Arming Our Enemies: How Parallel Imports Could Increase Antimicrobial Resistance

Colin Robert Crossman

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Arming Our Enemies: How Parallel Imports Could Increase Antimicrobial Resistance

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Arming Our Enemies: How Parallel Imports Could Increase Antimicrobial Resistance

Colin Robert Crossman†

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I. Introduction

In response to the high prices of pharmaceuticals, both in the developed world and the developing world, politicians, advocacy groups, and consumers have rallied around parallel imports as a way of reducing the prices of cutting-edge medicines. However, these policies, price reductions, and the concurrent rise in consumption inherent thereto may present a new problem for the class of pharmaceuticals most needed to prevent morbidity and mortality: antimicrobials.

Antimicrobial drugs, particularly antibiotics and antivirals, are susceptible to obsolescence by overuse. This happens when the

† The author would like to thank Arti Rai, Catherine Admay, Deanna Carrick, Lauren Dame and Ilse Weichers, all from Duke University, for their assistance and motivation throughout the production of this paper.
target of the antimicrobial drug develops resistance, a process that can occur with alarming rapidity. The speed with which microbial strains develop resistance can be controlled somewhat with proper use, whereas abuse can dramatically increase the rise of resistance.

This paper discusses the rise of resistant strains of microbes as a consequence of improper use and presents examples from both the developed and the developing world. It then presents the economic consequences of parallel imports, and places those consequences in context with the problem of microbial resistance. Finally, it discusses potential solutions to the problem, and reconciles those solutions with the policies of parallel imports.

II. Biology of Antibiotics

A. The First Antibiotic

The search for compounds which could kill infectious agents dates back to the late nineteenth century. Several compounds were indeed discovered, but each one possessed fatal flaws, and fell short of the “magic bullet” needed; they were excessively toxic to humans and their antibiotic effects were unpredictable. Penicillin, the first truly safe antibiotic agent, was discovered by Sir Alexander Fleming in 1928. A typical story of scientific serendipity occurred while Fleming was studying components of human tears. He had just returned from a vacation, and noticed that several unwashed bacteria plates had been left in his work area. On one of the plates, he noticed that a mold had taken root, and a clear halo—indicative of massive bacterial death—was present around the mold.

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2 See id. at 35-36. Pyocyanase and Salvarsan were two such compounds discovered in 1888 and 1910 respectively. Pyocyanase was toxic, difficult to administer, and did not have a long shelf life. Salvarsan, in contrast, was stable, but contained arsenic, and had extremely toxic side effects. Id. at 35-36.

3 See generally Penicillin’s Finder Assays its Future: Sir Alexander Fleming Says Improved Dosage Method is Needed to Extend Use, N.Y. TIMES, June 26, 1945.

4 See LEVY, supra note 1, at 37.

5 Id.

6 Id.
Fleming tested the phenomenon, and discovered that the mold produced a compound that was directly responsible for the bacterial death he observed.\textsuperscript{7} In honor of the mold's name, \textit{Penicillium notatum}, he called the compound penicillin.\textsuperscript{8} Fleming was unable to isolate large quantities of penicillin from the mold, however, and so was unable to test the compound in any animals.\textsuperscript{9} It was not until the late 1930s that large quantities of penicillin began to be synthesized, tested, and eventually made available to the military.\textsuperscript{10} In 1942, penicillin was made available to some members of the public and in 1944 to the general public.\textsuperscript{11}

In 1945, Fleming, who had become a minor celebrity due to his discovery, was interviewed by the New York Times.\textsuperscript{12} In that interview, he expressed concern about the result of converting penicillin into an oral drug, which would allow for easy access by the public and potentially allow the creation of resistant strains.\textsuperscript{13} Fleming observed some resistance, albeit in controlled settings, when initially experimenting with penicillin, even though he had limited access to the compound.\textsuperscript{14} By 1946, scientists observed the first clinical cases of penicillin resistance, the beginnings of wide-spread resistance to penicillin.\textsuperscript{15}

