONGRESS (2001), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049915.pdf (granting six-month extension for pediatric testing). Data exclusivity periods operate independently of patent law and have been the subject of several controversial bilateral trade negotiations. *See* MÉDECINS SANS FRONTIÈRES, BRIEFING NOTE, ACCESS TO MEDICINES AT RISK ACROSS THE GLOBE: WHAT TO WATCH OUT FOR IN FREE TRADE AGREEMENTS WITH THE UNITED STATES 4-6 (2004); Ken J. Harvey et al., *Will the Australia-United States Free Trade Agreement Undermine the Pharmaceutical Benefits Scheme?*, 181 MED. J. AUSTL. 256 (2004); Kevin Outterson, *Agony in the Antipodes: The Generic Drug Provisions in the Australia–USA Free Trade Agreement*, 2 J. GENERIC MED. 316 (2005), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=787224; M. Kevin Outterson, *Free Trade in Pharmaceuticals*, 181 MED. J. AUSTL. 260 (2004); *Teva Opposes 10-Year Data Exclusivity Provision for Israel*, GENERIC LINE, May 5, 2004; Hadas Manor, *US to Israel: Grant 5-Year Exclusivity for Ethical Drugs*, GLOBES ONLINE, July 1, 2004, http://www.globes.co.il/serveen/globes/docview.asp?did=810543&fid=942.

create access problems.[39] This literature is valuable and interesting, but generally does not analyze antibiotics separately.

More novel and germane to antibiotic resistance has been the attempt by a leading professional society and others to expand patent law as an incentive for new antimicrobial production, including introducing longer antibiotic patents.[40] The Infectious Diseases Society of America has suggested extensive patent changes without much relevant analysis of the interaction between patent law and antibiotic markets. Much more sophisticated analysis has come from the *Extending the Cure* report issued in 2007 by Anup Malani and Ramanan Laxminarayan under the auspices of the think tank Resources for the Future.[41]

This focus on intellectual property rights is certainly understandable given the value of patents to pharmaceutical innovation,[42] but Sector 2 is just one of six possible solution spaces for continued antibiotic effectiveness. In recent years, some authors have explored prize-based R&D approaches (Sector 6) with a range of quite remarkable proposals. Two of the most innovative thinkers in this area are James Love and Tim Hubbard,[43] and many other scholars are working on prize-related approaches to pharmaceutical innovation generally, including law professors Terry Fisher and Talha Syed, philosopher Thomas Pogge, and economist Aiden Hollis.[44] Antibiotic

39 *See* Kevin Outterson, *Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets*, 5 YALE J. HEALTH POL'Y L. & ETHICS 193 (2005).

40 BAD BUGS, *supra* note 10, at 4-5 (supporting patent extensions, wildcard patents, and other patent and tax-based incentives to promote antimicrobial development); LAXMINARAYAN ET AL., *supra* note 3, at 9-10 (listing patent modifications as potential policy options to incentive new antimicrobial development and discussing conservation); Spellberg, *Antibiotic Resistance*, *supra* note 9; Spellberg et al., *Societal Costs Versus Savings*, *supra* note 9; George H. Talbot et al., *Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America*, 42 CLINICAL INFECTIOUS DISEASES 657, 666 (2006) (supporting legislation proposed in Congress with the support of the Infectious Disease Society of America). *But see* Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 561-62 (criticizing the wild-card patent proposal); Outterson, *Antibiotic Resistance*, *supra* note 9.

41 LAXMINARAYAN ET AL., *supra* note 3, ch. 7.

42 BESSEN & MEURER, *supra* note 37.

43 James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV. 1519 (2007); Tim Hubbard & James Love, *A New Trade Framework for Global Healthcare R&D*, 2 PLOS BIOLOGY 147 (2004); James Love, *Prizes, Not Prices, to Stimulate Antibiotic R&D*, SCIENCE & DEV. NETWORK, Mar. 26, 2008, http://www.scidev.net/en/health/antibiotic-resistance/opinions/prizes-not-prices-to-stimulate-antibiotic-r-d-.html. *But see* Marlynn Wei, *Should Prizes Replace Patents? A Critique of the Medical Innovation Prize Act of 2005*, 13 B.U. J. SCI. & TECH. L. 25 (2007); Joseph A. DiMasi & Henry G. Grabowski, Patents and R&D Incentives: Comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D 2 (June 25, 2004), http://www.who.int/intellectualproperty/news/en/Submission3.pdf.

44 For book-length treatments of prize proposals, see WILLIAM W. FISHER, III & TALHA SYED, DRUGS, LAW, AND THE HEALTH CRISIS IN THE DEVELOPING WORLD (forthcoming 2010), *available at* http://www.tfisher.org/Drugs%20Contents.htm (selected chapters); AIDEN HOLLIS &

prizes might be offered for novel first-in-class drugs with powerful mechanisms against resistance or for antibiotics targeting specific resistance pathogens for which the drug pipeline appears to be inadequate.[45] Another possible antibiotic prize mechanism would purchase the patent rights to a novel antibiotic, holding the drug in a "Strategic Antibiotic Reserve."[46] The drug would not be marketed, and saved for only the most urgent cases, until such time as resistance to other drugs made it necessary to resort to the reserved drug.[47]

In Sector 3, the medical literature is quite extensive on antibiotic conservation programs,[48] but the legal scholarship is much thinner. A recent effort by Richard Saver admirably moves these Sector 3 issues forward, with a strong emphasis on the role of physicians in managing the demand for antibiotics.[49] Physicians often exhibit agency problems when their desire to make money conflicts with the best treatments for their patients; with antibiotics, an additional problem arises because the best course of treatment for a particular patient might impose a small but cumulatively significant cost on society through resistance.[50]

THOMAS POGGE, INCENTIVES FOR GLOBAL HEALTH, THE HEALTH IMPACT FUND: MAKING NEW MEDICINES ACCESSIBLE FOR ALL (2008); MICHAEL KREMER & RACHEL GLENNERSTER, STRONG MEDICINE: CREATING INCENTIVES FOR PHARMACEUTICAL RESEARCH ON NEGLECTED DISEASES (2004); *see also* William W. Fisher & Talha Syed, *Global Justice in Health Care: Developing Drugs for the Developing World*, 40 U.C. DAVIS L. REV. 581 (2007); Joseph E. Stiglitz, *Scrooge and Intellectual Property Rights: A Medical Prize Fund Could Improve the Financing of Drug Innovations*, 333 BRITISH MED. J. 1279 (2006). The economic and health policy literature is also significant. *See, e.g.*, Robert C. Guell & Marvin Fischbaum, *Toward Allocative Efficiency in the Prescription Drug Industry*, 73 MILBANK QUARTERLY 213 (1995); Steven Shavell & Tanguy Van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525 (2001); Brian D. Wright, *The Economics of Invention Incentives: Patents, Prizes, and Research Contracts*, 73 AM. ECON. REV. 691 (1983); Aiden Hollis, An Efficient Reward System for Pharmaceutical Innovation (Jan. 17, 2005), http://econ.ucalgary.ca/fac-files/ah/drugprizes.pdf. For a more philosophical approach, see Thomas Pogge, *Harnessing the Power of Pharmaceutical Innovation*, *in* THE POWER OF PILLS: SOCIAL, ETHICAL, AND LEGAL ISSUES IN DRUG DEVELOPMENT, MARKETING, AND PRICING 142 (Jillian Claire Cohen et al. eds., 2006).

45 For a list of likely pathogens for such a prize, see Louis B. Rice, *Federal Funding for the Study of Antimicrobial Resistance in Nosocomial Pathogens: No ESKAPE*, 197 J. INFECTIOUS DISEASES 1079 (2008).

46 The analogy is to the Strategic Petroleum Reserve, an idea I floated in 2005 and fleshed out in 2007. Outterson, *Vanishing Public Domain*, *supra* note 4, at 100 ("Postponing discovery of new antibiotics might be the best course so long as the present drugs are better managed."); *id.* at 116 ("Possible market-making techniques include patent buyouts, prizes, strategic stockpiles, and contractual purchase commitments."); Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 564 (not using the term, but calling for paying patent owners to hold important antibiotics "off-market as a conservation plan"); *see also* Kesselheim & Outterson, *supra* note 30, at 9. Bill Sage and David Hyman are also beginning to discuss this idea, *see* Sage & Hyman, *supra* note 3, at 21, and other researchers may have used similar terms as well.

47 For a discussion of vancomycin as an accidental model for the Strategic Antibiotic Reserve, see *infra* Part IV.C.

48 For a recent review of the medical literature, see Kesselheim & Outterson, *supra* note 30, at 6-7.

49 Saver, *supra* note 35 (emphasizing physician demand-side conservation issues).

50 Sage & Hyman, *supra* note 3, at 6-11 (discussing physician agency issues).

This brings us to Sector 1, the intersection of conservation and property rights. Some Sector 1 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. Another example is a catheter with patented anti-bacterial properties. Avoiding hospital-associated infections with improved catheters would reduce demand for antibiotics.

A more adventurous Sector 1 idea is to expand antibiotic patent rights as a conservation tool, allowing patent owners to more fully control the use of their products.[51] The basic proposal is to expand private property rights in antibiotics in order to promote conservation, resolving the tragedy of the antibiotic commons through enclosure and private ordering. Beginning in 2005, Eric Kades[52] suggested that patent-based property rights in antibiotic innovation lead to wasteful overuse as patent expirations approach.[53] He called for much longer patent terms in order to give the patent holder a long-term perspective on the antibiotic patent.[54] Later that same year, I analogized this situation to the ancient tort of waste, a classic temptation as a time-limited property right nears expiration.[55] We built upon prior work of economists and others working on patent-based incentives relating to antibiotic conservation.[56] In general, this work has been theoretical

[51] It appears that Kades introduced this concept to the legal literature. Kades, *supra* note 4, at 635-43, 653-59; *see also* LAXMINARAYAN ET AL., *supra* note 3, at 20; Carolyn Fischer, *Does the Monopolist Care About Resistance?*, *in* BATTLING RESISTANCE TO ANTIBIOTICS AND PESTICIDES: AN ECONOMIC APPROACH 288-92 (Ramanan Laxminarayan ed., 2003) [hereinafter BATTLING RESISTANCE]; John B. Horowitz & H. Brian Moehring, *How Property Rights and Patents Affect Antibiotic Resistance*, 13 HEALTH ECON. 575, 577-78 (2004); Ramanan Laxminarayan, *How Broad Should the Scope of Antibiotic Patents Be?*, 84 AM. J. AGRICULTURAL ECON. 1287 (2002) [hereinafter Laxminarayan, *Scope of Antibiotic Patents*]; Douglas Noonan, *An Economic Model of a Genetic Resistance Commons: Effects of Market Structure Applied to Biotechnology in Agriculture*, *in* BATTLING RESISTANCE, *supra*, at 263-87; Outterson, *Vanishing Public Domain*, *supra* note 4, at 80.

[52] Kades, *supra* note 4.

[53] LAXMINARAYAN ET AL., *supra* note 3, at 12; Kades, *supra* note 4, at 629-38.

[54] Kades, *supra* note 4, at 653-59. Success of the patent extension strategy as a conservation device would require drug companies to value future sales over present sales. If the discount rate was high (as in an inflationary economy), present sales would be strongly preferred. Even in normal economic times, future sales must be discounted. Therefore, as a conservation measure, patent extension will be least valuable in the early years of marketing an antibiotic, and more valuable if added when the patent faced immanent expiration. The effect on resistance is unknown.

[55] Outterson, *Vanishing Public Domain*, *supra* note 4, at 81-86; *see also* Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 563.

[56] LAXMINARAYAN ET AL., *supra* note 3, at 9-10, 12-13; Cars et al., *supra* note 35; Fischer,

rather than empirical. In two recent articles, I offered some anecdotal examples that might be considered evidence of the "patent holder waste" hypothesis,[57] but hard data was lacking. This Article is the first to test these emerging theories with empirical data from an important hospital-based antibiotic—vancomycin.

C. *Hypotheses Concerning Antibiotic Production and Conservation*

Generally speaking, knowledge is non-excludible (inappropriable) and nonrivalrous (inexhaustible); patent law seeks to solve the free-rider problem by awarding market exclusivity to the patent holder. Patent disclosure publicizes useful knowledge, and a patent's expiration makes such knowledge fully available to the public domain. Since knowledge is generally not rivalrous, temporary exclusive use does not diminish the public domain.

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. I have reviewed the literature and discussed these questions at length in prior articles,[58] but will briefly highlight seven important hypotheses that relate to these questions and place them in the context of the six sectors in Table 2 *infra*. Since these hypotheses are being proffered collectively for the first time, this Part is primarily descriptive.

supra note 51; Horowitz & Moehring, *supra* note 51; Ramanan Laxminarayan, *Introduction: On the Economics of Resistance*, *in* BATTLING RESISTANCE, *supra* note 51, at 9; Laxminarayan, *Scope of Antibiotic Patents*, *supra* note 51; Stéphane Mechoulan, *Market Structure and Communicable Diseases*, 40 CAN. J. ECON. 468 (2007); Noonan, *supra* note 51; Tomas J. Philipson & Stéphane Mechoulan, *Intellectual Property and External Consumptive Effects: Generalizations from Pharmaceutical Markets* 9, 13-14 (Nat'l Bureau of Econ. Research, Working Paper No. 9598, 2003), *available at* http://www.nber.org/papers/w9598.pdf?new_window=1 (arguing that optimal patent life is infinite if the good creates negative externalities, citing antibiotic resistance as one example). These authors also draw on two older articles. *See* Gardner Brown & David F. Layton, *Resistance Economics: Social Cost and the Evolution of Antibiotic Resistance*, 1 ENV'T & DEV. ECON. 349, 351 (1996); Clem Tisdell, *Exploitation of Techniques That Decline in Effectiveness with Use*, 37 PUB. FIN. 428, 436 (1982).

[57] Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 563. For a description of the "patent holder waste" hypothesis, see *infra* Part II.C.

[58] *Id.*; Outterson, *Vanishing Public Domain*, *supra* note 4, at 76-78.

Table 2. Hypotheses From Legal and Economic Theory on Continued Antibiotic Effectiveness

Hypothesis	Sector
H1. Patent holder waste	1
H2. Patent holder conservation	1
H3. Patent incentives are inadequate for production	2
H4. Resistance stimulates innovation	2
H5. Conservation dampens production	3
H6. Excessive regulation dampens production	4
H7. Antibiotic externalities are predominantly negative	All

The first two hypotheses—patent holder waste (H1) and patent holder conservation (H2)—are important foundations for property-based conservation efforts in Sector 1. The third and fourth hypotheses—patent incentives are inadequate for production (H3) and resistance stimulates innovation (H4)—relate to the production of novel antibiotic therapies in Sector 2. H5—conservation dampens production—evaluates the impact of Sector 3 conservation initiatives on the production of new antibiotics. H6—excessive regulation dampens production—evaluates the impact of regulatory changes in Sector 4 on the production of new drugs. H7 does not fit neatly into any particular Sector, but has important implications for several areas. The following Part explores each hypothesis in more depth.

Both economists and lawyers have suggested that expansions in patent law might encourage appropriate conservation of antibiotics.[59] Two hypotheses arise from this literature: patent holder waste (H1), and a related concept, patent holder conservation (H2).[60] Patent holder waste (H1) suggests that when companies hold time-limited property rights, they lack financial incentives to manage the antibiotic for the long-term public health. Facing patent expiration in a few years, a company might zealously market the drug, leading to premature resistance.[61] The remaining costs of that resistance are externalized when the patent expires.[62]

[59] *See supra* note 51 and accompanying text.

[60] The term "waste" is taken from the Statute of Gloucester, 6 Edw. 1, ch. 5 (1278). Outterson, *Vanishing Public Domain*, *supra* note 4, at 81-86; Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 563.

[61] LAXMINARAYAN ET AL., *supra* note 3, at 20; Fischer, *supra* note 51; Noonan, *supra* note 51; Horowitz & Moehring, *supra* note 51, at 578-80; Kades, *supra* note 4, at 635-43; Laxminarayan, *Scope of Antibiotic Patents*, *supra* note 51; Outterson, *Vanishing Public Domain*, *supra* note 4, at 80.

[62] This is a simplification in at least two ways. First, expiration of the patent is not a bright line moment for generic entry, as companies generally litigate generic entry and may have

Patent holder conservation (H2) is a related claim, suggesting that if patent holders were given longer and broader patent rights, they could manage resistance more efficiently. The classic analogy is the enclosure of the commons from Hardin's seminal article in *Science*.[63] Although they are related claims, patent holder waste (H1) and patent holder conservation (H2) should be distinguished because the empirical data for each proposition may diverge. For example, H1 predicts that patent owners will aggressively market antibiotics during the last few years of patent life. H2 makes a different claim—that if granted longer patents, the companies would manage antibiotic use for the long term. These propositions are logically distinct. If companies always sell to the extent the market will bear, then H1 may be true while H2 will be false. Put another way, H1 describes a potential problem while H2 is a possible solution.

A simplified example illustrates the difficulties with patent holder conservation. Assume that a patented antibiotic yields $100 million in sales per year, with ten years left in the patent term. With a discount (inflation) rate of five percent, the net present value of the expected income stream is approximately $772 million.[64] If additional marketing could add ten percent per year to net revenues, the company's net present value jumps by $413 million to $1.185 billion.[65] In this simplified example, conservation will not generate positive economic results for the company unless incremental resistance would have destroyed about thirty-five percent of the net present value sales during the patent period.[66] These calculations are very sensitive to the major assumptions: the discount (inflation) rate,[67] the increase in sales that could be achieved with unchecked marketing, and the response rate of resistance. Therefore, patent holder conservation depends upon both the effectiveness of advertising to change discretionary sales, as well as the effect of those marginal sales upon resistance during the patent period.

These hypotheses are theoretical predictions that should be empirically tested. For example, real-world changes in drug firm marketing behavior near the end of the patent term raise difficult questions for H1. Patent-based drug companies generally reduce their

multiple patents on a product or use. Second, branded sales do not automatically cease upon patent expiration. In both cases, the patent holder waste hypothesis is weakened in that the assumption of a time-limited property right is empirically disproven, or at least made significantly more complex.

63 Hardin, *supra* note 5, at 1243-48.

64 Net present value calculation made at Investopedia New Present Value Calculator, http://www.investopedia.com/calculator/NetPresentValue.aspx?viewed=1 (assuming $100 million in revenues each year for ten years with a five percent discount rate).

65 *Id.* (assuming a five percent discount rate and a ten percent increase in sales each year, i.e., $100 million in year 1, $110 million in year 2, $121 million in year 3, etc.).

66 $413 is 34.9% of $1185.

67 Higher discount rates make antibiotic conservation less attractive to companies.

marketing expenses several years in advance of patent expiration, perhaps due to the time lag between marketing investments and resulting drug sales.[68] To avoid creating positive externalities for generic rivals, the patent-based drug companies generally reduce marketing in the last few years of the patent.[69] This is exactly the opposite of the behavior predicted by patent holder waste (H1). Furthermore, after patent expiry, neither generic companies nor the former patent holder engage in much marketing,[70] suggesting that losing patent protection might actually reduce waste through less intensive marketing. Lichtenberg and Duflos find prescription drug utilization to be relatively flat after patent expiration, despite the entry of much cheaper generics. They hypothesize that the price effect and marketing effect roughly cancel one another out.[71] If this result holds true for antibiotics, then both the patent-holder waste (H1) and patent-holder conservation (H2) hypotheses suffer a direct empirical challenge.

The third hypothesis (patent incentives are inadequate for antibiotic production) is rooted in the relatively short treatment course[72] and low reimbursement rates for most antibiotics.[73] It is said that antibiotic markets remain inappropriately small compared to their health benefits.[74] This is another way of saying that the patent owner captures an inadequate percentage of the social welfare surplus created by the antibiotic. Absent attractive markets, companies will not invest appropriately in antibiotic R&D. Many methods could be employed to augment revenues during the patent term, including tax incentives

68 FRANK R. LICHTENBERG & GAUTIER DUFLOS, MANHATTAN INSTITUTE FOR MEDICAL RESEARCH, TIME RELEASE: THE EFFECT OF PATENT EXPIRATION ON U.S. DRUG PRICES, MARKETING, AND UTILIZATION BY THE PUBLIC (2009), http://www.manhattan-institute.org/html/mpr_11.htm.

69 *Id.*

70 *Id.*

71 *Id.* ("The two hypothesized effects of increased competition from generics—increased utilization due to falling prices, and decreased utilization due to reduced marketing—appear approximately to offset each other. . . . [T]he number of free samples declined sharply after patent expiration . . . ."). Their data was virtually all prescription drugs sold in the United States during 2000-2004, not just antibiotics.

72 J.H. Powers, *Antimicrobial Drug Development—The Past, the Present, and the Future*, 10 CLINICAL MICROBIOLOGY & INFECTION 23, 26 (2004) ("Finally, many antimicrobials are prescribed for treatment durations ranging from a single dose to 10 days of treatment. This short-term use limits the potential profitability of antibacterial drugs compared to other classes of drugs."); Sage & Hyman, *supra* note 3, at 8. While this maxim is oft-repeated, there is no inherent reason why reimbursement must be tied to length of treatment. Several recent biological drugs, especially in oncology, have prices in excess of $20,000 despite a short course of treatment. *See, e.g.*, Tito Fojo & Christine Grady, *How Much Is Life Worth: Cetuximab, Non-Small Cell Lung Cancer, and the $440 Billion Question*, 101 J. NAT'L CANCER INST. 1044 (2009). The problem is actually the reimbursement model, not the length of treatment.

73 *See infra* Part III.C.

74 Steven J. Projan, *Why Is Big Pharma Getting Out of Antibacterial Drug Discovery?*, 6 CURRENT OPINION IN MICROBIOLOGY 427, 427-28 (2003); Wenzel, *supra* note 2.

(Sector 4) and improved reimbursement (Sector 5), but longer patent terms are most frequently proposed as an additional incentive for antibiotic production. This view has many champions, including a well-known drug company representative;[75] the Infectious Diseases Society of America;[76] an intergovernmental conference in Europe;[77] and other leading infectious disease experts.[78] Others advance this claim in narrower circumstances. Ben Roin has argued that pharmaceutical patent incentives are particularly weak for obvious uses of existing drugs.[79] Roin calls for new periods of data exclusivity rather than longer patents.[80]

Fourth, resistance makes existing antibiotic drugs obsolete over time, creating market opportunities for new drugs.[81] To the extent that competition with existing drugs discourages market entry by a new drug,[82] resistance clears the field and facilitates introduction of new drugs. This is the resistance stimulates innovation hypothesis (H4). Resistance also encourages the production of antibiotics with novel features. Examples include new drug classes that bypass existing resistance mechanisms, such as ketolides,[83] glycylcyclines,[84] and some

[75] Projan, *supra* note 74, at 429-30.

[76] BAD BUGS, *supra* note 10; Brad Spellberg et al., *Trends in Antimicrobial Drug Development: Implications for the Future*, 38 CLINICAL INFECTIOUS DISEASES 1279 (2004); Talbot et al., *supra* note 40.

[77] Roger Finch & Pamela A. Hunter, *Antibiotic Resistance—Action to Promote New Technologies: Report of an EU Intergovernmental Conference Held in Birmingham, U.K., 12-13 December 2005*, 58 J. ANTIMICROBIAL CHEMOTHERAPY (SUPP. S1) i3 (2006).

[78] S. Ragnar Norrby, Carl Erik Nord & Roger Finch, *Lack of Development of New Antimicrobial Drugs: A Potential Serious Threat to Public Health*, 5 LANCET INFECTIOUS DISEASES 115 (2005); Wenzel, *supra* note 2; Barry Eisenstein, Editorial, *Antibiotic Research: The Kryptonite of Superbugs*, BOSTON GLOBE, Oct. 19, 2009, at 9 (calling for longer antibiotic patent periods; Eisenstein is the Senior Vice President of Scientific Affairs at Cubist Pharmaceuticals).

[79] Data exclusivity hinders FDA approval by generic companies, and hence delays market entry. The general effect is somewhat similar to patents, but the legal mechanism is different. *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 567 (2009).

[80] *Id. But see* Kevin Outterson, *Death from the Public Domain?*, 87 TEXAS L. REV. 45 (2009), http://www.texaslrev.com/seealso/volume-87/roin/death-from-the-public-domain.html (critiquing Roin's positions).

[81] *See infra* Part III.A.

[82] Powers, *supra* note 72, at 25-26 ("There are several reasons why antibacterials may be at a competitive disadvantage relative to other drugs. There is a high level of competition with drugs already on the market. As shown above, there are a number of agents within various classes still available. While resistance is an emerging problem in a relative sense, the majority of infectious diseases in terms of absolute numbers in the USA are still caused by susceptible pathogens.").

[83] C.E. Nord, D.J. Farrell & R. Leclercq, *Impact of Ketolides on Resistance Selection and Ecological Effects During Treatment for Respiratory Tract Infections*, 10 MICROBIAL DRUG RESISTANCE 255, 257 (2004) ("Overall, these findings suggest that ketolides may have a lower potential to select for resistance than existing MLS antibacterials, a factor that will be advantageous in terms of preserving their long-term utility."); *see also* Grit Ackermann & Arne C. Rodloff, *Drugs of the 21st Century: Telithromycin (HMR 3647)—The First Ketolide*, 51 J. ANTIMICROBIAL CHEMOTHERAPY 497, 506 (2003) ("[T]elithromycin did not lead to *Clostridium*

other antibiotics.[85] This second innovation effect is not limited to drugs, but includes innovation in complementary products such as diagnostic tests and conservation techniques.

Fifth, effective conservation measures will dampen the demand for antibiotics and therefore reduce the incentive to develop new ones.[86] Efforts to reduce unnecessary use of antibiotics necessarily impair the market for these products, reducing unit sales.[87] This is the conservation dampens production hypothesis (H5). But it is not clear whether H5 is a bad thing if the goal is healthy people rather than just more drugs. Conservation prevents infections, which is even better than successfully treating them.

Sixth, according to some drug companies, the FDA imposes unreasonable regulatory burdens prior to marketing approval that are particularly difficult to overcome for antibiotics.[88] These regulations are said to increase the expense of clinical trials, delay market entry, and generally discourage antibiotic production. This is the excessive regulation dampens production hypothesis (H6):

> The main reason why industry has left the field of antibiotic research and development is the poor return on investment owing to increasing costs of drug development, caused, in part, by increasing demands from regulatory authorities, and stricter pricing controls imposed by many governments.[89]

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difficile colonization.").

[84] Gary E. Stein & William A. Craig, *Tigecycline: A Critical Analysis*, 43 CLINICAL INFECTIOUS DISEASES 518, 518 (2006) ("[Tigecycline] overcome[s] the 2 major mechanisms of tetracycline resistance: tetracycline-specific efflux pump acquisition and ribosomal protection.").

[85] David L. Paterson, *Clinical Experience with Recently Approved Antibiotics*, 6 CURRENT OPINION PHARMACOLOGY 486 (2006) ("Pharmaceutical companies recognized the threat of increasing antibiotic resistance in organisms such as enterococci and staphylococci. Several new compounds were developed with activity against vancomycin-resistant enterococci and vancomycin-resistance *S. aureus*.").

[86] Kades, *supra* note 4, at 656; Outterson, *Vanishing Public Domain*, *supra* note 4, at 100, 119; Brad Spellberg et al., *The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America*, 46 CLINICAL INFECTIOUS DISEASES 155, 158 (2008).

[87] Norrby, *supra* note 78, at 117 ("Another problem for pharmaceutical companies is that the indications for which antibiotics are prescribed most commonly are now being questioned. The best examples are acute bronchitis, acute exacerbations of acute bronchitis, acute sinusitis, and acute otitis media, indications for which drastically reduced use is now advocated."); Powers, *supra* note 72, at 26 ("[C]linicians see the appropriate public health need to preserve older antimicrobial agents through judicious use, that is, not prescribing antibacterials to patients who do not have a bacterial infection. . . . Experts often also recommend reserving new agents for patients who may have disease caused by resistant pathogens, limiting the potential use of a new drug.").

[88] *See, e.g.*, Projan, *supra* note 74, at 429.

[89] Norrby, *supra* note 78, at 116-19 (suggesting relaxation of regulatory requirements in antibiotic clinical testing). *But see* Powers, *supra* note 72 at 26 ("However, there are no increased regulatory hurdles for antimicrobials, or specifically antibacterials, compared with other therapeutic classes.").

Finally, much of the legal and economic literature describes externalities from antibiotic use as predominantly negative (H7). The classic example is inappropriate use of an antibiotic by a patient with a viral upper respiratory infection, which threatens the public with resistant infections.[90] In this archetype, the doctor and patient both have inappropriate reasons to use the antibiotic despite the lack of medical need (antibiotics are ineffective against viruses). Society bears the costs of both resistance and inappropriate drug expenditures.

The medical literature describes these relationships with more complexity and subtlety.[91] In addition to negative externalities, the patient may be harmed directly (an internalized cost). Receiving antibiotics may expose the patient to significant personal risk. One mechanism is *Clostridium difficile*-associated disease (CDAD), which is a severe and sometimes life-threatening diarrheal disease triggered by antibiotic use (i.e., a nosocomial disease).[92] A second personal cost is promoting resistance in commensal bacteria in the patient's body.[93] Prior antibiotic use is a risk factor for infection by drug-resistant bacteria such as MRSA, increasing the relative risk by a factor of 2.1.[94] When certain antibiotics are used, the relative risk of MRSA is almost three times greater.[95] Similar results have been found for resistant pneumococci after the use of oral cephalosporins and penicillins, with each drug resulting in quite different patterns of resistance and susceptibility.[96] Twenty-five percent of patients receiving fourteen-day treatments of ciprofloxacin developed resistance to nalidixic acid or ciprofloxacin that was not detected before therapy began.[97] One third of

[90] *See, e.g.*, Kades, *supra* note 4, at 626-27.

[91] *See, e.g.*, Marc Lipsitch & Matthew H. Samore, *Antimicrobial Use and Antimicrobial Resistance: A Population Perspective*, 8 EMERGING INFECTIOUS DISEASES 347 (2002); *see also* Kesselheim & Outterson, *supra* note 30, at 4-5 (collecting sources); Outterson, *Vanishing Public Domain*, *supra* note 4, at 104-09.

[92] R.C. Owens, Jr. et al., *Antimicrobial-Associated Risk Factors for* Clostridium difficile *Infections*, 46 CLINICAL INFECTIOUS DISEASES S19 (2008); *see also infra* Part IV.B.

[93] Bruno Fantin et al., *Ciprofloxacin Dosage and Emergence of Resistance in Human Commensal Bacteria*, 200 J. INFECTIOUS DISEASES 390 (2009) (finding that ciprofloxacin use may select for resistance in commensal non-pathogenic bacteria).

[94] Evelina Tacconelli et al., *Does Antibiotic Exposure Increase the Risk of Methicillin-Resistant* Staphylococcus aureus *(MRSA) Isolation? A Systematic Review and Meta-Analysis*, 61 J. ANTIMICROBIAL CHEMOTHERAPY 26, 32 (2008). "This meta-analysis shows a clear association between exposure to antibiotics and MRSA isolation." *Id.* at 26.

[95] *Id.* at 33 ("This risk is almost three times greater after the use of quinolones and glycopeptides.").

[96] Matthew H. Samore et al., *Mechanisms by Which Antibiotics Promote Dissemination of Resistant* Pneumococci *in Human Populations*, 163 AM. J. EPIDEMIOLOGY 160, 166 (2006) ("The results of this study support the hypothesis that distinct antimicrobial classes promote pneumococcal resistance by different mechanisms.").

[97] Fantin et al., *supra* note 93, at 395.

these patients developed resistance to levofloxacin during ciprofloxacin therapy.[98] Antibiotics can directly harm some patients.

Information deficits also play a role. Even if the patient is directly harmed, the negative effect is not truly "internalized" if patients and physicians are not aware of the existence and magnitude of the damage. This situation is akin to a factory that is not aware that it is polluting or that the pollution is damaging its own property. Even with low transaction costs, optimal solutions require accurate knowledge.

In addition, some resistance externalities may be positive. Search and destroy infection control techniques in hospitals and long-term care facilities can reduce the spread of MRSA in a facility, but they also create positive externalities for competing facilities in the community when the patient is discharged.[99] Discharging only non-carriers makes infection control easier and cheaper for competitors within the same epidemiological "germ-shed."[100]

Finally, some antibiotics and patients display heterogeneous externality profiles. Some company-sponsored studies suggest that ketolides may inflict less ecological damage than some other antibiotics.[101] Some antibiotics are associated with higher risks of MRSA.[102] For some important infections (tuberculosis, HIV, influenza and Group A streptococci), treatment itself is a major tool for preventing transmission of susceptible strains. Negative resistance externalities might also be weighed differently if the patient is an African child with a high fever in a low-resource setting. All of these factors add to the complexity of the analysis. Any attempt to optimize antibiotic conservation and production incentives should understand the ecosystem prior to intervention. The next Part explores these contextual elements.

98 *Id.*

99 Put another way, transferring MRSA carriers to nursing homes or community hospitals, or discharging them to the community, imposes uncompensated external costs on competitors.

100 A "germ-shed" is roughly analogous to a watershed: regions that are epidemiologically interdependent and thus share positive and negative infectious disease externalities. Kevin Outterson, Germ-Sheds (unpublished manuscript, on file with author); Sage & Hyman, *supra* note 3, at 34.

101 Nord et al., *supra* note 83, at 255 ("Thus, it is prudent to evaluate the likely ecologic impact of new antibacterial agents—and their potential to select for resistance—before they are widely introduced into clinical practice."); *id.* at 257 ("Overall, these findings suggest that ketolides may have a lower potential to select for resistance than existing MLS antibacterials, a factor that will be advantageous in terms of preserving their long-term utility."); *see also* Ackermann & Rodloff, *supra* note 83, at 506 ("[T]elithromycin did not lead to *Clostridium difficile* colonization.").

102 Tacconelli et al., *supra* note 94, at 33 ("This risk is almost three times greater after the use of quinolones and glycopeptides.").

III. THE ECOLOGY OF RESISTANCE AND INNOVATION

Legal and economic models tend to oversimplify the biology of antibiotic resistance. The relationships are heterogeneous and complex, as are most ecological systems.[103] As Marc Lipsitch notes: "[T]he scale of the problem, and the rate at which resistance becomes a problem, is highly variable, depending on the antimicrobial agent, the pathogen and the setting in which transmission occurs."[104] For example, while resistance to penicillin is widespread for some bacterial species,[105] group A streptococci remain fully susceptible to penicillin after many decades of intensive use.[106] For other drugs and species, limited resistance emerged almost immediately.[107]

Resistance is not limited by the boundaries of a single patent application. Resistance frequently occurs across different drugs within a class,[108] and a few forms of resistance (some efflux systems and permeability changes) apply across multiple classes. In a recent clinical trial, treatment of healthy volunteers with a fourteen-day regime of ciprofloxacin triggered resistance to other members of the quinolone and fluoroquinolone class, including nalidixic acid and levofloxacin.[109] Resistance can also be transmitted across bacterial species.[110] Resistance within classes and between classes differs by both pathogen

103 Lipsitch, *supra* note 1.

104 *Id.* at 438.

105 *CDC's Role in Monitoring and Preventing Antimicrobial Resistance: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 110th Cong. 2 (June 24, 2008) (statement of Fred C. Tenover, Dir., Office of Antimicrobial Resistance, Center for Disease Control and Prevention) [hereinafter *CDC's Role Hearing*] ("To provide a sense of the problem, unpublished data from CDC's National Nosocomial Infection Surveillance System indicate that [more than ninety percent] of strains of *Staphylococcus aureus*, a bacterial species that causes a spectrum of illnesses from minor skin infections to serious life-threatening diseases, are no longer treatable with penicillin, while one third of *Streptococcus pneumoniae* isolates, a common cause of ear infections, pneumonia, and meningitis, are also no longer treatable with penicillin.").

106 Symposium, *Why Have Group A Streptococci Remained Susceptible to Penicillin?*, 26 CLINICAL INFECTIOUS DISEASES 1341 (1998).

107 *See, e.g.*, Ellie Hershberger et al., *Quinupristin-Dalfopristin Resistance in Gram-Positive Bacteria: Mechanism of Resistance and Epidemiology*, 38 CLINICAL INFECTIOUS DISEASES 92 (2004) (finding that resistance emerged not long after regulatory approval).

108 *See* Outterson, *Vanishing Public Domain*, *supra* note 4, at 94-99 (collecting sources).

109 Fantin et al., *supra* note 93, at 395; *see also* David C. Hooper, *Emerging Mechanisms of Fluoroquinolone Resistance*, 7 EMERGING INFECTIOUS DISEASES 337 (2001) (describing the mechanisms of fluoroquinolone resistance, including the role of transmission and selection in reservoir populations).

110 Cesar A. Arias & Barbara E. Murray, *Antibiotic-Resistant Bugs in the 21st Century—A Clinical Super-Challenge*, 360 NEW ENG. J. MED. 439, 443 (2009) ("Moreover, the common presence of these β-lactamase genes of gram-negative bacteria in transferable mobile elements means that these genes could reach virtually any gram-negative bacterium and become a major threat in the future.").

and drug,[111] so the relationships are complex and subject to revision as the biology becomes better known.

Many of the models for resistance mistakenly assume that resistance occurs primarily through single point mutations, based on the example of tuberculosis. If the avoidance of single point mutations is the goal, then policy makers will insist on preventing suboptimal dosing or premature suspension of antibiotic therapy. For this reason, patients are often told to complete the full course of antibiotics. But single point mutation is rare in some drug-bug combinations, meaning that this advice may be counterproductive in some cases. Resistance to some drugs is acquired only through complex exchanges of genetic material, and the novel strains thereby created may gain an advantage in transmitting to other hosts for many reasons other than treatment of the infection of interest with the drug of interest.[112] Such mechanisms of indirect selection for resistant strains may include treatment of patients who do not suffer from the organism of interest but who harbor it on their bodies, or treatment with other antibiotics (besides the one of interest) to which the same strains happen to be resistant.[113] For these patients, a completely different strategy might be appropriate, including early cessation of antibiotic therapy.[114]

Several examples from Lipsitch and Samore illustrate other potential models for acquisition of a resistant infection, focusing on a population perspective rather than simply a single patient. First, if a hospital ward is already colonized with resistant bacteria, treating a patient with an antibiotic as a surgical prophylactic (preventative treatment) might clear an ecological niche for the rapid growth of resistant infections like MRSA in the patient.[115] Second, patients may enter the hospital colonized with both susceptible and resistant species; treatment with an antibiotic clears the susceptible species and may

111 *See, e.g.*, Richard J. Ryan, Chris Lindsell & Paul Sheehan, *Fluoroquinolone Resistance During 2000-2005: An Observational Study*, 8 BMC INFECTIOUS DISEASES 71 (2008) (associating empiric use of moxifloxacin, a fluoroquinolone marketed as Avelox®, with increased resistance by Gram negative bacteria; use of other tested fluoroquinolones (ciprofloxacin, levofloxacin, and gatifloxacin) was associated with a decrease in resistance by Gram negative organisms).

112 Lipsitch & Samore, *supra* note 91 (describing four models of antimicrobial resistance).

113 Hooper, *supra* note 109, at 339 ("Thus, for all three organisms in which fluoroquinolone resistance has become problematic despite a requirement for multiple mutations, other epidemiologic factors (of transmission and ongoing selection in reservoir populations of organisms) appear to be at work.").