\begin{itemize}
\item \textsuperscript{7} \textit{Id.} at 38.
\item \textsuperscript{8} \textit{Id.}
\item \textsuperscript{9} \textit{Id.} at 44.
\item \textsuperscript{10} \textit{See} \textit{LEVY, supra} note 1, at 43-44.
\item \textsuperscript{11} On November 29, 1942, the Cocoanut Grove, a Boston, Massachusetts bar, was the scene of a horrible fire. Several hundred people were killed and many survivors were severely burned. At the time, the prognosis for burn victims was grim, as infections routinely took advantage of easy access and weakened bodies. The Cocoanut Grove victims were different, however. The United States Government released a substantial quantity of penicillin to the victims and in what was the largest clinical trial of the compound, nearly every patient treated with the penicillin avoided infection. \textit{Id.} at 1-7.
\item \textsuperscript{12} \textit{Penicillin's Finder Assays its Future: Sir Alexander Fleming Says Improved Dosage Method Is Needed to Extend Use}, \textit{N.Y. TIMES}, June 26, 1945, at 21.
\item \textsuperscript{13} \textit{Id.} ("The greatest possibility of evil in self-medication is the use of too-small doses, so that, instead of clearing up the infection, the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed on to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save.")
\item \textsuperscript{14} \textit{LEVY, supra} note 1, at 7-8.
\item \textsuperscript{15} \textit{Id.} at 11. Stephen R. Palumbi, \textit{Humans as the World's Greatest Evolutionary Force}, 293 \textit{SCIENCE} 1786 (2001) (indicating that up to fifty percent of bacterial agents...
B. The Evolution of Resistance

According to Dawkins, "[l]ife results from the non-random survival of randomly varying replicators." Resistance to antimicrobials is a result of such evolution.\(^{16}\) Given a sufficient amount of time and a large enough population, a particular life-form will find some way to adapt to a particular environmental stimulus.\(^{17}\)

Traditional theory, such as that stated by Dawkins, holds that this adaptation occurs as a result of natural variation.\(^{18}\) The natural variation arises due to the incidence of errors in the genetic material of the organism.\(^{19}\) Though environmental factors, such as radiation and chemical exposure, are known to cause genetic damage—and hence errors—they play only a small role in the creation of errors in microorganisms.\(^{20}\) The vast majority of the errors in their genetic material are caused by the microorganisms themselves, due to sloppy copying.\(^{21}\)

When any cell replicates, it must generate a total copy of its genetic material.\(^{22}\) The machinery that does the copying is tremendously precise, and includes substantial error checking processes, as too many errors may cause the death of the daughter cells.\(^{23}\) However, occasionally a mistake is made, and any such

\(^{16}\) Arthur McGrath, Dawkins' God: Genes, Memes, and the Meaning of Life, 37 (2005) (summarizing Richard Dawkins, The Blind Watchmaker 128-37 (1996), "evolution can . . . be seen as the outcome of the non-random survival of randomly varying replicators."). Dawkins didn't use this formulation anywhere (Google print search for: Dawkins "Nonrandom survival").

\(^{17}\) See generally Palumbi, supra note 15, at 1786 (discussing the causes and impacts of human-induced microbial evolution).

\(^{18}\) See McGrath, supra note 16, at 315-18.

\(^{19}\) Id.

\(^{20}\) Id.

\(^{21}\) Id.


\(^{24}\) See id. at 235-36 (explaining the replication mechanisms of Escheridia coli and certain mammals).
errors are passed to the daughter cells.\textsuperscript{25} The errors that survive the error checking process become part of the inherent variation of the species.\textsuperscript{26}

When presented with selective pressure, the effects of the errors become apparent. Some errors may be deleterious—under selective pressure, the organisms which possess such errors will die off at an increased rate.\textsuperscript{27} Other errors may be advantageous, allowing a particular organism to survive when its unlucky brethren die off more quickly.\textsuperscript{28} In this way, the organisms which possess traits allowing them to cope with the selective pressure begin to compose a greater percentage of the population. Essentially, those organisms, and their progeny, are able to reproduce—and avoid dying—at higher rates than other organisms. This effect is made more prominent as the penalty for not possessing a trait is increased.\textsuperscript{29}

Thus far, this article has addressed only classical theory. There are several complicating factors that radically increase the ability of organisms to discover and incorporate advantageous traits.