114 A study is underway in the Netherlands to test prospectively whether a common fourteen-day antibiotic course of treatment can be shortened to seven days. Cees van Nieuwkoop et al., *Treatment Duration of Febrile Urinary Tract Infection (FUTIRST trial): A Randomized Placebo-Controlled Multicenter Trial Comparing Short (7 Days) Antibiotic Treatment with Conventional Treatment (14 Days)*, 9 BMC INFECTIOUS DISEASES 131 (2009).

115 Lipsitch & Samore, *supra* note 91, at 349 (describing four models of antimicrobial resistance).

induce growth in the resistant bacteria.[116] Finally, if the bacterial population within an individual includes a mixture of resistant and susceptible bacteria, as is often the case, treatment will increase the burden of resistant bacteria in the treated person and the risk of transmission of these bacteria, increasing the chance of infection with resistant species, even to people who were never treated.[117] The common theme of these mechanisms is that none of them requires the new appearance of a resistant strain within a treated individual, but rather all rely on the indirect effects of treatment, frequently creating negative externalities. Legal and economic studies of antibiotic resistance should not ignore these indirect treatment effect externalities.

Simplistic models of resistance miss too much biological complexity. We should expect no less heterogeneity and complexity when we introduce legal variables. The conclusions we draw about appropriate policy responses to resistance may need to be carefully tailored to the complex ecology of drug-bug interactions. Legal and economic models have an uncanny penchant for simplifying assumptions, but the relationship between resistance and innovation should not be among them. Normal legal arguments supporting innovation and new drug production may not apply to antibiotics, and antibiotic conservation may yield unique social welfare gains that might not otherwise be expected.

The following three sub-Parts explore these contextual issues in depth: (A) innovation in the face of resistance; (B) balancing conservation and production; and (C) the role of insurance reimbursement.

A. *Resistance May Promote Innovation*

The conventional wisdom is that resistance undermines antibiotic innovation. Fear of resistance may discourage companies from introducing new antibiotics into the market.[118] This Part directly challenges this proposition. Resistance may plausibly affect innovation through three mechanisms: (1) clearing out competitor drugs; (2) affecting sales during the patent period; and (3) steering innovation towards novel classes.

116 *Id.*
117 *Id.*
118 Projan, *supra* note 74, at 428.

1. Resistance Facilitates Competitive Entry

Resistance facilitates market entry by destroying competing drugs and thereby creating new markets for antibiotic drugs.[119] The U.S. Food and Drug Administration (FDA) approves drugs based upon their safety and effectiveness. For most drugs, effectiveness is a static determination.[120] Approved drugs can lose relative effectiveness over time as better drugs enter the market, but this is simply the natural effect of competition and innovation. Antibiotics are not immune to this competitive dynamic, but they suffer an additional market threat as resistance erodes the *absolute* effectiveness of the drug. Resistance destroys existing antibiotics by rendering them absolutely less effective over time. Penicillin and methicillin were excellent antibiotics and would have retained greater market share but for resistance, which paved the way for subsequent less desirable blockbuster drugs like ciprofloxacin, erythromycin, levofloxacin, and vancomycin. These follow-on drugs would have faced more difficult competition absent resistance, which diminished both the relative and, more importantly, the absolute effectiveness of penicillin and methicillin.

2. Resistance Does Not Appear to Significantly Harm Sales During the Patent Term

Patent-based drug companies face a disincentive only if resistance appears at commercially significant levels during the patent term. Begin with the assumption that that economically significant resistance occurs no earlier than patent expiration.[121] If so, then resistance does not undermine patent-based incentives for innovation. This is an

119 An early version of this was offered by David Shlaes in 2003: "Resistance creates markets; use creates resistance." David M. Shlaes, *The Abandonment of Antibacterials: Why and Wherefore?*, 3 CURRENT OPINION IN PHARMACOLOGY 470, 471 fig.1 (2003); *see also* Kesselheim & Outterson, *supra* note 30, at 7 (noting that firms are targeting the MRSA market); THE GLOBAL ANTIBACTERIALS MARKET: R&D PIPELINES, MARKET ANALYSIS AND COMPETITIVE LANDSCAPES (Arrowhead Publishers, 2007) ("The global anti-infective market is currently valued at US$66.5 billion with antibacterial agents accounting for over [fifty percent] of sales. The antibacterial market is set to grow to over US$45.0 billion by 2012, driven by the uptake of newer antibacterial agents . . .").

120 The FDA evaluates safety and efficacy, not comparative effectiveness. The U.S. Congress recently funded some comparative effectiveness research but did not change the FDA approval process. Paige Goodwin & Kevin Outterson, Editorial, *From Comparative Effectiveness to Cost Effectiveness?*, 14 PHARMA PRICING & REIMBURSEMENT 126 (2009).

121 To be precise, I mean the earlier of patent expiration per the FDA Orange Book or the date of first generic entry in the United States. This date sets the baseline period of marketing exclusivity that the company should reasonably expect from U.S. patent law.

important point: When economically significant resistance is delayed until after patent expiry, the drug company receives the full economic benefit of the patent period.[122] The company may also benefit from resistance that reduces competition from prior drugs. A myriad of other factors might interrupt the commercial plans of the drug company, but premature resistance would not be among them.[123] This assumption, if true, would mean that the relationship between resistance and innovation held a positive sign: Increased resistance would increase innovation.[124]

As noted above, this second point rests on the assumption that economically significant resistance does not occur during the patent term. This assumption can be empirically tested. One method would be to compare sales data for leading antibiotics with their patent expiration dates. A recent study identified the top ten hospital antibiotics, by days of therapy per 1,000 patient-days.[125] The following analysis looks at these ten hospital antibiotics. Proprietary sales data from IMS Health establish that all of these leading antibiotics were still generating significant sales after generic entry.[126] Four of these drugs (cefazolin, metronidazole, vancomycin, and clindamycin) have been off patent for at least a decade, and yet still sell in sufficient volume to make the top ten list. For vancomycin and metronidazole, sales actually accelerated after patent expiration, as will be discussed in Part IV *infra*. Only levofloxacin remained on patent in early 2009, with expiration due in 2010; gatifloxacin was removed from the U.S. market in 2006 for safety concerns, but sold well up to that point. The four remaining antibiotics on the list have recently experienced patent expiration, which permits us

122 The question of *ex post* experiences and *ex ante* projections of resistance will be discussed shortly.

123 For a discussion of these other factors, see Projan, *supra* note 74; S.J. Projan & D.M. Shlaes, *Antibacterial Drug Discovery: Is It All Downhill from Here?*, 10 CLINICAL MICROBIOLOGY & INFECTION (SUPP. 4) 18 (2004).

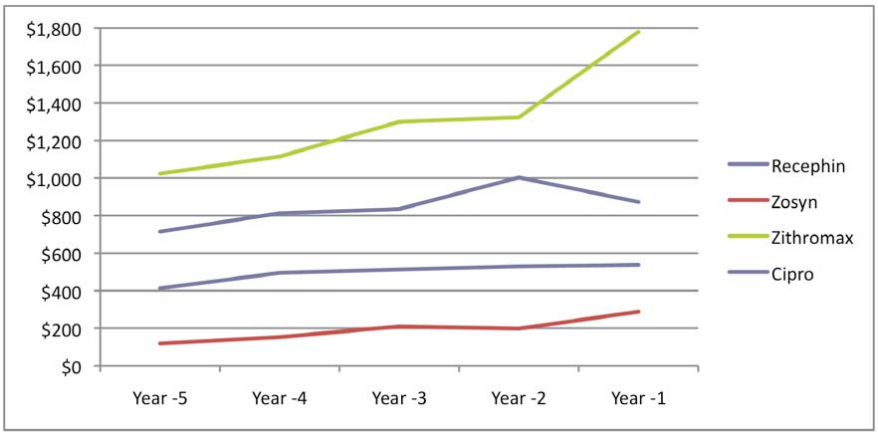
124 In this simple model, resistance reduces the existing stock of generic competitors and does not harm the innovator molecule until after patent expiration. Both signs are positive for the production of innovative new antibiotics.

125 Conan MacDougall & Ronald E. Polk, *Variability in Rates of Use of Antibacterials Among 130 US Hospitals and Risk-Adjustment Models for Interhospital Comparison*, 29 INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY 203, 206 (2008). The top ten hospital antibiotics in these U.S. hospitals, from August 2002 to July 2003, in descending order, were: levofloxacin, cefazolin, ceftriaxone, metronidazole, vancomycin, piperacillin-tazobactam, gatifloxacin, azithromycin, ciprofloxacin and clindamycin. For a similar list, also see Amy L. Pakyz, Conan MacDougall, Michael Oinonen & Ronald E. Polk, *Trends in Antibacterial Use in US Academic Health Centers: 2002 to 2006*, 168 ARCHIVES OF INTERNAL MED. 2254, 2258 (2008).

126 I chose sales as the relevant metric rather than published reports of resistance, primarily because the task is to measure the effect of resistance on R&D incentives. Published reports of resistance to a specific pathogen may affect sales, but other factors (including marketing and medical need) may nonetheless intervene to drive overall sales. Measuring sales directly seems the most accurate method.

to observe U.S. sales in the five years prior to generic entry. Chart 1 presents this data.

Chart 1. U.S. Sales (in Millions of Constant Year -5 Dollars) in the Five Years Prior to Generic Entry[127]



Resistance does not appear to have significantly undercut sales for the patent holders at the end of the terms,[128] although we do not know the counterfactual (i.e., what sales would have been absent any resistance). We are also unable to measure the effect of reduced marketing in the last years of patent life. Nevertheless, it would be difficult to conclude that resistance was economically significant during the patent term for these drugs.[129]

The data on Zithromax® (azithromycin) and Cipro® (ciprofloxacin) deserve special mention. One might be tempted to see evidence of H1 patent holder waste in the last full year of the core

[127] Proprietary data from IMS Health Inc. MIDAS™ database, 1997-2007 (Antibiotics ATC Level 4, J1C1, MNF YTD Oct. 2004) (on file with author) [hereinafter *IMS Data*]. This data includes all branded forms of Recephin® (ceftriaxone), Zosyn® (piperacillin-tazobactam), Zithromax® (azithromycin), and Cipro® (ciprofloxacin). Since the data covers different years for each antibiotic, a uniform annual deflator of 2.9% was applied; this was the average Consumer Price Index for All Urban Consumers (CPI-U) for 2002-2006.

[128] These conclusions are tentative, for antibiotic sales also fluctuate with cycles of infectious disease and other exogenous factors unrelated to resistance. I have not adjusted the data for the overall level of infections in a given year.

[129] The simplified example suggested that relatively high levels of commercially significant resistance would be required in order to make conservation economically desirable for the patent holder. *See supra* notes 64-67. The data sample in this Part may have a significant selection bias, as it is comprised of only the most successful antibiotics, which will not include antibiotics decimated by resistance. A possible response is that some antibiotics are more vulnerable to resistance than others, and since the goal is population health, we should focus on the antibiotics most used in the population. These issues deserve more attention.

Zithromax® patent,[130] but, despite significant levels of resistance,[131] unit sales of azithromycin remained strong in 2009. Pfizer may have aggressively marketed Zithromax® (the evidence is not clear), but it is harder to prove that waste resulted.

The spike in Cipro® (ciprofloxacin) sales in Year-2 includes sales generated by the anthrax scare in the United States following the terrorist attacks of September 11, 2001 and the subsequent mailing of several packages containing anthrax spores in October 2001. The decline in the following year may reflect regression to the mean. In any case, the decline in 2002 has little to do with resistance, as ciprofloxacin retains significant sales in the United States even today.[132]

A second way to approach this question would be to identify the date when an antibiotic encountered resistance sufficient to decimate sales, and then compare that date with patent expiry. Such examples are difficult to identify. Very high levels of resistance may be necessary before sales are damaged. Azithromycin resistance levels in the United States have declined slightly from 31% in 2000 to 28.9% 2004,[133] and yet U.S. sales remain robust and growing, with the sales of the branded product Zithromax® nearly doubling during the period.[134] Indeed, Zithromax® was the best selling antibiotic on Chart 1, despite high resistance levels in the years immediately prior to generic entry. High levels of resistance during the patent term do not necessarily undercut the patent holder's return on investment.

An important example of robust sales despite resistance is broad-spectrum oral penicillin, the poster child for resistance. Penicillin enjoyed annualized U.S. sales exceeding $1.38 billion in 2004, confirming that sales remain strong many decades after introduction, despite the presence of penicillin-resistant bacteria.[135] In June 2008, the Director of the CDC Office of Antimicrobial Resistance testified before Congress that certain tested strains of *Staphylococcus aureas* were "[ninety percent] resistant to penicillin."[136] Apparently, ninety percent resistance to *Staphylococcus aureus* does not foreclose a major commercial U.S. antibiotic market. Resistance levels differ widely across different bug-drug combinations. Physicians are prescribing

130 The core Zithromax® patent expired in November 2005. Pfizer Inc. Annual Report (Form 10-K), at 9 (Mar. 1, 2006).

131 Stephen G. Jenkins, Steven D. Brown & David J. Farrell, *Trends in Antibacterial Resistance Among* Streptococcus pneumoniae *Isolated in the USA: Update from PROTEKT US YEARS 1-4*, 7 ANNALS CLINICAL MICROBIOLOGY & ANTIMICROBIALS 1, 4 tbl.2 (2008).

132 In addition, the generic entry of ciprofloxacin was highly litigated, which may be a complicating factor. *See, e.g.*, *In re* Ciprofloxacin Hydrochloride Antitrust Litig., 544 F.3d 1323 (Fed. Cir. 2008).

133 Jenkins et al., *supra* note 131.

134 *IMS Data*, *supra* note 127.

135 *IMS Data*, *supra* note 127.

136 *CDC's Role Hearing*, *supra* note 105.

penicillin for other pathogens, such as group A streptococci.[137] In any event, penicillin continues to be a blockbuster drug, even at generic pricing, despite high resistance levels for some bacteria.

A final example of sales despite some resistance is levofloxacin, the most-used hospital antibiotic and the most recent member of the "top 10" list[138] to be approaching patent expiration.[139] Recent clinical articles describe levofloxacin as a highly desirable antibiotic without widespread resistance to commercially significant pathogens.[140] In short, it does not appear that clinically important hospital antibiotics have been economically weakened through resistance during their patent terms.[141]

3. Resistance Drives Companies Toward More Innovative Products

Any fear of resistance during the patent term skews R&D towards antibiotic projects that are less likely to suffer early resistance. In early stage testing of new antimicrobial compounds, researchers evaluate likely resistance profiles. Compounds for which resistance could be easily achieved are likely to be set aside early in the R&D process.[142] The fear of economically significant resistance may generate social welfare gains by directing research towards novel antibiotics with stronger resistance profiles rather than me-too extensions of existing classes. Private losses are possible here if research into novel classes is uniquely more expensive. But private gains are also plausible, if novel antibiotics are more able to attract venture capital, licensing, and eventual clinical sales.

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137 *Why Have Group A Streptococci Remained Susceptible to Penicillin?*, *supra* note 106.

138 MacDougall & Polk, *supra* note 125.

139 Generic entry for levofloxacin is expected in 2010. *See* Johnson & Johnson Quarterly Report (Form 10-Q), at 28-29 (Aug. 4, 2009) (discussing litigation in 2009 to delay approval of the Abbreviated New Drug Application (ANDA) filed by Lupin); Johnson & Johnson Annual Report (Form 10-K), at 2 (Feb. 20, 2009) (disclosing that levofloxacin patent expires on Dec. 20, 2010).

140 V.R. Anderson & C.M. Perry, *Levofloxacin: A Review of Its Use as a High-Dose, Short-Course Treatment for Bacterial Infection*, 68 DRUGS 535 (2008); David Felmingham, Rafael Canton & Stephen G. Jenkins, *Regional Trends in B-Lactam, Macrolide, Fluoroquinolone and Telithromycin Resistance Among* Streptococcus pneumoniae *Isolates 2001-2004*, 55 J. INFECTION 111, 113 tbl.1 (2007) (finding levofloxacin resistance to be quite low, around one percent in 2004); Jenkins et al., *supra* note 133.

141 One objection to this analysis is the failure to consider the *ex ante* expectations of the patent owner rather than their *ex post* experience with resistance. *Ex ante* projections are more relevant to the investment decisions of patent owners. The data used in this Article focuses on the *ex post* experience as a proxy for expectations.

142 In the author's experience, many anti-infective biotech companies highlight the resistance profiles of their compounds at investor conferences.

To summarize, resistance may plausibly affect innovation through three mechanisms: (1) clearing out competitor drugs; (2) affecting sales during the patent period; and (3) steering innovation towards novel classes. The first proposition appears to be well supported and the result encourages the production of new drugs, a unique advantage for antibiotic innovation. The second proposition appears to be unsupported by the available data, meaning it has little or no effect on antibiotic innovation. The third is supported by anecdotal evidence from industry, and may plausibly yield positive private and public gains, but the definitive exploration of this issue is not undertaken in this Article.

With these caveats in mind, resistance appears to have an overall positive effect on the production of innovative antibiotics. This result erodes the foundation of claims that antibiotics possess unique qualities that require additional production incentives, as Sector 2 proponents often claim. Indeed, the opposite conclusion seems appropriate: Antibiotics require fewer innovation incentives than other types of drugs.

B. *Conservation Reduces Demand for New Antibiotics, but May Yield Overall Social Welfare Gains*

One response to resistance is antibiotic conservation, careful rationing or stewardship of these drugs to prolong clinical effectiveness. Many antibiotics are overused in clinically improper settings. Encouraging the rational use of antibiotics is a conservation measure.[143] Other Sector 3 conservation measures include public health practices to reduce the incidence and spread of infectious disease and infection control in the hospital, clinic, and community.[144]

Conservation is a sound strategy for reducing resistance, but these efforts appear to work at cross-purposes with incentives to produce novel antibiotics. Conservation efforts, if successful, necessarily reduce the unit sales of antibiotics, which is the central idea in H5—conservation dampens production. Antibiotic stewardship and rational use programs can be considered anti-marketing campaigns. Infection control efforts, if successful, reduce the spread of dangerous infections and reduce the need for antibiotic treatments.

Conservation also prolongs the clinical usefulness of existing products, which makes competitive entry more difficult. It seems clear

143 LEVY, *supra* note 30. Rational use also has other benefits: lower costs, fewer significant side effects, and fewer interactions with other drugs.

144 Saver, *supra* note 35, at 431 (emphasizing the need to focus on physician demand-side issues that drive antibiotic misuse).

that Sector 3 (public health conservation) is in tension with Sector 2 (production of new drugs). As shown in Part III.A.2 *supra*, the threat of commercially significant resistance emerging during the patent term is modest. The same cannot be said for the commercial threats of national conservation programs, which may be funded by governments and reduce unit sales significantly.[145] Drug companies should not fear the effect of resistance on their cash flows, but should be greatly concerned about well-funded Sector 3 conservation programs.

In normal pharmaceutical markets, reducing the flow of innovative new products might be considered negative. In every other disease category, society should celebrate the arrival of improved therapies. In antibiotic markets, this might not be true. If existing antibiotic therapies remain effective, we do not yet need new ones. Remember that the goal is continued antibiotic effectiveness, not new drugs per se. If patients receive effective treatment, or better yet, avoid infection in the first instance, then the social welfare goals have been met.