In some instances, microorganisms presented with a selective pressure can “intentionally” increase their genetic error rate.\textsuperscript{30} In

\textsuperscript{25} As an example, the error rate for Pfu DNA Polymerase is generally on the order of $1 \times 10^6$ errors per base pair. That means that for every 1 million base pairs copied, there will be only one error. \textit{See} Stratagene.com, FAQ: What is the Error Rate for Pfu DNA Polymerase?, http://www.stratagene.com/lit/faq/faq.aspx?qid=149. In actual \textit{in vivo} systems, the error rate is closer to $1 \times 10^{-9}$. \textit{See} ALBERTS ET AL., \textit{supra} note 23, at 236.

\textsuperscript{26} \textit{See} ALBERTS ET AL., \textit{supra} note 23, at 237.

\textsuperscript{27} \textit{Id.} at 236-37.

\textsuperscript{28} The definitions of “advantageous” and “disadvantageous” with respect to genetic errors do not imply some sort of objective standard. Such terms are only meant to imply survivability relative to the currently considered selective pressure. Indeed, what may be advantageous in one context may be highly disadvantageous in other contexts. Take, for example, the Pekinese dog breed. The breed was bred to emphasize features attractive to certain humans. Those very features—snub nose, conspicuous lack of biting teeth, small body size—would convey a tremendous disadvantage in the wild. The Pekinese, however, is precisely designed for its role as a lap dog.

\textsuperscript{29} Antibiotics and other antimicrobials represent the ultimate selective pressure. All organisms, which do not possess a solution to the selective pressure, die. \textit{See} MCGRATH, \textit{supra} note 16, at 178-79.

these cases, when a selective pressure is applied, the microorganisms increase their error rate, which consequently increases their ability to find errors which effectively neutralize the selective pressure. Though this is a tool for most bacteria, for some viruses, it is a standard condition. Human Immunodeficiency Virus (HIV), by its nature as a retrovirus, incorporates a tremendous number of errors in its genetic material.\(^{31}\)

In other instances, microorganisms can share their successful traits with other microorganisms.\(^{32}\) Though they possess only one genome, they also often possess subgenomic strands of DNA called plasmids which also may confer traits.\(^{33}\) These plasmids can be passed back and forth between microorganisms.\(^{34}\) Sometimes, a plasmid confers a trait which directly influences a microorganism's ability to survive, and often that trait is an antibiotic resistance of some sort.\(^{35}\)

Microorganisms can occasionally absorb genetic material from their surrounding environment.\(^{36}\) Even if selective pressure causes a disproportionate number of sensitive microorganisms to perish, some resistant organisms will also inevitably die. If a trait which confers resistance is transferable, it is possible that a sensitive organism will absorb some errant genetic material from the resistant organism and "learn" resistance, regardless of the differentiation between the species.\(^{37}\)

Finally, certain microorganisms possess special constructs that

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\(^{31}\) See John D. Roberts et al., *The Accuracy of Reverse Transcriptase From HIV-1*, 242 SCIENCE 1171, 1172 (1988). Reverse transcriptase, especially the reverse transcriptase of HIV, is highly error-prone. HIV's reverse transcriptase has an error rate of one in 2000, or three orders of magnitude more error-prone than other polymerases. *Id.*

\(^{32}\) See generally LEVY, supra note 1, at 71-114.

\(^{33}\) See id. at 72.

\(^{34}\) See id. at 82-88.

\(^{35}\) See id. at 72-74.

\(^{36}\) See id. at 79.

\(^{37}\) See id. at 88-93.
allow them to alter their own genetic code in particular ways. For instance, the influenza virus periodically reshuffles parts of its genetic material, to generate resistance to our immune systems.\(^{38}\) This reshuffling results in slightly different surface proteins, and therefore a different outward appearance.\(^{39}\) In other contexts, an organism may activate/deactivate their resistances as needed.\(^{40}\)

**C. Manifestations of Resistance**

Using all the tools of evolution and transformation discussed above, microbes routinely learn a variety of methods to defeat antimicrobial drugs. These methods fall into one of two essential categories; microbes can defeat antimicrobial drugs by either destroying them or avoiding them.\(^{41}\)

In a very few instances, the microbes learn ways to destroy the drug.\(^{42}\) The microbes generate proteins which speed the degradation of the drug so rapidly that the drug does not have much chance to adversely affect the organism.\(^{43}\) In some cases, depending on the efficiency of the degradation mechanism, increased doses of the drug may continue to provide therapeutic benefit.\(^{44}\) However, eventually the increased doses will engage the same selection machinery, causing the organism to adapt again. Penicillins, cephalosporins, and streptomycins all fall victim to drug-destroying processes.\(^{45}\)

\(^{38}\) This is why influenza vaccines must be administered every year, and why the vaccine manufacturers attempt to predict the next transition of the influenza virus. John Treanor, *Influenza Vaccine—Outmaneuvering Antigenic Shift and Drift*, 350(3) NEW ENG. J. MED. 209, 218-20 (2004).

\(^{39}\) This is like a criminal having plastic surgery to avoid detection by the authorities. *Id.*


\(^{41}\) See LEVY, supra note 1, at 96.

\(^{42}\) See *id.* at 98-99.

\(^{43}\) *Id.* at 98.


\(^{45}\) See LEVY, supra note 1, at 97-102.
Avoidance measures are more varied, but they all accomplish the same purpose—they lessen or eliminate the ability of the antimicrobial drug to affect the microbe.\textsuperscript{46} In some cases, the microbe engages mechanisms to minimize absorption of the drug, such as pumping the drug out of the microbe or blocking entry.\textsuperscript{47} Other avoidance measures involve the microbe altering the target proteins in such a way as to render the antimicrobial drug impotent.\textsuperscript{48}

In some ways, avoidance measures are more worrisome than measures which eliminate the drugs.\textsuperscript{49} Many of these drugs are capable of persisting in nature for long periods of time; the environmental presence of antimicrobials will contribute to the emergence of resistant strains, as the drugs exert a selective pressure.\textsuperscript{50}

Though the prospect of antimicrobial resistance is disturbing, the ability of viruses, fungi, and eukaryotic parasites to effectively develop resistance to treatment compounds is just as troubling. For instance, HIV replicates so rapidly that the virus can effectively find resistance to such treatment compounds during the course of treatment in a particular individual.\textsuperscript{51} Indeed, the virus is so adept at working around treatments that more exotic treatment strategies utilizing several simultaneous, non-overlapping modes of attack is now the standard protocol. Malaria treatments, such as quinine and chloroquine, have also met a similar fate.\textsuperscript{52}

\textsuperscript{46} Id. at 97.

\textsuperscript{47} Id. at 99.

\textsuperscript{48} See generally id. at 102 (discussing the fact that many antibiotics persist in the environment killing off susceptible bacteria in the natural systems and leaving only the resistant bacteria to survive).

\textsuperscript{49} Id. at 102; see also Shunwoo Yang & Kenneth Carlson, \textit{Routine Monitoring of Antibiotics in Water and Wastewater with a Radioimmunoassay Technique}, 38 \textit{WATER RES.} 3155, 3156 (2004).

\textsuperscript{50} See Yang & Carlson, \textit{supra} note 49, at 3156.

\textsuperscript{51} See, e.g., Barbara A. Backlaws, \textit{Quantification of the Reservoir of HIV-1}, 5(6) \textit{TRENDS MICROBIOL} 215 (1997) (showing the quantization of viral load in follicular dendritic cells is \(1.5 \times 10^8\)); Mark Dubyl et al., \textit{Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents: The Panel for Clinical Practices for Treatment of HIV}, 137(5.2) \textit{ANNALS INT. MED.} 381, 381-433 (2002); M. Piatak, et al., \textit{High Levels of HIV-1 In All Stages of Infection Determined by Competative PCR}, 259(5102) \textit{SCIENCE} 1749 (1993).