Furthermore, the case for innovation presupposes that new drugs are better than old ones. This assumption is not uniformly true.[146] If a new drug is no better than the old, then the health gains from innovation are zero. From a societal perspective, the net effect is negative, due to the expense of R&D. If a new drug is not better and entails unknown safety risks, then innovation results in an even greater social welfare loss. Since resistance degrades the absolute efficacy of established antibiotics over time, it may be easier to show that a new antibiotic is medically superior to the then-available alternatives. Social planners—

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[145] *See, e.g.*, Elifsu Sabuncu et al., *Significant Reduction of Antibiotic Use in the Community After a Nationwide Campaign in France, 2002-2007*, PLOS MED., June 2, 2009, http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000084 (studying a French national campaign over six years that resulted in a 26.5% reduction in the number of antibiotic prescriptions); Benedikt Huttner & Stephan Harbarth, *"Antibiotics Are Not Automatic Anymore"—The French National Campaign to Cut Antibiotic Overuse*, PLOS MED., June 2, 2009, http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000080 (noting that said campaign cost €500 million).

[146] *See, e.g.*, Margaret Gilhooley, *Drug Preemption and the Need to Reform the FDA Consultation Process*, 34 AM. J.L. & MED. 539 (2008); Margaret Gilhooley, *Vioxx's History and the Need for Better Procedures and Better Testing*, 37 SETON HALL L. REV. 941 (2007) (detailing the Vioxx safety recall); Aaron S. Kesselheim et al., *The Rise and Fall of Natrecor for Congestive Heart Failure: Implications for Drug Policy*, 25 HEALTH AFF. 1095 (2006) (detailing safety issues with a new drug); Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308 (2007); Ray Moynihan, Iona Heath & David Henry, *Selling Sickness: The Pharmaceutical Industry and Disease Mongering*, 324 BRITISH MED. J. 886 (2002) (questioning the medical need for some new drugs); Mary K. Olson, *The Risk We Bear: The Effects of Review Speed and Industry User Fees on New Drug Safety*, 27 J. HEALTH ECON. 175 (2008) (finding increased safety problems with new drugs approved in an accelerated timeframe); Michael A. Steinman et al., *Characteristics and Impact of Drug Detailing for Gabapentin*, PLOS MED., Apr. 24, 2007, http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0040134 (examining the off label promotion of a drug for indications for which evidence of efficacy was lacking).

or a federal comparative effectiveness agency[147]—should prefer new therapies that represent substantial clinical improvements, but the FDA does not require proof of superior efficacy for antibiotics, just safety and noninferiority.[148]

But let us assume that a certain new antibiotic is actually a better drug than existing therapies. It still does not follow that we should prioritize innovative production at the expense of conservation. Most new antibiotics carry serious side effect risks, including adverse reactions, liver toxicity, and other serious risks of organ failure.[149] The properly framed societal choice is not between vancomycin and penicillin with high levels of resistance, but between vancomycin with all its dangerous side effects and fully effective penicillin protected by conservation. Penicillin was the better drug, and conservation of that better drug would have resulted in a social welfare gain by both prolonging the usefulness of penicillin and delaying the necessity of using more dangerous antibiotics. In some European countries, clinicians have successfully conserved older antibiotics in order to reduce the need to resort to more dangerous drugs such as vancomycin.[150]

Finally, experts suggest that the low-hanging fruit in antibiotic research may have been already discovered.[151] If true, investments in antibiotic R&D will yield declining marginal returns. As each new antibiotic becomes more expensive, the value of conservation rises, if both are properly priced in the market. In Part III.C.1 *infra*, I demonstrate that they are not. In energy policy, we see a significant relationship between increased energy prices and the demand for conservation and renewable energy technologies. If antibiotic markets are a similar exhaustible resource, then from a societal perspective,

147 American Recovery and Reinvestment Act of 2009, tit. VIII, Pub. L. No. 111-4, 123 Stat. 115 (allocating funding for comparative effectiveness research); *see also* Goodwin & Outterson, *supra* note 120.

148 Clinical drug trials include a treatment arm and a control arm, generally using a placebo. In antibiotic trials, placebos are considered unethical, and therefore the control arm utilizes an antibiotic that is the standard of care. The treatment arm must show noninferiority to the control arm. Brad Spellberg and others at the IDSA suggest that the noninferiority standard should be weakened to approximate a placebo-controlled trial conducted in a pre-antibiotic era. Brad Spellberg et al., *Antimicrobial Agents for Complicated Skin and Skin-Structure Infections: Justification of Noninferiority Margins in the Absence of Placebo-Controlled Trials*, 49 CLINICAL INFECTIOUS DISEASES 383 (2009); Dennis L. Stevens, Editorial, *Antimicrobial Agents for Complicated Skin and Skin-Structure Infections: Noninferiority Margins, Placebo-Controlled Trials, and the Complexity of Clinical Trials*, 49 CLINICAL INFECTIOUS DISEASES 392 (2009). This proposal would make it easier to achieve FDA approval for efficacy.

149 For example, vancomycin, a major hospital antibiotic, replaced methicillin for treatment of MRSA despite significant limitations including poor tissue penetration and potential liver toxicity. Marin H. Kollef, *Limitations of Vancomycin in the Management of Resistant Staphylococcal Infections*, 45 CLINICAL INFECTIOUS DISEASES S191 (2007).

150 Personal communication with Ursula Theuretzbacher (on file with author).

151 *See* Outterson, *Vanishing Public Domain*, *supra* note 4, at 77, and sources cited therein.

conservation should be an increasingly important policy element, in contrast to new production. Of course, conservation is never fully effective over time, so even the most robust conservation program must also be paired with some new production of antibiotics.

C. *Insurance Reimbursement Significantly Influences Resistance and Conservation*

The third contextual issue is money: Insurance reimbursement for antibiotics affects innovation and conservation in dramatic ways. For all the ink spilt on intellectual property issues, relatively little has been said about reimbursement for antibiotic conservation.[152] This is a major weakness of the existing literature, as reimbursement systems may prove to be of equal or greater importance to many of the institutions and people directing antibiotic use.

On the question of pharmaceutical innovation, much of the literature tinkers with the patent system; but in a world of government insurance programs, reimbursement changes can have a much more direct and powerful effect on company revenues.[153] The patent-based drug industry recently announced an $80 billion "contribution" to the Obama health care reform efforts, including changes in Medicare and Medicaid reimbursement.[154] As Bill Sage and David Hyman put it, federal reimbursement "offers the longest lever for altering antibiotic usage and infection control patterns."[155] Few patent policy levers are of this magnitude and immanence; for a best-selling antibiotic, even a substantial extension to the patent term would increase the net present value of cash flows by a modest amount.[156] By contrast, changes in

152 Two notable exceptions are LAXMINARAYAN ET AL., *supra* note 3, especially at ch. 3 and ch. 6, and Sage & Hyman, *supra* note 3, at 28.

153 *Prescription Drugs—An Overview of Approaches to Negotiate Drug Prices Used by Other Countries and U.S. Private Payers and Federal Programs: Hearing Before the S. Comm. on Finance*, 110th Cong. (2007) (statement of John Dicken, Dir., U.S. Gov't Accountability Office), *available at* http://www.gao.gov/new.items/d07358t.pdf [hereinafter *Prescription Drugs*]; U.S. DEPT. OF COMMERCE, INT'L TRADE ADMIN., PHARMACEUTICAL PRICE CONTROLS IN OECD COUNTRIES: IMPLICATIONS FOR U.S. CONSUMERS, PRICING, RESEARCH AND DEVELOPMENT, AND INNOVATION (2004), *available at* http://www.ita.doc.gov/td/chemicals/drugpricingstudy.pdf [hereinafter PRICE CONTROLS] (discussing the large impact that European drug pricing reimbursement systems have on drug companies); *Drug Importation: Would the Price Be Right? Hearing Before the S. Committee on Health, Education, Labor and Pensions*, 109th Cong. (2005) (statement of Kevin Outterson), [hereinafter *Drug Importation*] (offering a critique of the U.S. Department of Commerce study).

154 Laura Meckler & Alicia Mundy, *For Drug Makers, Concessions Have a Bright Side*, WALL ST. J., June 23, 2009, at A4.

155 Sage & Hyman, *supra* note 3, at 28.

156 *See* Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 562 (calculating the net present value of patent term extensions for antibiotics).

hospital, physician, and prescription drug reimbursement currently being discussed in Congress could shift tens of billions of dollars immediately.[157]

While drug patents are undeniably valuable to the pharmaceutical companies, their impact on the other institutional players in the U.S. health care sector is limited. For providers such as hospitals and physicians, reimbursement systems such as Medicare, Medicaid, and private insurance company reimbursement are much more important.[158] Similarly, patients are little affected by antibiotic drug patents as long as they are insured,[159] but the structure of the insurance reimbursement system directly affects the financial incentives presented to patients regarding antibiotic therapy.[160] Just as bacteria live in complex ecological systems, principals and agents in the U.S. health care sector inhabit a space populated with powerful institutions that should not be ignored in theoretical models. In the following Parts, we will examine the impact of reimbursement on incentives for drug companies, providers (hospitals, physicians), and patients. My claim is that many elements of reimbursement affect antibiotic resistance in complex patterns.

1. Drug Company Reimbursement

The first example of reimbursement complexity is the amount paid to drug companies for their products.[161] Patent law theorists are especially fond of market-based price signals for patented products because the market sets the value of the patent. If a patented product does not draw much consumer interest, the patent owner will either adjust the price or accept smaller unit sales. If the product is wildly successful, the magnitude of market demand directly affects the patent-based profits that are collected. In theory, the market for patented products thus rewards products in proportion to consumer demand in the market, an important advantage over other methods that may lack a market test.

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157 1 CONGRESSIONAL BUDGET OFFICE, BUDGET OPTIONS: HEALTH CARE (2008), *available at* http://www.cbo.gov/ftpdocs/99xx/doc9925/12-18-HealthOptions.pdf.

158 Sage & Hyman, *supra* note 3, at 28.

159 On a static basis, patents increase the cost of all health care and thus the social cost of insurance, but this effect does not specifically alter antibiotic incentives. On a dynamic basis, theory suggests that health care innovation may raise quality and lower costs, but it is hard to find empirical support for this in the expensive, innovative, and mixed quality environment of the U.S. health sector.

160 LAXMINARAYAN ET AL., *supra* note 3, ch. 3 (discussing the role of insurance on antibiotic resistance).

161 *See, e.g.*, PRICE CONTROLS, *supra* note 153; *Drug Importation*, *supra* note 153; *Prescription Drugs*, *supra* note 153.

But the market does not set pharmaceutical prices in high-income countries, including the United States.[162] U.S. drug reimbursement prices are negotiated through a complex process with significant government intervention benefiting specific payors.[163] Favored payors include Medicaid,[164] the Veterans' Administration (VA),[165] and public health clinics under § 340b.[166] The current Medicare law prohibits the government from negotiating drug prices on behalf of private Medicare Part D plans.[167] A professed goal of the Democratic leadership in Congress is to reverse this ban, which might result in near-monopsony (oligopsony) purchasing power by Medicare as a purchaser.[168]

Even private pharmaceutical reimbursement markets contain an interesting mixture of near-monopsony and competition. Many health plans subcontract their prescription drug plans to a small number of pharmaceutical benefit managers (PBMs). Three PBMs dominate the market,[169] and one of these large PBMs (Caremark) was recently purchased by CVS, a large drug store chain.[170] This market structure limits price negotiations to a small number of participants.

Many factors affect the outcome of these negotiations, especially efforts to influence agents acting on behalf of the patient. If a drug is generic with many bioequivalent competitors, PBMs can negotiate quite low reimbursement rates in a fairly competitive market. If the drug is both important medically and has no good substitutes, the drug company wields significant market power in setting prices. An

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162 *See* PRICE CONTROLS, *supra* note 153 (discussing the large impact that European drug pricing reimbursement systems have on drug companies); *Prescription Drugs*, *supra* note 153.

163 Kevin Outterson & Aaron S. Kesselheim, *How Medicare Could Get Better Prices on Prescription Drugs*, 28 HEALTH AFF. w832 (2009) (web exclusive).

164 42 U.S.C. § 1396r-8 (2006) (outlining mandatory and supplemental Medicaid drug rebate programs).

165 Veterans Health Care Act of 1992, Pub. L. 102-585, §§ 601, 603, 106 Stat. 4943 (limiting prices for prescription drugs purchased by the VA and certain other federal agencies); *id.* at § 602 (referencing the 340B program under the Public Health Service Act); 38 U.S.C. § 8126 (2006).

166 42 U.S.C. § 256b (2006) (codifying section 340B of the Public Health Service Act); GOV'T ACCOUNTABILITY OFFICE, PRESCRIPTION DRUGS: EXPANDING ACCESS TO FEDERAL PRICES COULD CAUSE OTHER PRICE CHANGES (2000), *available at* http://www.gao.gov/archive/2000/he00118.pdf. Section 340B also applies to other special categories of favored providers, including certain disproportionate share hospitals, urban Indiana health centers, and other specified providers serving special populations. *See* U.S. Department of Health and Human Services, Health Resources and Services Administration, HRSA—340B Drug Pricing Program/Pharmacy Affairs, http://www.hrsa.gov/opa/introduction.htm (last visited Jan. 15, 2010).

167 Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, sec. 101(a)(2), § 1395w-111, 117 Stat. 2066, 2092-99 (codified as 42 USC § 1395w-111(i) (2006)); *see* Outterson & Kesselheim, *supra* note 163.

168 Outterson & Kesselheim, *supra* note 163.

169 Medco Health Solutions, Inc., Express Scripts, Inc., and CVS Caremark Corporation are the largest. Some large health plans and retail pharmacy chains have PBM capabilities in-house. CVS Caremark Corp., Annual Report (Form 10-K), at 8, 21 (Feb. 27 2008).

170 *Id.* at 3. The acquisition closed on March 22, 2007. *Id.*

intermediate case is a drug with possible substitutes,[171] especially if the PBMs can credibly threaten to refuse to purchase the drug. This creates a potential conflict between the medical needs of the patient and the financial goals of the PBM and the insurance company. One role of direct-to-consumer advertising and physician detailing (personal marketing by drug companies) is to diminish the latitude of PBMs in this situation by driving consumer and physician demand for a particular drug. PBMs react by creating restrictive formularies,[172] with tiered copays for different types of drugs,[173] but they must consider consumer and provider preferences when creating and enforcing a formulary.[174] Drug companies give financial support to some patient advocacy groups and deploy the groups to fight formulary restrictions and increased copays, frequently without disclosing the conflicts of interest.[175] Some drug companies have responded to copay increases for branded drugs by issuing coupons, which may distort patients' perceived cost of such drugs.[176] Drug companies also engage in off-label marketing, expanding sales into conditions lacking FDA approval.[177]

More broadly, many commentators are concerned with the mismatch between reimbursement and medical need—consumer demand builds markets for drugs with modest population health impact, while companies fail to mount impressive R&D programs for many important diseases. This problem has three foundations.

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171 Substitutions may come within a drug class, or substitutions from other therapies such as surgery.

172 A formulary is a list of drugs that a health plan will cover. Formularies may impose restrictions on more expensive drugs, including higher co-payments or multiple tiers of co-payments. For example, a formulary might impose a $0 co-pay on generic drugs, a $15 co-pay on preferred drugs, and a $50 co-pay on non-preferred drugs.

173 *Prescription Drugs—Overview of Approaches to Control Prescription Drug Spending in Federal Programs: Hearing Before the Subcomm. on Federal Workforce, Postal Service and the District of Columbia of the H. Comm. on Oversight and Government Reform*, 111th Cong. (2009) (statement of John E. Dicken, Dir., Health Care, Gov't Accountability Office), *available at* http://www.gao.gov/new.items/d09819t.pdf.

174 Agency costs are present in the PBM relationship as well. PBMs serve as agents of the consumer when negotiating access and prices, but they have their own interests as well, which may be in conflict. National Legislative Association on Prescription Drug Pricing, Pharmacy Benefit Managers Policy Background, http://www.reducedrugprices.org/pbm_policy.asp (last visited Jan. 15, 2010) (detailing potential conflicts of interest regarding PBMs).

175 H. Marcy Bortner, Conflicted Advocates: Pharmaceutical Companies' Funding of Patient Advocacy Groups: Report to the West Virginia Pharmaceutical Cost Management Council (Apr. 6, 2005) (unpublished report, on file with author); Tinker Ready, *Divided Loyalties?: Nonprofit Health Advocacy Groups Like to Portray Themselves as Patients' Allies; Can They Serve Corporate Benefactors at the Same Time?*, WASH. POST, Feb. 7, 2006, at F1.

176 Chana Joffe-Walt, *Drug Coupons Hide True Costs from Consumers*, NPR, Oct. 20, 2009, http://www.npr.org/templates/story/story.php?storyId=113969968.

177 Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427 (2008).

First, global medical need and wealth are not equally distributed or correlated. In fact, the very opposite characterizes our world.[178] For this reason, pharmaceutical companies develop ever-lengthening lists of drugs for the lifestyles of wealthy consumers in high-income countries, while devoting relatively little to treating diseases particular to the poor.[179] This disparity is less salient within high-income countries with comprehensive health insurance programs that cover pharmaceuticals.

The second foundation is the problem of information asymmetries regarding pharmaceuticals. Consumers are not well informed about the risks and benefits of prescription drugs, including antibiotics. Even physicians are overwhelmed by the flood of peer-reviewed literature and end up relying to some extent on intermediaries such as drug marketers. These informational asymmetries are present for other consumer products as well, but the stakes are higher and the process is different for drugs. If we are talking about toasters or coffee shops, revealed consumer preferences may be a fine methodology for allocating goods and services in the market; we may feel differently for antibiotics with the potential for both internal and external harm from either using too much or too little, and the potential for a collapse in a common pool resource.

Some view direct-to-consumer (DTC) marketing as a remedy to this information gap;[180] others consider DTC marketing a corporate tool that exploits information asymmetries, creating false demand for cures to spurious diseases.[181] DTC advertising is not widely used for antibiotics in the United States at the present time.[182]

Finally, agency costs introduce distortions into consumer pharmaceutical markets.[183] The patient must rely on a physician to decide how and when to prescribe. In general, agency costs include shirking and self-dealing. Shirking in this context would include a lazy

178 Pogge, *supra* note 44.

179 Kevin Outterson, *Should Access to Medicines and TRIPS Flexibilities Be Limited to Specific Diseases?*, 34 AM. J.L. & MED. 279 (2008).

180 *See* Peter J. Pitts, *Turning Point or Tipping Point: New FDA Draft Guidances and the Future of DTC Advertising*, 23 HEALTH AFF. w259 (2004) (web exclusive). *But see* Matthew F. Hollon, *Direct-to-Consumer Advertising: A Haphazard Approach to Health Promotion*, 293 JAMA 2030 (2005).

181 *See, e.g.*, MARCIA ANGELL, THE TRUTH ABOUT DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT (2005); JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS (2005); RAY MOYNIHAN & ALAN CASSELS, SELLING SICKNESS: HOW THE WORLD'S BIGGEST PHARMACEUTICAL COMPANIES ARE TURNING US ALL INTO PATIENTS (2006); Matthew Perrone, *Disease May Not Be Real, but the Drug Profits Are*, HOUSTON CHRON., Feb. 9, 2009, at A4.

182 West Virginia Pharmaceutical Cost Management Council Direct to Consumer Advertising Data, CY2008 (on file with author) (reporting no DTC expenditures for any antibiotic).

183 Despite concerns about physician agency costs, most observers still appear to prefer that antibiotics be sold through physician agency in the form of a prescription as opposed to over-the-counter.

decision to prescribe, without adequately considering all of the potential factors in this patient's case. Self-dealing would include direct or indirect financial rewards that come from prescribing. Both are present in antibiotic markets.[184] One legal mechanism to address self-dealing in health care is the Stark II law. The theory behind Stark II is that physicians cannot be trusted to refer to an entity if they stand to gain financially from the transaction. Outpatient prescriptions are "designated health services" (DHS) under Stark II, and physicians are prohibited from making a referral for DHS if they have a financial relationship with the entity receiving the referral. Writing a prescription is a referral for Stark II purposes. Federal law thus effectively prohibits prescribing physicians from having financial interests in pharmacies located in their office buildings, out of fear that the physicians will be tempted to over prescribe in order to capture additional pharmacy sales.[185] Federal law considers agency costs in prescriptions to be quite significant. Reimbursement systems and the rules policing improper utilization should also be designed with agency costs in mind, with the knowledge that prescriptions might be influenced by considerations other than the patient's health.[186]

The health insurance market is a network of relationships rife with potential agency costs. The health plan sponsor (frequently an employer, association, or government entity) is an agent acting on behalf of the patient, but it may make cost saving decisions adverse to the patient's health.[187] PBMs are themselves agents of the health plans, but have been troubled by conflict-of-interest allegations when taking secret discounts from drug companies to promote certain drugs.[188] Even

184 Saver, *supra* note 35, at 431.

185 42 U.S.C. §1395nn (2006).

186 LAWRENCE P. CASALINO, PHYSICIAN SELF-REFERRAL AND PHYSICIAN-OWNED SPECIALTY FACILITIES 18 (Robert Wood Johnson Foundation, Research Synthesis Report No. 15, 2008) (finding agency cost issues in physician self-referral in specialty facilities and recommending changes in reimbursement and legal changes to address the problem); GOV'T ACCOUNTABILITY OFFICE, MEDICARE PART B IMAGING SERVICES: RAPID SPENDING GROWTH AND SHIFT TO PHYSICIAN OFFICES INDICATE NEED FOR CMS TO CONSIDER ADDITIONAL MANAGEMENT PRACTICES (2008), *available at* http://www.gao.gov/new.items/d08452.pdf (discussing agency cost issues in Part B); MEDICARE PAYMENT ADVISORY COMMISSION, REPORT TO CONGRESS: PHYSICIAN-OWNED SPECIALTY HOSPITALS (2005) (discussing agency costs in physician-owned hospitals).

187 To a significant degree, the recent history of managed care is the struggle over agency costs. For a summary of the backlash against managed care, see Alain C. Enthoven, Helen H. Schauffler & Sara McMenamin, *Consumer Choice and the Managed Care Backlash*, 27 AM. J.L. & MED. 1 (2001).

188 *See* Christy A. Rentmeester & Robert I. Garis, *Rebates and Spreads: Pharmacy Benefit Management Practices and Corporate Citizenship*, 33 J. HEALTH POL. POL'Y & L. 943 (2008); Allison Dabbs Garrett & Robert Garis, *Leveling the Playing Field in the Pharmacy Benefit Management Industry*, 42 VAL. U. L. REV. 33 (2007); Greg Radinsky, *The Spotlight on PBMs: Federal Enforcement of the Anti-Kickback Statute on the Pharmaceutical Benefit Management Industry*, 36 J. HEALTH L. 213 (2003).

patients do not act solely as principals, since insurance subsidizes drug spending at the point of care, increasing both appropriate and inappropriate purchases.[189] This effect is magnified by direct-to-consumer advertising in the United States, boosting consumer demand for a product reimbursed by insurance.[190] While these agency costs have many effects, an important one is dilution of the effectiveness of the price mechanism. Pharmaceutical reimbursement in the United States should not be confused with market-based pricing.

The macroeconomic effect of non-market pricing could result in drug price levels that are either super- or sub-optimal from a social perspective.[191] Antibiotics are a significant drug market, ranked as the third most profitable class of drugs in 2004.[192] Nevertheless, a leading company researcher suggests that antibiotic reimbursement is sub-optimal. Steve Projan suggests that three factors uniquely disfavor antibiotic reimbursement: (1) conservation reduces unit sales; (2) the short duration of therapy (two weeks or less, compared to decades for drugs like Lipitor®); and (3) low prices for antibiotics, driven by both administered pricing and generic drugs.[193] The first factor is a core element in H5—conservation dampens production. As discussed in Part III.B *supra*, conservation reduces unit sales, but it may actually promote better types of production and yield net overall social welfare gains. The second and third factors (duration and price) support the argument that reimbursement is a key driver.

Drug companies could promote better reimbursement models for antibiotics. Consider the recent introduction of high-priced oncology drugs. As of 2009, more than ninety percent of the oncology drugs introduced in the prior four years cost more than $20,000 for a twelve-week course of treatment.[194] These prices are defended by studies demonstrating their cost-effectiveness in terms of quality-adjusted life years (QALYs) or similar metrics. In another paper, Aaron Kesselheim and I make the normative claim that if antibiotics generate significant health returns, they should bear an appropriate price, without regard to the length of treatment.[195] A comparative-effectiveness review of antibiotics might call for dramatically higher reimbursement to drug

189 *See infra* Part III.C.3 and sources cited therein.

190 *Id.*

191 Outterson, *supra* note 39.

192 Powers, *supra* note 72, at 25 ("Today, antimicrobials are the third most profitable class of drugs for pharmaceutical companies, surpassed only by central nervous system and cardiovascular drugs. The market for antimicrobials is between $26 [billion] and $45 [billion] per year.").

193 Projan, *supra* note 74, at 428; *see also* BAD BUGS, *supra* note 10, at 17.

194 Fojo & Grady, *supra* note 72, at 1045 n.17 & tbl.1.

195 *See* Kesselheim & Outterson, *supra* note 30, at 12-13.

companies,[196] especially if drug companies only capture a small share of the social welfare generated from antibiotic usage.

If the only concern was production of new antibiotics, greater reimbursements and subsidies[197] might be effective. But conservation must also be considered. Deploying tax and reimbursement incentives to make production of antibiotics appear artificially cheap is a serious error, akin to subsidizing relatively cheap petroleum as supplies dwindle. If we were to analogize a carbon tax to antibiotics, government policy might consider making antibiotic production more expensive.[198] And yet, leading groups suggest myriad tax and patent incentives to reduce the cost of antibiotic production.[199] These may be rational strategies in normal pharmaceutical markets, but may yield social welfare losses when applied to exhaustible resources like antibiotics.

2. Provider Incentives for Hospitals and Physicians

Despite the strong case for conservation and stewardship, many U.S. academic medical centers do not sustain effective programs.[200] One significant factor is reimbursement: Historically, hospitals have had few economic incentives to invest in antibiotic conservation. Infection control has generally been an unreimbursed cost,[201] even when proven effective.[202] Appropriate use and careful stewardship may drive

196 Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 564-65 ("The most market-based remedy for inadequate innovation is to pay more for outstanding innovation.").

197 Drug company reimbursement can come through other channels as well. Some government policies can be considered indirect reimbursement as they reduce the cost of R&D and production. Tax incentives, orphan drug credits, and government support for early-stage research can be considered indirect reimbursement mechanisms as they reduce the cost for companies to bring products to market.

198 By contrast, Kades proposed making antibiotic consumption rather than production more expensive. Kades, *supra* note 4, at 635-52.

199 *See, e.g.*, BAD BUGS, *supra* note 10, at 4-5.

200 Pakyz, *supra* note 125; Richard P. Wenzel, *Health Care-Associated Infections: Major Issues in the Early Years of the 21st Century*, 45 CLINICAL INFECTIOUS DISEASES S85, S87 (2007) ("With respect to basic infection control, there needs to be little tolerance for any lack of hand hygiene. The lack of hygiene compliance is a major failing of modern physicians and other health care workers that implies both medical and ethical breaches. It cannot be tolerated, because it is a key quality-of-care issue, and it should be made unacceptable, a part of the annual review process, and a reason for disciplinary action in hospitals.").

201 *See* Kesselheim & Outterson, *supra* note 30, at 6-7.

202 Susan S. Huang et al., *Impact of Routine Intensive Care Unit Surveillance Cultures and Resultant Barrier Precautions on Hospital-Wide Methicillin-Resistant* Staphylococcus aureus *Bacteremia*, 43 CLINICAL INFECTIOUS DISEASES 971 (2006) (finding that routine surveillance for MRSA in the ICU followed by contact isolation of MRSA cases yielded a large and statistically significant reduction in MRSA bacteremia).

unhappy doctors and patients away,[203] and infection control programs are not inexpensive to create and sustain. In fact, hospitals and doctors have generally gained revenues from additional infections, whether acquired in the community or the hospital. Most of the economic incentives do not favor conservation by providers.[204]

Economic incentives are powerful in hospital reimbursement. In fiscal year 1983, Congress switched hospitals from cost-based reimbursement to prospective payment. The program is now called the inpatient prospective payment system (IPPS).[205] IPPS has led to remarkable changes in the average length of stay and the delivery of medical services.[206] Under IPPS, patients need to be moved out of hospitals more quickly for financial reasons. These pressures select for antibiotics, such as linezolid,[207] that can be started intravenously and then switched to oral doses for post-discharge use, creating unknown effects on resistance.

Reporting infection data is one way to force a hospital to internalize some of the costs of nosocomial (hospital-associated) infection. Some states, notably Pennsylvania, require reporting of some of this data.[208] Medicare is also moving in this direction as a condition for reimbursement.[209] Routine testing of patients for MRSA on admission may also illustrate another negative externality: Hospitals

203 Sage & Hyman, *supra* note 3, at 15; Saver, *supra* note 35, at 431.

204 Outterson, *supra* note 100.

205 Social Security Act § 1886(d), 42 U.S.C. § 1395ww(d) (2006). In 1997, Congress created a special exception for 1100 rural hospitals (called critical access hospitals). MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO CONGRESS: ISSUES IN A MODERNIZED MEDICARE PROGRAM ch. 7 (2005), *available at* http://www.medpac.gov/publications/congressional_reports/June05_ch7.pdf. Critical access hospitals are now exempt from IPPS and are reimbursed on a cost basis.

206 Jack Ashby, Stuart Guterman & Tim Greene, *An Analysis of Hospital Productivity and Product Change*, 19 HEALTH AFF. 197, 202-04 (2000) (discussing the role of Medicare prospective payment on declining length of stay in hospitals). *But see* Gerard F. Anderson, Uwe E. Reinhardt, Peter S. Hussey & Varduhi Petrosyan, *It's the Prices, Stupid: Why the United States Is So Different from Other Countries*, 22 HEALTH AFF. 89 ex. 5 (2003) (finding U.S. average length of stay in 2000 to be only slightly below the Organization for Economic Co-Operation and Development (OECD) median).

207 Paterson, *supra* note 85, at 487 ("The availability of both intravenous and oral formulations has facilitated switch therapy, whereby intravenous therapy is commenced and oral therapy is substituted upon hospital discharge.").

208 *See* Pennsylvania Health Care Cost Containment Council, Hospital-Acquired Infections in Pennsylvania, http://www.phc4.org/hai (last visited Jan. 15, 2010) (containing interactive databases of hospital-acquired infections).

209 In the Medicare Modernization Act of 2003, Congress offered a "pay for reporting" bonus to hospitals, paying additional Medicare reimbursement (through the Annual Payment Update or APU) in exchange for reporting some hospital quality measures, including some hospital-associated infection data. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066. The law was amended through the Deficit Reduction Act of 2005, Pub. L. No. 109-171, § 5001(a), 120 Stat. 4 (amending section 1886(d)(3)(B) of the Social Security Act, 42 U.S.C. §1395ww(d)(4) (2002)). The first ten hospital quality measures were proposed for reporting as of November 1, 2003.

and long-term care facilities with poor records of infection control may be exporting MRSA to other hospitals, economically damaging the competition, as discussed in Part II.C *supra* concerning hypothesis H7 (antibiotic externalities are predominantly negative).

Physicians are also subject to pressures to prescribe antibiotics in the community, especially empirical (best-guess) therapy while waiting for a diagnostic test result to confirm bacterial origin. As Richard Saver has recently described, the cultural, legal, and financial incentives in the United States support overutilization rather than rational use or conservation, leading to premature resistance.[210] Since physicians write prescriptions, any plan to socially optimize antibiotic use must overcome these barriers.

3. Consumer Pricing Through Insurance

Most U.S. drug purchases are paid through health insurance. Health insurance changes the price elasticities of prescription drugs, making them more affordable to the patient at the point of care. Flattening the price elasticity curve increases consumer demand for prescription drugs, which, on balance, may be a good thing. But increased demand can be counterproductive if the drugs are used inappropriately (wasted); are unsafe for that patient (internal costs); or contribute to resistance generally (internal and external costs). The structure of consumer out-of-pocket payments may encourage inappropriate use. Pricing systems that make antibiotics cheap at the point of care may stimulate unnecessary demand.[211] For example, Wal-Mart's $4 generics program is problematic if it stimulates inappropriate overutilization of antibiotics.[212] Pharmacies at the Publix grocery chain announced a rival offer of free generic antibiotics, including amoxicillin, cephalexin, sulfamethoxazole/trimethoprim, ciprofloxacin, penicillin, ampicillin, and erythromycin.[213] Free antibiotics are the opposite of Pigovian taxes to correct for antibiotic negative externalities.[214]

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210 Saver, *supra* note 35, at 431.

211 LAXMINARAYAN ET AL., *supra* note 3, at 69-70 (discussing the policy option of increasing co-pays to discourage inappropriate antibiotic use).

212 Posting of Sarah Rubenstein to the Wall Street Journal Health Blog, http://blogs.wsj.com/health/2009/05/04/wal-mart-tries-to-step-on-pharmacy-benefit-managers-turf/ (May 4, 2009, 10:55 EST).

213 Press Release, Publix, Publix Pharmacies Launch Free Prescription Drug Program in All Operating Areas (Aug. 6, 2007), *available at* http://www.publix.com/about/newsroom/NewsReleaseItem.do?newsReleaseItemPK=2636.

214 *See* Outterson, *Vanishing Public Domain*, *supra* note 4, at 80, and sources cited therein; Sage & Hyman, *supra* note 3, at 16.

In summation, this Part III has argued that: (1) resistance stimulates innovation (H4); (2) conservation should be increasingly favored over production of new antibiotics with more dangerous side effect profiles; and (3) insurance reimbursement systems are a key policy lever for antibiotic effectiveness and may be more effective than patent law. We now proceed to the case study on vancomycin.

IV. TESTING THE PREDICTIONS: A CASE STUDY OF VANCOMYCIN

Vancomycin is a major antibiotic with a relatively well-developed literature on resistance.[215] A recent study found vancomycin to be the single most commonly used antibacterial in U.S. hospitals.[216] Two other antibiotics experienced significant increases in utilization during the study period, namely carbapenems (fifty-nine percent increase) and piperacillin-tazobactam (eighty-four percent increase).[217] Among the three, only vancomycin was fully off patent and thus directly relevant for this Article. Accordingly, the focus will be on vancomycin, with references to other drugs as appropriate.[218]

A major public health concern is the potential emergence of vancomycin-resistant Enterococci (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA).[219] A review study on vancomycin introduced the situation: "*Staphylococcus aureus* resistance to vancomycin is one of the greatest concerns in infectious diseases. Over the past 50 years this common pathogen has demonstrated a remarkable ability to overcome many classes of antibiotics; however, vancomycin has largely remained unscathed."[220]

This Part IV.A compares the case history of vancomycin with the seven hypotheses described in Table 2 *supra*. The biological focus will be on two major infections treated by vancomycin: *Clostridium difficile*-associated disease (CDAD) treated with oral vancomycin, and methicillin-resistant *Staphylococcus aureus* (MRSA) treated with intravenous vancomycin.[221] The institutional focus will be on two

215 A PubMed search for "vancomycin and resistance" yielded 8092 articles, including 1123 review articles. PubMed, http://preview.ncbi.nlm.nih.gov/pubmed (last visited Jan. 25, 2010).

216 Pakyz et al., *supra* note 126, at 2258.

217 *Id.*

218 Given the significant increases in utilization of carbapenems and piperacillin-tazobactam, these examples should be explored in a future study as possible examples of patent holder waste.

219 *See, e.g.*, BAD BUGS, *supra* note 10.

220 James S. Lewis II & Michael W. Ellis, *Approaches to Serious Methicillin-Resistant* Staphylococcus aureus *Infections with Decreased Susceptibility to Vancomycin: Clinical Significance and Options for Management*, 20 CURRENT OPINION INFECTIOUS DISEASES 568 (2007).

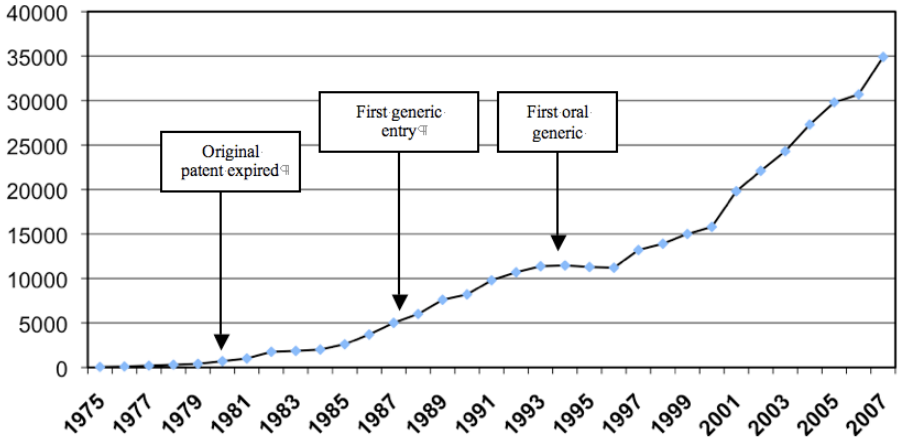
221 We will also explore important infections other than MRSA and CDAD in certain contexts, including VRE.

actors: drug companies and hospitals.[222] We begin by exploring the market for vancomycin, including its patent history, to uncover the relationships between resistance, conservation, and production. Part IV.B then explores some unique questions about antibiotic class coordination. Part IV.C offers some conclusions regarding the seven hypotheses.

A. *The Market for Vancomycin*

Vancomycin may be a natural experiment in the merits of limited antibiotic use in a drug's early years, preserving bacterial susceptibility (non-resistance) for times of greater clinical necessity. Vancomycin retains significant clinical effectiveness more than fifty years after its introduction, due in part to modest sales in its first decades.

Chart 2. U.S. Vancomycin Sales, in Kilograms, 1975-2007[223]



Vancomycin remains a major antibiotic today, and is often an antibiotic of last resort. Eli Lilly & Company introduced vancomycin in 1958 to treat infections no longer susceptible to penicillin.[224] Shortly after its introduction, vancomycin was suspected of various toxicities and was

[222] While many studies of antibiotics also focus on community prescription by doctors, Saver, *supra* note 35, vancomycin is generally prescribed in hospitals and institutions in the United States.

[223] Data from 1997 to 2007 are from *IMS Data*, *supra* note 127 (U.S. R&H, Antibiotics J1X1); data from 1975-1996 are from Herbert A. Kirst et al., *Historical Yearly Usage of Vancomycin*, 42 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1303 (1998).

[224] Ruth Brown & Richard Wise, *Vancomycin: A Reappraisal*, 284 BRITISH MED. J. 1508 (1982).

quickly overtaken in the market by methicillin and other synthetic penicillins.[225] Limited utilization in the 1960s and 1970s conserved vancomycin for important uses that emerged in the 1980s and beyond. In 1982, an article in the *British Medical Journal* suggested exactly this linkage: "Probably the high cost and potential toxicity will help to preserve this very useful agent from abuse, which experience shows usually leads to resistance emerging—a rare problem as yet with vancomycin."[226]

Note that the successful initial conservation of vancomycin was largely a medical accident rather than a deliberate patent holder strategy (compare H2, patent holder conservation).[227] The key was vancomycin's relative clinical profile during the first two and a half decades following its introduction in 1958.[228] The early preservation of vancomycin was not due to thoughtful conservation efforts. Guidelines came much later, beginning in 1995 with the publications by the CDC and the Hospital Infection Control Practices Advisory Committee.[229] These guidelines, and others that followed, encouraged clinicians to use metronidazole as the first-line treatment for CDAD, primarily to slow resistance to vancomycin.[230]

Vancomycin's sales and patent data do not fit the patent holder waste hypothesis (H1). The U.S. Patent and Trademark Office issued the first vancomycin patent to Eli Lilly & Company in 1962. During the patent period, vancomycin was a relatively poor seller. Sales became significant only after the original patent expired in December 1979.[231] From patent expiration until first competitive entry, vancomycin sales grew as medical needs changed, especially after 1984. The growing sales of patent-expired vancomycin attracted the attention of other companies. The first intravenous vancomycin Abbreviated

225 *Id.*; Donald P. Levine, *Vancomycin: A History*, 42 CLINICAL INFECTIOUS DISEASES S5 (2006).