\textsuperscript{52} See J. Kevin Baird, \textit{Effectiveness of Antimalarial Drugs}, 352 \textit{NEW ENG. J. MED.}
Viral resistance is not restricted to the blight of HIV. The current avian influenza, H5N1, has already shown resistance to the most capable preventative measure: Tamiflu. Furthermore, ninety-one percent of the 2005-2006 human influenza strain, Influenza H3N2, show resistance to both amantadine and rimantadine, two older anti-influenza drugs. Though the H5N1 avian influenza virus has shown only limited ability to infect humans, it has caused a tremendous frenzy about the potential for a new pandemic. Though such fears have, as yet, been unrealized, the virus may eventually mutate to a strain which is human-communicable. That eventuality would be all the more deadly if the only compound known to provide succor is useless. Indeed, the fear of an epidemic has itself resulted in Roche, the manufacturer of Tamiflu, massively increasing production, and allowing some degree of ad-hoc parallel imports.

D. Combating Resistance

The occurrence of resistance is the natural result of the

1565, 1569-72 (2005). Quinine was discovered to have anti-malarial qualities in the mid-eighteenth century. *Id.* It has been so widely dispersed that today it is even available over the counter as an ingredient of Tonic Water. During World War II, chloroquine was developed as an alternative to quinine. By 1957, chloroquine resistance was seen in Asia, and is now globally prevalent. *Id.* For unknown reasons, quinine remains effective against most malaria, however quinine-resistance strains have recently been discovered. *Id.*

53 See Menno D. de Jong, et. al, Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection, 353 NEW ENG. J. MED. 2667, 2667 (2005). Two Vietnamese girls who were given Tamiflu prophylaxis developed Tamiflu resistant H5N1 (avian flu). Fortunately, the avian flu has not yet become a human contagion, and so the particular resistant strain will not likely spread. Tamiflu resistance is believed to be the result of a single point mutation in the virus. If true, this makes the likelihood that tamiflu sensitive strains will.

54 Lawrence K. Altman, This Season’s Flu Virus is Resistant to 2 Standard Drugs, N.Y. TIMES, Jan. 15, 2006, at Sec. 1.

55 Olivia Judson, Evolution Is in the Air, N.Y. TIMES, Nov. 6, 2005, at Section 4.


58 See Tom Wright, Roche Plans Big Increase in Tamiflu Production, N.Y. TIMES, Nov. 10, 2005, at C6; see also Bloomberg News, Roche Tells Indonesia that it Can Produce Tamiflu Without a License, N.Y. TIMES, Nov. 26, 2005, at C3.
intersection of the forces of evolution with medical science. At best, medicine can only delay the inevitable resistance through designing novel therapies.

While proper therapeutic use will inevitably lead to resistance, two activities radically increase the speed with which the microbes can evolve solutions to a compound. The first problem is unnecessary use of the compound; the second is under-use or sub-therapeutic dosing for an indicated use. When compounds are improperly used in these ways, selection pressures are generated, but the therapeutic outcomes are either unrelated to the use of the compound, or are insufficiently complete. In addition, excessive and improper use of antibiotics can make diagnosis of other conditions more difficult.

Unnecessary use of an antimicrobial occurs when the compound is administered to treat a condition for which the compound is wholly unsuited or is genuinely irrelevant. Partly due to the astounding success that antimicrobials have had and partly due to the fact that most people simply don’t understand disease processes, there has been a huge number of doses used in this way. Patients demand antibiotics to treat non-bacterial infections, such as the common cold; some even demand antibiotics for prophylaxis, when such prophylaxis is totally unnecessary.

The tendency of patients to consume sub-therapeutic doses, partial courses, or to under-use the antimicrobials is problematic. Antimicrobial under-use is a thornier problem than simple misuse. In the under-use scenario, the initial condition did indeed warrant the use of the particular antimicrobial consumed. However the

59 See LEVY, supra note 1, at 115, 124.

60 See, e.g., Calvin M. Kunin & Yung-Ching Liu, Excessive Use of Antibiotics in the Community Associated with Delayed Admission and Masked Diagnosis of Infectious Diseases, 35(3) J. MICROBIOL. IMMUNOL. INFECT. 141 (2002).