226 Brown & Wise, *supra* note 224, at 1509.

227 Perhaps a major first-in-class antibiotic patent should be purchased in every country and held in strategic reserve for the protection of future global public health. The analogy is to the Strategic Petroleum Reserve. The concept of a Strategic Antibiotic Reserve will be explored in a future article.

228 Patents may have kept the cost higher than substitutable alternatives, but Eli Lilly could have experimented with pricing elasticities to stimulate demand. Vancomycin's medical limitations were the key market constraint.

229 Centers for Disease Control and Prevention, *Recommendations for Preventing the Spread of Vancomycin Resistance: Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC)*, MORBIDITY & MORTALITY WKLY. REP. (RECOMMENDATIONS & REP.), Sept. 22, 1995, *available at* http://www.cdc.gov/mmwr/PDF/RR/RR4412.pdf.

230 Dale N. Gerding, *Metronidazole for* Clostridium difficile*-Associated Disease—Is It Okay for Mom?*, 40 CLINICAL INFECTIOUS DISEASES 1598, 1598 (2005) (reserving oral vancomycin for "severe, potentially life-threatening cases or when oral metronidazole cannot be used").

231 Levine, *supra* note 225, at S7; U.S. Patent No. 3,067,099 (filed Sept. 16, 1955) (issued Dec. 4, 1962).

New Drug Application (ANDA) was approved on March 17, 1987,[232] nearly eight years after vancomycin's patent expiration. Another competitor received five intravenous vancomycin ANDA approvals from 1988 to 1992.[233] While sales continued to grow in the following decades, the upward trend line was already firmly established prior to competitive generic entry. Sales leveled off in the mid-1990s, corresponding with entry of the first oral generic.[234] In the last decade, vancomycin sales have experienced significant growth. As described in Parts IV.A.1 and IV.A.2 *infra*, medical need, rather than clever marketing, drove sales.

Other explanations are possible as well. One could argue that the upturn in sales after patent expiration was a last-ditch attempt by Eli Lilly to obtain profits from a disappointing drug. If that was the case, sales should have spiked *prior* to expiration, as an example of patent holder waste (H1). But the sales data in Chart 2 demonstrate relatively flat sales until 1980, after patent expiration. Another complicating factor is that patent expiration did not lead to immediate generic competition in the years prior to the Hatch-Waxman Act.[235] Perhaps patent holder waste is only a problem after Hatch-Waxman, which suggests a more limited reform to antibiotic patents.

Levine identifies two medical developments explaining the remarkable growth in vancomycin use in the early 1980s: expansion of the clinical indications for oral vancomycin against intestinal infections such as CDAD; and the emergence of MRSA driving demand for intravenous vancomycin.[236] These two environmental changes radically altered the market for both forms of vancomycin. As described in the following Parts, vancomycin sales were a response to medical need, not a marketing or patent story. If so, then vancomycin is not a good example of patent holder waste (H1).

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232 ANDA 062663 (APP Pharmaceuticals); *see* U.S. Food and Drug Administration, Drugs@FDA, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [hereinafter Drugs@FDA] (search "Search by Drug Name, Active Ingredient, or Application Number" for "062663").

233 ANDAs 062911, 062912, 062931, 062933, and 063076 were filed by Hospira during this period for injectible vancomycin. *See* U.S. Food and Drug Administration, Orange Book Active Ingredient Search, http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm [hereinafter U.S. FDA, Orange Book] (search "Search by Active Ingredient" for "vancomycin").

234 Due to the high cost of oral vancomycin, some physicians administered the intravenous version orally. Kirst et al., *supra* note 223.

235 *See* Kevin Outterson, *Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets*, 5 YALE J. HEALTH POL'Y L. & ETHICS 193, 215-16 (2005).

236 Levine, *supra* note 225.

1. Oral Use of Vancomycin for CDAD

Vancomycin is not well absorbed in the body. For most infections it must be given intravenously. For some infections in the intestinal tract, oral use is appropriate. The FDA has approved oral vancomycin to treat two intestinal conditions: *Clostridium difficile*-associated disease (CDAD), and enterocolitis caused by *Staphylococcus aureus*, including methicillin-resistant strains.[237] CDAD is a painful, long-lasting, and potentially deadly diarrheal disease. Medical expenses related to CDAD are significant, in the range of $2,400 to $7,100 per case,[238] with over 250,000 cases in 2005.[239] The market was worth $600 million to $1.7 billion in 2005. Today, CDAD remains a billion dollar business[240] and is primarily associated with antibiotic use.[241]

Prior broad-spectrum antibiotic use dramatically alters the natural flora in the intestines, permitting more virulent and toxic strains of *Clostridium difficile* to flourish in the vacant ecological niche. Antibiotic use is a frequent cause of CDAD, which makes it a nosocomial (hospital-associated) infection.[242] Oral vancomycin is the only drug approved by the FDA for the treatment of this condition, but

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237 The label for Eli Lilly's oral vancomycin includes treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. See the FDA-approved drug label for Vancocin HCl (vancomycin), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50606slr020_vancocin_lbl.pdf (last visited Jan. 15, 2010). *See also* Dale N. Gerding, *Is There a Relationship Between Vancomycin-Resistant* Enterococcal *Infection and* Clostridium difficile *Infection?*, 25 CLINICAL INFECTIOUS DISEASES S206 (1997); ViroPharma Inc., Annual Report (Form 10-K), at 1 (Mar. 2, 2006).

238 Erik R. Dubberke et al., *Short- and Long-Term Attributable Costs of* Clostridium difficile*-Associated Disease in Nonsurgical Inpatients*, 46 CLINICAL INFECTIOUS DISEASES 497 (2008).

239 L. Clifford McDonald, *Confronting* Clostridium difficile *in Inpatient Health Care Facilities*, 45 CLINICAL INFECTIOUS DISEASES 1274 (2007). Only a small portion of these expenses are for drugs; the largest component is longer hospitalizations and medical services.

240 The patent holder for oritavancin estimates the U.S. cost of nosocomial diarrhea at over $1.1 billion annually, primarily as a result of increased hospital stays. Targanta Therapeutics, Pipeline—Oritavancin Program, http://www.targanta.com/pipeline/oritavancin.html (last visited Jan. 15, 2010).

241 David B. Blossom & L. Clifford McDonald, *The Challenges Posed by Reemerging* Clostridium difficile *Infection*, 45 CLINICAL INFECTIOUS DISEASES 222 (2007) (noting that CDAD is a health care-associated disease associated with antibiotic use in the hospital).

242 Gaetano Privitera et al., *Prospective Study of* Clostridium difficile *Intestinal Colonization and Disease Following Single-Dose Antibiotic Prophylaxis in Surgery*, 35 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 208 (1991). Oral vancomycin use is also a risk factor for intestinal fungal infections by *Candida* species. Ines Zollner-Schwetz et al., *Oral and Intestinal* Candida *Colonization in Patients Undergoing Hematopoietic Stem-Cell Transplantation*, 198 J. INFECTIOUS DISEASES 150 (2008). Other studies have found similar effects from metronidazole and ciprofloxacin. Robert Krause et al., *Role of* Candida *in Antibiotic-Associated Diarrhea*, 184 J. INFECTIOUS DISEASES 1065 (2001).

generic metronidazole is used off-label as the first-line treatment for CDAD.[243]

The FDA has approved only two New Drug Applications (NDAs) for oral forms of vancomycin: Eli Lilly's Vancocin® and Lederle's Vancoled.[244] Eli Lilly was the first to market, receiving approval from the FDA on April 15, 1986.[245] Lederle's oral vancomycin was approved on October 15, 1993, but sales were disappointing.[246] The bloom was off the rose for oral vancomycin in the mid-1990s as concerns mounted about vancomycin-resistant Enterococci (VRE). The volume of medical literature on vancomycin exploded from 1994 to 1997, and hospital clinicians increasingly restricted its use.

Oral vancomycin was historically a relatively small portion of total vancomycin consumption in the United States,[247] but a larger percentage of the sales revenues due to higher unit prices, peaking at about eighty percent of the glycopeptide class revenues in FY 1994.[248] Eli Lilly's oral Vancocin® sales peaked in 1994, declining significantly until 2003.[249] The peak in 1994 coincided with published guidelines suggesting restrictions on the use of oral vancomycin for CDAD in order to limit the spread of VRE.[250] This Sector 3 conservation program appears to have reduced sales in the 1990s, consistent with H5, conservation dampens production. Sales in the last decade are shown in Chart 3:

243 ViroPharma Inc., Annual Report (Form 10-K), at 2 (Mar. 2, 2006).

244 *See* Drugs@FDA, *supra* note 232 (search for "vancocin" and "vancoled"); U.S. FDA, Orange Book, *supra* note 233 (search for "vancomycin"). Eli Lilly transferred the rights to Vancocin to Baxter Healthcare, which was awarded NDA 050606 on April 15, 1986, and subsequently to ViroPharma, which received NDA 050671 on April 29, 1993.

245 *See* Drugs@FDA, *supra* note 232 (search for "vancocin"; follow "VANCOCIN HYDROCHLORIDE" hyperlink; then follow "NDA #050606" hyperlink; then follow "Approval History, Letters, Reviews, and Related Documents" hyperlink); Levine, *supra* note 225, at S7 fig.2. Apparently, some oral consumption occurred prior to approval in 1985.

246 *See* Drugs@FDA, *supra* note 232 (search for "vancoled"; follow "ANDA #063321" hyperlink; then follow "Approval History, Letters, Reviews, and Related Documents" hyperlink); Levine, *supra* note 225, at S7 fig.2.

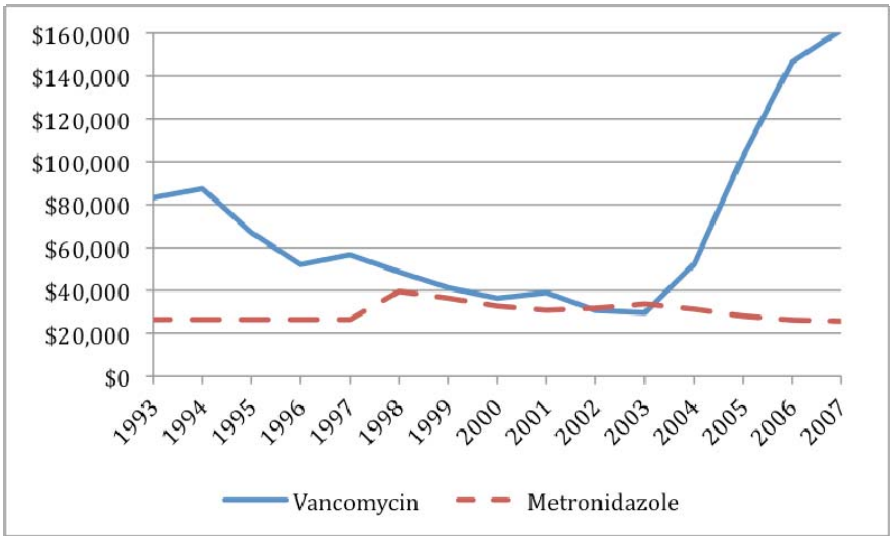
247 *IMS Data*, *supra* note 127 (Antibiotics ATC Level 4, J1C1); *see also* Kirst et al., *supra* note 223, at 1303 (noting that the intravenous version of vancomycin could be given orally as well); Levine, *supra* note 225, at S7.

248 *IMS Data*, *supra* note 127 (Antibiotics ATC Level 4, J1C1, FYE Oct. 1994).

249 *Id.*

250 Hospital Infection Control Practices Advisory Committee, *Recommendations for Preventing the Spread of Vancomycin Resistance*, 16 INFECTION CONTROL & HOSP. EPIDEMIOLOGY 105 (1995).

Chart 3. Oral Vancomycin[251] and Oral Metronidazole Sales,[252] U.S. Sales 1993-2007[253] (in Thousands of 1997 U.S. Dollars)



The patent holder waste hypothesis (H1) suggests, by analogy, that competitive market entry by Lederle in 1993 would have resulted in overzealous marketing and waste.[254] That does not seem to have been the case here. Perhaps Lederle's timing was poor, but overall constant dollar sales of oral vancomycin declined from 1993-2003.[255] Sales of Lederle's oral vancomycin (Vancoled) were very small, less than seven percent of the glycopeptide class in 1994 and falling rapidly thereafter.[256] Vancoled sales dwindled through the next decade, falling to $183,000 in 2002 before Lederle discontinued its product.[257]

The market for oral vancomycin changed dramatically in 2004. Eli Lilly followed Lederle by exiting the U.S. oral vancomycin market in November 2004, selling its U.S. rights to ViroPharma for $116 million

[251] *IMS Data*, *supra* note 127 (Antibiotics ATC Level 4, J1C1, J1X1 Vancocin and Vancoled).

[252] *IMS Data*, *supra* note 127 (Antibiotics ATC Level 4, J1C1, Metronidazole G1A1 Trichomonacides and A2B4 Bismuth antiulcerants). Since metronidazole is not approved for CDAD, it is difficult to know exactly what IMS category is appropriate, but I excluded the topical uses, leaving primarily tablet forms.

[253] Oral metronidazole sales prior to 1997 are not available and have been estimated by the author. Dollar amounts were adjusted by the author according to the Consumer Price Index: All Urban Consumers, U.S. City Average. *See* U.S. Dep't of Labor, Bureau of Labor Statistics, Consumer Price Index: All Urban Consumers (CPI-U), U.S. City Average, ftp://ftp.bls.gov/pub/special.requests/cpi/cpiai.txt (last visited Jan. 15, 2010).

[254] *See supra* Part II.C.

[255] *IMS Data*, *supra* note 127 (FYE Oct. 2004); *see also* Levine, *supra* note 225, at S7 fig.2.

[256] *IMS Data*, *supra* note 127 (FYE Oct. 1994).

[257] *IMS Data*, *supra* note 127 (FYE Oct. 2002).

cash plus royalties on future sales.[258] The royalty structure gave ViroPharma a strong financial incentive to keep sales above $65 million.[259] ViroPharma was remarkably successful, almost doubling the sales targets in 2005, with net sales exceeding $125 million.[260] This was by far the best sales year in the history of oral vancomycin. In nominal dollars, sales reached $166.7 million in 2006,[261] $203.7 million in 2007,[262] and $232.3 million in 2008, driven by both unit sales and price increases.[263] The dramatic jump in sales of oral vancomycin certainly looks like patent holder waste (H1) and perhaps also a negation of patent holder conservation (H2), but on closer examination the facts do not fit the theory.

Two possible explanations will now be explored for these dramatic sales figures. The first is a property rights story, driven by aggressive marketing. The second is a medical story, driven by epidemiological factors beyond the company's control.

Certainly the royalty structure gave ViroPharma a strong incentive to keep sales above $65 million per year. Until October 2008, ViroPharma was completely dependent on sales of Vancocin®.[264] While other products are in development, Vancocin® accounts for one hundred percent of the company's current product sales.[265] And yet, as late as December 31, 2006, ViroPharma did not have a sales staff.[266] Doctors prescribe Vancocin® primarily in hospitals and long term care facilities, and a very small marketing staff of six people achieved the tremendous increase in sales:

> We currently have a limited marketing staff and do not have a sales staff. We focus on educational initiatives, including thought leader development, physician education, and the targeted education of health professionals, by utilizing a small number of regional medical

258 ViroPharma Inc., Annual Report (Form 10-K), at 1, 6, 40 (Mar. 15, 2005). ViroPharma acquired the U.S. rights to Vancocin from Eli Lilly & Company in November 2004. Eli Lilly retained rights in the rest of the world and continued to produce the active pharmaceutical ingredient under contract with ViroPharma until 2006. The royalty structure is found on page 40, and models sales in the range of $44-$65 million per year. *Id.*

259 ViroPharma paid a fifty percent royalty in 2005 on sales between $44 million and $65 million, but no royalty for sales above or below that corridor. The royalty percentage falls to thirty-five percent from 2006 to 2011, when it expires. ViroPharma Inc., Annual Report (Form 10-K), at 4 (Mar. 2, 2006).

260 *Id.* at 36 (without adjustment for inflation).

261 ViroPharma Inc., Annual Report (Form 10-K), at 36 (Feb. 28, 2007).

262 ViroPharma Inc., Annual Report (Form 10-K), at 36 (Feb. 28, 2008).

263 ViroPharma Inc., Annual Report (Form 10-K), at 47 (Mar. 2, 2009).

264 ViroPharma Inc., Annual Report (Form 10-K), at 17 (Mar. 2, 2006); ViroPharma Inc. Quarterly Report (Form 10-Q), at 7 (May 4, 2009) (describing acquisition of Lev Pharmaceuticals, Inc. and their drug, Cinryze).

265 ViroPharma Inc., Annual Report (Form 10-K), at 51 (Mar. 2, 2009).

266 ViroPharma Inc., Annual Report (Form 10-K), at 8 (Feb. 28, 2007).

> science liaisons. As of December 31, 2006, we have six members in our regional medical scientist team.[267]

In the first quarter of 2008, ViroPharma finally spent $2.7 million for a hospital sales force to promote Vancocin®.[268] By the end of 2008, these expenses had grown to $12.6 million for the Vancocin® sales force.[269] Sales growth has declined even as marketing expenses have significantly increased, and the great bulk of sales growth occurred before any marketing began. Vancocin® is not a marketing-driven story.

The more likely explanation for this dramatic growth lies in the CDAD market and growing resistance to metronidazole. Some strains of *Clostridium difficile* evolved into a "hypervirulent" pathogen of growing concern since 2001, driving the demand for therapy.[270] Researchers have not yet identified the mutation responsible for this more dangerous form of *Clostridium difficile*.[271] The primary alternative to oral vancomycin has been metronidazole, but it faces increasing treatment failure for this severe form of CDAD.[272] Hospitalizations affected by CDAD have grown from 98,000 in 2000 to an estimated 250,000 in 2005.[273] This accounts for the majority of Vancocin®'s growth[274]:

> Vancocin has been reserved by physicians for patients who have failed metronidazole therapy, who have relapsed or who are suffering from severe forms of CDAD. We believe that the epidemiological shift that has contributed to increased incidence and severity of CDAD has led to an increase in the use of Vancocin.[275]

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267 *Id.*

268 ViroPharma Inc., Annual Report (Form 10-K), at 8 (Feb. 28, 2008); ViroPharma Inc., Quarterly Report (Form 10-Q), at 20 (Apr. 30, 2008).

269 ViroPharma Inc., Annual Report (Form 10-K), at 49 (Mar. 2, 2009).

270 McDonald, *supra* note 239, at 1274 (noting that the hypervirulent strain of *Clostridium difficile* emerged in 2001 when it developed high levels of fluoroquinolone resistance); Dale N. Gerding, Carlene A. Muto & Robert C. Owens, Jr., *Measures to Control and Prevent* Clostridium difficile *Infection*, 46 CLINICAL INFECTIOUS DISEASES S43, S43 (2008).

271 Ruth Murray et al., *Truncation in the tcdC Region of the* Clostridium difficile *PathLoc of Clinical Isolates Does Not Predict Increased Biological Activity of Toxin B or Toxin A*, 9 BMC INFECTIOUS DISEASES 103 (2009).

272 Gerding is quite careful in his evaluation of the recent data on metronidazole treatment failure. Gerding, *supra* note 230, at 1600. The marketer of Vancocin® is less cautious. ViroPharma Inc., Annual Report (Form 10-K), at 2 (Feb. 28, 2008) ("We believe that changes in the epidemiology of CDI, in particular the increasing frequency of severe disease, and data suggesting that failure or relapse occur more commonly in patients treated with metronidazole have led to an increase in the use of Vancocin.").

273 McDonald, *supra* note 239. Research in 2009 confirms that CDAD continues to be a serious problem. Jyotsna Jagai & Elena Naumova, *Clostridium difficile-associated Disease in the Elderly, United States*, 15 EMERGING INFECTIOUS DISEASES 343 (2009).

274 ViroPharma Inc., Annual Report (Form 10-K), at 1 (Feb. 28, 2007).

275 ViroPharma Inc., Annual Report (Form 10-K), at 2 (Mar. 2, 2006).

This finding is consistent with the claim that resistance stimulates innovation (H4). A product's obsolescence through resistance[276] creates a market for another substitutable product. Here, for example, resistance created CDAD, and wrought destruction on existing treatments such as metronidazole, opening the way for oral vancomycin.[277] Of course oral vancomycin was not a new treatment, but it had been temporarily sidelined due to its side effects and cost. Metronidazole was originally the better drug, but with resistance metronidazole lost absolute efficacy, and at some point metronidazole became relatively less effective than oral vancomycin, especially for the hypervirulent form of CDAD.[278]

Several other observations can be drawn that contrast with some theoretical predictions. A key assumption in the patent holder waste hypothesis (H1) is the threat of competitive entry by generic firms, leading to a tragedy of the antibiotic commons.[279] The oral vancomycin (Vancocin®) story is quite different. First, despite generic entry in 1993 and the expiration of the last core oral patent in 1996, Vancocin® remains the only oral form of vancomycin on the U.S. market today.[280] But sales at current levels attract competitive attention. In March 2006, ViroPharma filed an administrative petition to stay the approval of a competitive oral vancomycin product on the grounds of inadequate bioequivalence.[281] ViroPharma is relying on non-patent intellectual property and regulatory barriers to defend its lucrative market from

276 It appears that metronidazole's growing treatment failure is not a result of resistance to metronidazole itself, but due to increased use of other antibiotics. Daniel M. Musher et al., *Relatively Poor Outcomes After Treatment of* Clostridium difficile *Colitis with Metronidazole*, 40 CLINICAL INFECTIOUS DISEASES 1586, 1589 (2005) ("Specific resistance to metronidazole was probably not a factor, because strains of *C. difficile* resistant to this drug have not been identified at our medical center."). For fluoroquinolones, the mechanism is accumulated resistance. McDonald, *supra* note 239.

277 Evidence-based guidelines from the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of American (IDSA) have noted the shifting need for oral vancomycin to treat severe or recurrent CDAD. *See* ViroPharma Inc., Annual Report (Form 10-K), at 2 (Feb. 28, 2008). The triggering event was the emergence in 2001 of the hypervirulent strain exhibiting high levels of fluoroquinolone resistance. McDonald, *supra* note 239; Rocco Ricciardi et al., *Increasing Prevalence and Severity of* Clostridium difficile *Colitis in Hospitalized Patients in the United States*, 142 ARCHIVES SURGERY 624 (2007).

278 *See supra* Part III.A.1.

279 *See supra* Part II.C.

280 ViroPharma Inc., Annual Report (Form 10-K), at 2, 11, 25 (Mar. 2, 2009).

281 Letter from Michel de Rosen, Chief Executive Officer, ViroPharma Inc., to Andrew C. von Eschenbach, Acting Commissioner of Food and Drugs, FDA (Mar. 17, 2006), *available at* http://www.fda.gov/OHRMS/DOCKETS/dockets/06p0124/06p-0124-let0001.pdf. The petition was filed pursuant to 21 C.F.R. § 10.35. *See also* ViroPharma Inc., Annual Report (Form 10-Q), at 9 (Apr. 30, 2008). This filing compelled the company to evaluate an impairment or change in the useful life of its vancomycin-related intangibles under SFAS No. 144. *Id.* I resist the urge to explore the impact of U.S. public accounting standards on antibiotic resistance, but perhaps someone else will engage in such an exploration.

generic competition.[282] In 2009, ViroPharma devoted millions of dollars in legal fees to continue to delay market entry by this potential competitor.[283] Non-patent barriers can significantly delay generic entry.

Second, the threat of competitive generic entry has stimulated paradigm-breaking R&D at ViroPharma. The company has begun a research program to isolate non-toxigenic strains of *Clostridium difficile* to be used as a re-colonization treatment after oral vancomycin.[284] This is an interesting project, headed by a leading *Clostridium difficile* scientist, Dr. Dale Gerding. This small research program might side step the entire question of resistance by colonizing the ecological space with non-toxic *Clostridium difficile* bacteria.[285] Phase I trials should begin in 2009.[286] Not all responses to the threat of competitive generic entry waste the antibiotic commons, a point that is relevant to both H4 (resistance stimulates innovation) and H1 (patent holder waste).

Third, while H2 (patent holder conservation) suggests private coordination under a single patent holder, Eli Lilly chose to fragment its rights to oral vancomycin by a license to ViroPharma, diminishing its ability to coordinate on a global basis. This license occurred just as oral vancomycin sales took off. Eli Lilly retained the rights outside the United States, and also continued to produce (for a time) intravenous vancomycin. This property fragmentation occurred despite concerns that oral vancomycin might contribute significantly to resistance. Available data suggests that oral prescriptions of vancomycin may create proportionately higher risks of VRE, but the datasets are remarkably small.[287] If the case is to be made for patent-based coordination as an effective conservation strategy, oral vancomycin for CDAD is not a good example. If scholars proffer other antibiotics as

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[282] Of course, Vancocin® has faced generic competition from metronidazole for years. My statement refers to generic vancomycin.

[283] ViroPharma Inc., Annual Report (Form 10-K), at 49 (Mar. 2, 2009) (noting that legal fees to delay the ANDA were $3.3 million in 2007, $4 million in 2008, and the company will spend at "higher levels in future periods"). If generic entry boosted sales, then this litigation might still be socially desirable as a conservation tool (H2). As seen above, generic entry does not necessarily increase unit sales, since marketing tapers off with generic entry. *See* Lichtenberg & Duflos, *supra* note 68.

[284] ViroPharma Inc., Annual Report (Form 10-K), at 4 (Feb. 28, 2008).

[285] For a careful caution on probiotic commensal therapies, see Bernard Dixon, *It's a Little Bit More Complicated than That*, 9 LANCET INFECTIOUS DISEASES 399 (2009).

[286] ViroPharma Inc., Annual Report (Form 10-K), at 6 (Mar. 2, 2009).

[287] In 1997, Gerding tried to suggest that oral vancomycin contributed modestly to VRE overall, given the small volume of oral prescriptions at the time, but he did not deny the relatively greater effect. Gerding, *supra* note 239 (noting as unclear the relationship between route of administration and resistance); Levine, *supra* note 225, at S7. Other studies also raise concerns, *e.g.*, Philippe Van der Auwera et al., *Influence of Oral Glycopeptides on the Fecal Flora of Human Volunteers: Selection of Highly Glycopeptide-Resistant Enterococci*, 173 J. INFECTIOUS DISEASES 1129 (1996), but the relationships remain unclear. Neil Woodford, *Glycopeptide-Resistant Enterococci: A Decade of Experience*, 47 J. MED. MICROBIOLOGY 849 (1998). All of these studies occurred before the explosion of oral vancomycin use since 2004.

examples of patent holder waste (H1), this study of oral vancomycin suggests that we must carefully study the patent holder's incentives before reaching any conclusions. Next, we turn to another major use of vancomycin, as an intravenous treatment for MRSA.

2. Intravenous Vancomycin for MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major public health hazard with growing significance.[288] The infectious disease community has been tracking the rise of MRSA for decades,[289] and vancomycin is today the most frequently chosen antibiotic for MRSA.[290] The increased prevalence of MRSA increases demand for vancomycin[291] and other useful antibiotics. While antibiotic innovation in general is said to be moribund,[292] MRSA innovation appears to be flourishing, with many compounds in clinical trials.[293] This is a plausible example of hypothesis H4 (resistance stimulates innovation).[294] The multibillion-dollar MRSA market has attracted significant market entrants with new products in the pipeline. In the 2009 "Fierce 15" list of the most promising small biotech companies, four were working on anti-infective therapies, including novel treatments for multi-drug resistant gram-negative bacteria, MRSA, *Pseudomonas aeruginosa*, and novel vaccines for genital herpes and

288 Eili Klein, David L. Smith & Ramanan Laxminarayan, *Hospitalizations and Deaths Caused by Methicillin-Resistant* Staphylococcus aureus*, United States, 1999-2005*, 13 EMERGING INFECTIOUS DISEASES 1840 (2007); R. Monina Klevens et al., *Invasive Methicillin-Resistant* Staphylococcus aureus *Infections in the United States*, 298 JAMA 1763 (2007).

289 *See, e.g.*, BAD BUGS, *supra* note 10; ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS, SHADOW EPIDEMIC: THE GROWING MENACE OF DRUG RESISTANCE 6 (2004), *available at* http://www.tufts.edu/med/apua/print/GAARD.pdf. For examples abroad, see COMM. ON SCI. & TECH., HOUSE OF LORDS, SCIENCE AND TECHNOLOGY—SEVENTH REPORT: RESISTANCE TO ANTIBIOTICS AND OTHER ANTIMICROBIAL AGENTS ¶ 1.5 (1998), *available at* http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/081vii/st0702.htm; and Nordberg et al., *supra* note 2.

290 Klevens et al., *supra* note 288.

291 Klein et al., *supra* note 288, at 1844; Donald P Levine, *Vancomycin: Understanding Its Past and Preserving Its Future*, 101 S. MED. J. 284 (2008) (noting that the increased use of vancomycin in the 1980s to treat MRSA has led to the emergence of VRE and VRSA).

292 BAD BUGS, *supra* note 10; Norrby et al., *supra* note 78; Talbot et al., *supra* note 40; Wenzel, *supra* note 2. *But see* Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 562.

293 Ursula Theuretzbacher, *Future Antibiotics Scenarios: Is the Tide Starting to Turn?*, 34 INT'L J. ANTIMICROBIAL AGENTS 15 (2009) (finding in the past decade a wave of Gram-positive innovation driven by resistance, especially MRSA, and predicting a coming wave of Gram-negative innovation, also driven by resistance); Klein et al., *supra* note 288, at 1844.

294 Theuretzbacher, *supra* note 293, at 15 ("Still, many years passed before an ever-increasing mass of critical public health concerns regarding the rapid rise of MRSA forced open a market niche window leading to a wave of anti-Gram-positive R&D mainly in small companies.").

pandemic and seasonal influenza.[295] Drug companies are attracted to these markets.

A recent article by Klein, Smith, and Laxminarayan reviewed the costs of MRSA in the United States. They drew similar conclusions on the relationship between MRSA and demand for vancomycin:

> Another important implication of our analysis is that the increasing incidence of MRSA in hospitalized patients, whether the infection was acquired in the hospital or the community, is likely to increase the demand for vancomycin. Despite several new (daptomycin, linezolid, tigecycline) and old (trimethoprim-sulfamethoxazole, clindamycin) antimicrobial drugs available for treatment of MRSA infections, vancomycin has remained the first-line drug for treating MRSA. This pattern has broad implications for the future control of MRSA as well as other pathogens. S. aureus infections resistant to vancomycin are already emerging, and vancomycin-resistant enterococci are already a major problem in hospitals. Vancomycin use should be restricted to methicillin-resistant S. aureus infections and used only for MRSA infections in situations where other drugs are not appropriate.[296]

Note the interesting relationship between VRE and emerging MRSA markets. If vancomycin were not showing some signs of resistance, the incentive to create new compounds would be weakened.[297] Of course, if vancomycin were immune to resistance, the medical need for new antibiotics would be much less pressing. The potential obsolescence of vancomycin and other antibacterial agents is a very important factor in creating new markets for MRSA drugs.[298] Prominent examples include telavancin, a glycopeptide patented by Theravance.[299] Researchers have reported Phase 3 trials demonstrating noninferiority of telavancin against vancomycin for hospital-associated pneumonia (HAP) caused by MRSA and complicated skin and skin structure infections (cSSSI) caused by MRSA.[300] If approved by the

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295 Posting of Christopher P. Singer to Patent Docs: Biotech and Pharma Patent Law and News Blog, http://www.patentdocs.org/2009/06/fiercebiotech-announces-fierce-15-for-2009.html (June 30, 2009).

296 Klein et al., *supra* note 288, at 1844 (citations omitted).

297 Indeed, in the words of Theravance's scientists, "[t]he emergence and spread of bacterial resistance to vancomycin, in important antibiotic to treat serious infections caused by gram-positive bacteria, has prompted active research to discover new glycopeptides and semisynthetic analogs with improved antimicrobial properties." Deborah L. Higgins et al., *Telavancin, a Multifunctional Lipoglycopeptide, Disrupts Both Cell Wall Synthesis and Cell Membrane Integrity in Methicillin-Resistant* Staphylococcus aureus, 49 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1127 (2005).

298 Theuretzbacher, *supra* note 293, at 15 ("Antibiotics focused on Gram-positive bacteria, including MRSA, are proving to be commercially attractive and are encouraging investment in R&D, as has been shown with the commercial success of Pfizer's linezolid and later Cubist's daptomycin in the USA.").

299 Higgins et al., *supra* note 297.

300 Samuel E. Wilson et al., *Telavancin Versus Vancomycin for the Treatment of Complicated*

FDA, the market for telavancin will have been created, in large part, by growing resistance to vancomycin and the fear of a widespread outbreak of vancomycin-resistant *S. aureus* (VRSA). Similar concerns motivated the research programs for daptomycin, tigecycline, and linezolid, three first-in-class antibiotics.[301] But none of these drugs work better than vancomycin against MRSA,[302] at least not yet.

Conversely, effective conservation methods dampen the immediate need for new antibiotics.[303] Linezolid is a new first-in-class antibiotic that is increasingly used in lieu of vancomycin for ventilator-associated pneumonia.[304] As Paterson notes, the clinical evidence for preferring linezolid to vancomycin is subject to important questions,[305] another way of saying that, absent resistance, vancomycin might be the better drug. Linezolid is still under patent, which means the company can attempt to persuade doctors to switch to linezolid based on these studies. If intravenous vancomycin were still patented, it is likely that the patent holder would market to physicians to point out the weaknesses in these studies and to try to curtail the switch to linezolid.[306] In this case, becoming generic may actually reduce the marketing pressures to prescribe vancomycin and allow the patented competitor to market without contradiction. From a medical standpoint, this may mean less than optimal prescribing, as physicians act on a biased version of the medical evidence. These marketing practices also weaken the patent holder conservation hypothesis (H2), since preserving linezolid for future use might better serve social welfare so long as vancomycin remains effective. This is an interesting cross-class effect: In order for patent holder conservation (H2) to work, a single

Skin and Skin-Structure Infections Associated with Surgical Procedures, 197 AM. J. SURGERY 791 (2009). For a summary of the ATTAIN 1 and ATTAIN 2 clinical studies, see *Theravance Announces FDA Acceptance of Telavancin NDA for the Treatment of Hospital-Acquired Pneumonia*, MED. NEWS TODAY, Apr. 12, 2009, http://www.medicalnewstoday.com/articles/145436.php.

301 Theuretzbacher, *supra* note 293; Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 560-61.

302 Arias & Murray, *supra* note 110, at 440-41.

303 *See, e.g.*, Huang et al., *supra* note 202 (finding that routine surveillance for MRSA in the ICU followed by contact isolation of MRSA cases yielded a large and statistically significant reduction in MRSA bacteremia).

304 Paterson, *supra* note 85.

305 *Id.* at 487 ("However, there are two important caveats to these findings. Firstly, these results are a subgroup analysis of a larger study that showed no overall difference between linezolid and vancomycin for hospital-acquired pneumonia. Indeed, the FDA does not recognize claims of superiority of linezolid over vancomycin for this condition. Secondly, the vancomycin dosage used in these studies was 1 g every 12 h given intravenously. Many clinicians are now using larger doses of vancomycin and aiming for trough concentrations of vancomycin of $\leq$ 20 mg/L. A randomized trial is now underway comparing linezolid with higher doses of vancomycin for hospital-acquired pneumonia.").

306 In the U.S. market, generic drug manufacturers do not market to physicians or consumers. Pharmacies generally dispense only one generic version of a particular drug.

company would need to hold exclusive rights to both vancomycin and linezolid. Since intravenous vancomycin has been off patent since 1980, patent holder conservation (H2) does not appear to be possible for linezolid.

Other interesting incentive effects were at play with vancomycin and MRSA which support the resistance stimulates innovation hypothesis (H4). The original patent ('099) was filed on September 16, 1955.[307] For many other successful drugs, the innovator company and others race to file follow-on patents for incremental improvements to the drug. These drugs are sometimes derisively labeled "me-too" or "evergreen" drugs, but follow-on antibiotic innovation can improve important characteristics, such as reducing toxicity or improving mechanisms against resistance. Vancomycin was not a successful drug at launch, or indeed for its first twenty-five years. Eli Lilly apparently did not file follow-on patent applications for vancomycin until the early 1980s.[308] Eli Lilly resurrected a moribund research program as MRSA began to emerge. The new patents included both process patents[309] and compound patents on novel glycopeptides.[310] As of 2009, vancomycin was still the only glycopeptide approved for use in the United States. The FDA recently denied Targanta's application for a second glycopeptide (oritavancin), and that compound's future remains uncertain.[311] MRSA was responsible for resurrecting intravenous vancomycin.

Veterinary use of glycopeptides (e.g., avoparcin) weakens the patent holder conservation hypothesis (H2), suggesting that a patent holder may not make decisions to maximize human health. The small human market for vancomycin in the 1960s and 1970s led Eli Lilly to

307 U.S. Patent No. 3,067,099 (filed Sept. 16, 1955) (issued Dec. 4, 1962).

308 Most of the early patents citing the '099 patent were from Eli Lilly & Company, including the first fourteen: U.S. Patent No. 4,440,753 (filed Mar. 15, 1982); U.S. Patent No. 4,462,942 (filed July 30, 1982); U.S. Patent No. 4,495,179 (filed Dec. 16, 1983); U.S. Patent No. 4,537,770 (filed Oct. 18, 1984); U.S. Patent No. 4,547,488 (filed Apr. 16, 1984); U.S. Patent No. 4,548,924 (filed Apr. 16, 1984); U.S. Patent No. 4,548,925 (filed Apr. 16, 1984); U.S. Patent No. 4,552,701 (filed Apr. 16, 1984); U.S. Patent No. 4,558,008 (filed Dec. 13, 1983); U.S. Patent No. 4,558,009 (filed Dec. 27, 1983); U.S. Patent No. 4,559,323 (filed Aug. 2, 1984); U.S. Patent No. 4,604,239 (filed June 11, 1985); U.S. Patent No. 4,639,433 (filed Aug. 14, 1985); U.S. Patent No. 4,643,987 (filed Aug. 14, 1985). All of these were filed in the early 1980s and issued from 1984 to 1987.

309 Including the '753, '942, and '179 patents. All of these patents were issued to Eli Lilly & Company.

310 These included the '488, '924, '925, '701, '008, '433, and '987 patents and U.S. Patent No. 4,698,327 (filed Apr. 18, 1986). All of these patents were issued to Eli Lilly & Company.

311 Reuters, *Targanta Drug Appears Similar to Rival—US FDA Staff*, FORBES.COM, Nov. 17, 2008, http://www.forbes.com/feeds/afx/2008/11/17/afx5703072.html. Oritavancin was initially developed by Lilly, then out-licensed to InterMune, who finally sold it to Targanta. Oritavancin was rejected by FDA in December 2008 due to lack of evidence of effectiveness in one of their studies that was done many years ago by Eli Lilly. Targanta has been recently acquired by The Medicines Company and may (or not) plan a new Phase 3 program for oritavancin.

focus more on animal uses of glycopeptides, especially in Europe.[312] Eli Lilly's research teams were focused on antibiotics for use in animal feeds, resulting in several patents filed in the mid- to late-1970s.[313] In addition, several of the 1984-1987 flurry of Eli Lilly patents citing '099 were for animal growth promotion with low-dose antibiotics in feed.[314] Researchers have identified these growth promotion uses of glycopeptide antibiotics as troublesome for resistance.[315] Europe has now banned their use, and the FDA also restricted the off-label use of glycopeptides in animals.[316]

Eli Lilly deployed scientific uncertainty to claim they were not deliberately wasting glycopeptides through the sale of avoparcin animal feeds. The company raised skeptical questions about the scientific evidence for human resistance through the animal feed mechanism. In 1998, three Lilly scientists wrote: "In view of these data, the need to invoke a second mechanism for the spread of vancomycin-resistant bacteria in humans due to avoparcin use in Europe remains open to debate."[317] Eli Lilly eventually lost this debate.[318] These events weaken

312 Kirst et al., *supra* note 223, at 1303 (noting that avoparcin, an animal feed glycopeptide, was never approved in the United States but was widely used in Europe).

313 U.S. Patent No. 4,083,964 (filed Sept. 13, 1976) (issued Apr. 11, 1978) (increasing feed efficiency through antibiotics in animal feed); U.S. Patent No. 4,122,168 (filed May 23, 1977) (issued Oct. 24, 1978) (detailing new antibiotic A-35512, useful as an antibiotic against dental caries and for growth promotion in animal feed); U.S. Patent No. 4,331,594 (filed Nov. 14, 1980) (issued May 25, 1982) (detailing new antibiotic A-21978, an antibacterial agent and useful in growth promotion in poultry). All of these patents were assigned to Eli Lilly and Company.

314 Including the '770, '323, '239, '545, and '331 patents. All of these patents were issued to Eli Lilly & Company.

315 Frank Møller Aarestrup et al., *Glycopeptide Susceptibility Among Danish* Enterococcus faecium *and* Enterococcus faecalis *Isolates of Animal and Human Origin and PCR Identification of Genes Within the VanA Cluster*, 40 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1938 (1996); A.E. Van den Bogaard et al., *High Prevalence of Colonization with Vancomycin- and Pristinamycin-Resistant Enterococci in Healthy Humans and Pigs in the Netherlands: Is the Addition of Antibiotics to Animal Feeds to Blame?*, 40 J. ANTIMICROBIAL CHEMOTHERAPY 454 (1997); W. Witte, *Impact of Antibiotic Use in Animal Feeding on Resistance of Bacterial Pathogens in Humans*, *in* ANTIBIOTIC RESISTANCE: ORIGINS, EVOLUTION, SELECTION AND SPREAD (Derek Chadwick & Jaime Goode eds., 1997). *But see* Kirst et al., *supra* note 223, at 1303 (noting the lack of relationship between animal glycopeptide use in Europe and resistance to vancomycin). For studies on other antibiotic classes used in animal feeds, see H. GREGG CLAYCAMP & BARRY H. HOOBERMAN, FDA CENTER FOR VETERINARY MEDICINE, VIRGINIAMYCIN RISK ASSESSMENT: RISK ASSESSMENT OF STREPTOGRAMIN RESISTANCE IN *ENTEROCOCCUS FAECIUM* ATTRIBUTABLE TO THE USE OF STREPTOGRAMINS IN ANIMALS (Nov. 23, 2004) (draft for comment), http://www.fda.gov/downloads/AnimalVeterinary/NewsEvents/CVMUpdates/UCM054722.pdf.

316 Extralabel Animal Drug Use; Fluoroquinolones and Glycopeptides; Order of Prohibition, 62 Fed. Reg. 27,944 (May 22, 1997) (codified as amended at 21 C.F.R. § 530.41 (2009)). For a recent overview, see Terence J. Centner, *Regulating the Use of Non-Therapeutic Antibiotics in Food Animals*, 21 GEO. INT'L ENVTL. L. REV. 1 (2008); *see also* David L. Smith et al., *Animal Antibiotic Use Has an Early but Important Impact on the Emergence of Antibiotic Resistance in Human Commensal Bacteria*, 99 PROC. NAT'L ACAD. SCI. 6343 (2002).

317 Kirst et al., *supra* note 223, at 1304.

318 The evidence is stronger today on the linkage between antibiotic use in animals and the

the patent holder conservation hypothesis (H2). Drug companies may not be trustworthy as long-term stewards of antibiotics, even in the absence of generic competition.

Eli Lilly's animal feed research program also requires a modification to the patent holder waste hypothesis (H1): Facing a small and temporarily unimportant human market, the company had no reason to conserve vancomycin and could profit from sales in animal feeds. If waste occurred here,[319] the cause was the small human market, not the time-limited nature of patents. A longer term on the '099 patent would not have delayed Eli Lilly's diversification given the small human market. This is an important constraint on using this data to support longer patent terms.

B. *Class Coordination*

Vancomycin also presents a natural illustration of the difficulties of class coordination, which would be required for patent holder conservation (H2). A solution to the resistance problem discussed by some is to expand antibiotic patent scope to encompass the entire class, giving full ownership of the class to a single company or a group of companies operating a patent pool under an antitrust waiver.[320] In this world, Eli Lilly would have had a perpetual patent on all glycopeptides.[321] These proposals raise a host of issues, some of which I have discussed previously.[322] Class-based patents are an unwieldy path to continued antibiotic effectiveness.

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transfer of mobile genetic elements of resistance to the human population through the global food trade. Remi M. Ajiboye et al., *Global Spread of Mobile Antimicrobial Drug Resistance Determinants in Human and Animal* Escherichia coli *and* Salmonella *Strains Causing Community-Acquired Infections*, 49 CLINICAL INFECTIOUS DISEASES 365, 370 (2009) ("These data suggest that food-producing animals are a major reservoir for integrons carrying antimicrobial drug-resistant genes."); Ellie Herschberger et al., *Quinupristin-Dalfopristin Resistance in Gram-Positive Bacteria: Mechanism of Resistance and Epidemiology*, 38 CLINICAL INFECTIOUS DISEASES 92, 96 (2004) ("Considering the effect that antimicrobial resistance as on human health and also its economic impact, measures to preserve these agents and delay the development of resistance are urgently needed. This includes judicial use of antibiotics for infection in humans, control measures to prevent the spread of resistant pathogens in health care facilities, and the decrease of resistance in reservoirs such as the environment and animal husbandry.").

319 Waste is difficult to prove in agricultural uses because the relationship between agricultural use and human infection with resistant bacteria is complex and occasionally counterintuitive. *See* Marc Lipsitch, Randall S. Singer & Bruce R. Levin, *Antibiotics in Agriculture: When Is It Time to Close the Barn Door?*, 99 PROC. NAT'L ACAD. SCI. 5752 (2002).

320 LAXMINARAYAN ET AL., *supra* note 3, at 13; Laxminarayan, *Scope of Antibiotic Patents*, *supra* note 51. For prior critiques of this concept, see Outterson, *Vanishing Public Domain*, *supra* note 4, at 94-99; and Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 563.

321 Ironically, Eli Lilly discovered and out-licensed vancomycin, oritavancin, and daptomycin.

322 Outterson, *Vanishing Public Domain*, *supra* note 4, at 94-99; Outterson et al.,

As discussed in Part IV.A.1 *supra*, Eli Lilly effectively controlled the glycopeptide class but did not act to conserve it. To the contrary, it fragmented property rights in the class through licensing. Nevertheless, it might be possible empirically to test patent holder conservation (H2) with vancomycin. In the United States, vancomycin has never faced patented competition within the glycopeptide class,[323] but in Europe, a second glycopeptide has been marketed for several years. If patent holder conservation (H2) on a class basis was an effective strategy, one hypothesis worth testing would be a comparison of the U.S. and E.U. glycopeptide markets. The patent holder conservation hypothesis (H2) would predict less resistance in the United States and more resistance within the glycopeptide class in Europe over the past decades since Europe has faced competition within the class. Older data on comparative glycopeptide resistance levels in the United States and Europe do not give a clear result.[324] Perhaps other factors such as conservation efforts in Europe have offset any patent holder waste effect.[325] An empirical study should be undertaken to resolve this question.

Class-based resistance also afflicts fluoroquinolones. The leading hospital antibiotic, levofloxacin, is a member of the fluoroquinolone class,[326] as is ciprofloxacin (Cipro®), a major generic antibiotic. From current medical evidence on resistance, a patent-based conservation strategy to protect levofloxacin may well require the "re-patenting" of ciprofloxacin,[327] which recently entered the public domain, and perhaps other members of the fluoroquinolone class. While this would be a boon to levofloxacin's patent owner (Ortho McNeil), it would raise many legal and practical problems. First, granting class-based antibiotic patents is a quite radical departure from existing practice, dramatically widening the scope of patents. Second, re-patenting public domain ciprofloxacin might be quite difficult. Generic ciprofloxacin is a global best seller, with many manufacturers in multiple countries. Third,

Antimicrobial Patents, *supra* note 4, at 563.

323 Oritavancin is not yet approved in the United States. U.S. FDA, Orange Book, *supra* note 233 (searching for "oritavancin" returns no hits) (last visited Jan. 15, 2010). Another glycopeptides is teicoplanin (marketed in Europe by sanofi-aventis as Targocid®). It has been used for many years outside the United States.

324 *Compare* Kirst et al., *supra* note 223, at 1303-04, *with* Henrik Caspar Wegener, *Historical Yearly Usage of Glycopeptides for Animals and Humans: The American-European Paradox Revisited*, 42 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 3049 (1998).

325 Kirst et al., *supra* note 223, at 1303-04 (explaining that Europe controls the hospital use of vancomycin more tightly than the United States).

326 Levofloxacin is the leading antibiotic used in U.S. hospitals. MacDougall & Polk, *supra* note 125.

327 Re-patenting is not possible under existing law; this discussion is theoretical. Bayer would also need to control its copyrights and trademarks in Cipro®, even if it had allowed them to lapse during the unpatented period.

mathematical models of resistance do not clearly specify the best course of action for class coordination; it seems likely that class coordination actions designed to minimize resistance would expand the risk of treatment failure in particular patients, an unsavory dilemma.[328] Finally, the Constitutional basis for re-patenting the public domain seems open to challenge. As interesting as these issues are, we will save them for another day, for at present Congress does not appear interested in class-based patents or re-patenting the public domain.

One complicating factor for patent holder conservation is the ability of drugs to create resistance in other antibiotic classes.[329] Vancomycin is associated with increased resistance to daptomycin.[330] Daptomycin is the first-in-class lipopeptide, also discovered by Eli Lilly, but now licensed to Cubist Pharmaceuticals; daptomycin entered the U.S. market in 2003 as Cubicin®.[331] These two drugs (vancomycin and daptomycin) are in different classes (glycopeptides and lipopeptides, respectively), and vancomycin has been generic for decades. Patent-based coordination would be very difficult between these drugs. Class-based coordination to protect daptomycin would require giving Cubist Pharmaceuticals patent control over both lipopeptides and glycopeptides, privatizing both the public domain (vancomycin) and taking by eminent domain or compulsory license all ongoing research projects by other companies in these classes, such as Theravance's telavancin, a glycopeptide for which Theravance is currently seeking FDA approval, and oritavancin, a glycopeptide controlled by Targanta for which the company is also seeking FDA approval.

A final interesting point is that the need to coordinate resistance between vancomycin and daptomycin could have been avoided: Eli Lilly & Company discovered both compounds but chose to fragment the rights—licensing oral vancomycin to ViroPharma for U.S. use only (geographical fragmentation), and licensing daptomycin to Cubist Pharmaceuticals (class-based fragmentation). In both cases, it may be presumed that Eli Lilly was well positioned to understand these drugs; in fact, it probably had the best information available concerning its discoveries. And yet Lilly chose to fragment its rights voluntarily. It is hard to reconcile this history with H2 (patent holder conservation); at the very least, we cannot assume that a single patent holder will conserve an antibiotic class through superior coordination.

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328 Y. Claire Wang & Marc Lipsitch, *Upgrading Antibiotic Use Within a Class: Tradeoff Between Resistance and Treatment Success*, 103 PROC. NAT'L ACAD. SCI. 9655 (2006).

329 *See* Outterson, *Vanishing Public Domain*, *supra* note 4, at 94-99 (collecting sources).

330 Pakyz et al., *supra* note 125; Jean B. Patel et al., *An Association Between Reduced Susceptibility to Daptomycin and Reduced Susceptibility to Vancomycin in* Staphylococcus aureus, 42 CLINICAL INFECTIOUS DISEASES 1652 (2006).

331 Outterson et al., *Antimicrobial Patents*, *supra* note 4, at 560.

C. *Comparing Hypotheses to the Vancomycin Case Study*

From the foregoing discussion of vancomycin, we can summarize in Table 3 several conclusions about the seven hypotheses.

Table 3. Case Study Results Regarding Vancomycin and Other Antibiotics

Hypothesis	Case Study Results
H1. Patent holder waste	• Patent holders' actions with vancomycin do not appear to fit the patent holder waste paradigm, as the patent had already expired • Even with non-patent barriers, the actions of the sole marketer of vancomycin were not consistent with patent holder waste • Drug companies may have sold some antibiotics without much regard to resistance, but the impact on vancomycin resistance during the patent term was small, so waste was not created • Marketing by the patent owner typically declines in the last few years of patent life, which is contrary to H1
H2. Patent holder conservation	• Little evidence was found that patent holders exercised long-term stewardship to conserve vancomycin • Eli Lilly did not promote class-based conservation, but fragmented property rights • Generic entry might actually decrease sales when brand name marketing is suspended
H3. Patent incentives are inadequate for production	• Market demand and medical need for vancomycin were more important than patent incentives • Reimbursement may be a more effective policy lever than patent law • Non-patent barriers to free-riding can be important

H4. Resistance stimulates innovation	• Penicillin and methicillin resistance stimulated the development of vancomycin • MRSA and CDAD greatly stimulated the vancomycin market • MRSA stimulated many new research programs, anticipating resistance to vancomycin
H5. Conservation dampens production	• Conservation reduces unit sales, but may promote overall social welfare • Most of the conservation of vancomycin was not deliberate policy, but the result of environmental factors such as available substitutes in the early years with fewer side effects
H6. Excessive regulation dampens production	• Not examined here, as the FDA regulations in question arose largely after vancomycin reached the market
H7. Antibiotic externalities are predominantly negative	• CDAD, and to a lesser extent, MRSA are negative effects of antibiotic use that directly harm the patient taking antibiotics • Both CDAD and MRSA also generate negative externalities beyond particular patients and institutions as resistant infections spread to others • Proper internalization of antibiotic costs to the patient often fails due to information deficiencies • Some MRSA- and CDAD-related germ-shed externalities will be positive under conservation programs

Patent holder waste (H1) and patent holder conservation (H2) emerge from this case study having sustained significant damage. Patent holders did not appear to engage in waste near the end of the patent term, but they also did not carefully nurture important antibiotics for the long-term good of society. Generic entry may not be the resistance disaster that some assume, as marketing pressures subside in the last few years of patent life and thereafter. In any case, one cannot make a case for longer patents as a conservation tool based on the

vancomycin experience. Sales data from other leading hospital antibiotics bolstered the conclusions from vancomycin.[332]

The vancomycin case study strongly challenges the third hypothesis (H3, patent incentives are inadequate for production). The shorter seventeen-year patent term[333] was sufficient for the discovery and commercialization of vancomycin without additional incentives,[334] and non-patent incentives such as FDA rules relating to marketing approval protected follow-on innovation. More importantly, market demand was more significant than patent status for vancomycin. Patents proved inadequate when medical need did not materialize, and once the medical need was clear, the patents had expired. This evidence should be considered in light of the broken market linkages between medical need and actual reimbursement to drug companies, as discussed in Part III.C. If the goal is improved health on a population basis, modifying patents will have little benefit so long as reimbursement is not sufficiently tied to medical need.[335] The vancomycin case study suggests that if reimbursement is sufficient, patents will be less important. Perhaps H3 should be modified with three plausible extensions for antibiotic markets:

- H3a: Reimbursement incentives are inadequate for production;
- H3b: Reimbursement is a powerful policy lever for production; and
- H3c: Reimbursement policy is more important than patent policy.

This Article does not go so far as to claim to have firmly established any of these alternative hypotheses, but it offers them for further study in light of the vancomycin experience.

The evidence is strong for the hypothesis that resistance stimulates innovation (H4), which indeed is central to the history of vancomycin for both CDAD and MRSA. These results are consistent with the theoretical analysis in Part III.A, and they upend conventional wisdom from the IDSA and similar policy advisors. Resistance is not a hindrance to innovation, but actually promotes it.

The fifth hypothesis (H5, conservation dampens production) appears to be correct, but most of the U.S. market response to vancomycin followed external environmental factors other than policy-driven conservation. The experience with vancomycin is not inconsistent with this claim; this claim is simply unproven. The

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332 *See supra* Chart 1 and accompanying text.

333 At the time, patent terms in the United States were seventeen years from issue. After adoption of the World Trade Organization TRIPS Agreement in 1994, the United States changed its patent term to twenty years from filing.

334 This statement approaches a tautology in a study of a commercialized drug.

335 *See* Projan, *supra* note 74; Wenzel, *supra* note 2.

theoretical analysis in Part III.B also challenges the policy impact of H5, suggesting that conservation may actually promote socially valuable outcomes.

Through an accident of history, vancomycin was set aside for decades. The tantalizing question is whether we can deliberately replicate these conditions for other important antibiotics. One possible approach would be a public purchase of the patent at a generous price commensurate with the value of the drug. The companies would be paid for their valuable patents based on a prize model rather than through current sales. For a generic drug like vancomycin, to the extent we are concerned about post-patent waste, the federal government could assert control without the need to compensate a patent holder. A few important antibiotics should be put on the shelf for decades and reserved only for the most extreme cases, creating a Strategic Antibiotic Reserve.[336]

The sixth hypothesis (H6, excessive regulation dampens production) was not a significant factor with vancomycin, as vancomycin reached the market many years before the relevant FDA regulations.

Finally, hypothesis H7 (antibiotic externalities are largely negative) remains an open question, although some interesting questions have been raised. If Medicare begins to punish hospitals financially for MRSA infections, the externalities of hospital infection control will become a much more salient topic. It also appears that some major costs are actually internal but go unrecognized by patients, physicians, and institutions due to a lack of information. The solution here would be better information on the negative consequences of consuming antibiotics; this information is not likely to come from the patent holders. Finally, some conservation programs will generate positive externalities within a germ-shed.[337]

CONCLUSION

This Article reminds us to test theory against experience. It is said that battle plans often fail to survive first contact with the enemy. In the present study, the case study with vancomycin calls for significant changes to our theoretical models.

When faced with a common pool resource problem, context matters. We should not reflexively choose solutions from our favorite

336 *See supra* note 46 and sources cited therein.
337 *See supra* note 100 and sources cited therein.

Sector, but must evaluate which tools will be most effective in the specific situation.

For antibiotics, the conventional wisdom emphasizes IP-based solutions. This Article counsels caution before we expand antibiotic intellectual property rights, lest our good intentions result in a counterproductive reduction in antibacterial effectiveness. The most effective and immediate solutions might be based on conservation rather than production, and on reimbursement rather than patent law.