61 See LEVY, supra note 1, at 117.

62 Id. at 124.


64 See LEVY, supra note 1, at 289.

65 Id. at 290.
patient either ceased using it prior to taking a full course of the drug, or the patient was not taking a sufficient dose of the drug.\textsuperscript{66} One of the most common reasons for under-use to occur is that patients stop taking the antimicrobial when they feel better.\textsuperscript{67} Unfortunately, the remaining, neglected doses would have helped to thoroughly cleanse the body of the microbe. The microbes that remain have an increased likelihood of discovering resistance, since they have been exposed to the compound, but not killed by it.\textsuperscript{68}

**III. Implications of the Economics of Parallel Imports and Drug Subsidization on Antibiotic Resistance**

**A. Background**

The rising price of drugs is of perennial and growing concern for health care providers and policy makers.\textsuperscript{69} High drug prices limit access to medicines, and have the tendency to leave the poorest untreated and suffering.\textsuperscript{70} These prices are especially egregious considering that the actual production cost for most drugs is relatively trivial.\textsuperscript{71}

The main expense in drug production is not the cost of manufacturing approved drugs, but rather the costs associated with drug discovery: research, development, and clinical trials.\textsuperscript{72} These

\textsuperscript{66} Id.

\textsuperscript{67} See Cipro Package Insert, http://www.univgraph.com/bayer/INSERTS/CIPRO TAB.pdf. This is exacerbated by the fact that antimicrobials, especially more modern ones like ciprofloxacin (Cipro), can cause several unpleasant and annoying side effects. Id. Cipro, for instance, often causes hypersensitivity to sunlight, diarrhea, and nausea, and has adverse interactions with dairy, antacids, caffeine, and alcohol. Id.

\textsuperscript{68} See \textit{Levy}, supra note 1, at 292.


\textsuperscript{70} See Kahn, supra note 69.

\textsuperscript{71} See Ernst R. Berndt et al., \textit{Information, Marketing, and Pricing in the US Antulcer Drug Market}, 85(2) \textit{AM. ECON. REV.} 100 (1995). Actual manufacturing costs will vary by drug, but have been reported to be as low as ten percent of the sales price. \textit{Id.}

\textsuperscript{72} Joseph A. DiMasi et al., \textit{The Price of Innovation: New Estimates of Drug
discovery costs are so high that recouping the costs through the marketplace would be nearly impossible if competitors are allowed to begin producing the product immediately.

In order to solve this problem, drug researchers are granted patents over their discoveries, which temporarily provides them certain exclusive rights to their discoveries. By granting the discoverer a limited monopoly, the discoverer can manipulate that monopoly to provide a sufficient return to recoup the costs inherent in the discovery. Drug manufacturers, of course, seek patents in every jurisdiction that they deem important to their markets—giving them similar exclusive rights around the world.

The ability of the drug manufacturers to control prices, however, is incomplete. Unless the drug is truly novel, and addresses a disease previously uncontrollable, it is likely that there are several drugs that already exist that are capable of providing some relief. Even if a drug has the advantage of having no substitutes, it must still compete with a patient’s decision to forgo the treatment.

Patents also give their holders the ability to engage in market segmentation and price discrimination. By placing the ability to

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Development Costs, 22 J. HEALTH ECON. 151, 152 (2003).

73 The exclusive rights are: making, using, offering to sell, selling or importing into the United States. See 35 U.S.C. §217(a) (2005).

74 The Pharmaceutical industry spends, on average, fifteen years bringing a new drug to market. This research and development includes searching for and testing compounds, and also the clinical trials which test the promising compounds for safety and efficacy. See Prafulla Joglekar & Morton Paterson, A Closer Look at the Risks and Returns of Pharmaceutical R&D, 5(2) J. HEALTH ECON. 153 (1986). But see Michael S. Wilkes et al., Direct-to-Consumer Prescription Drug Advertising: Trends, Impact, and Implications, 19(2) HEALTH AFF. 110 (2000).

75 For example, Viagra, the first erectile dysfunction medication, was the first drug that was found which could address the condition. Contrast Viagra with a novel painkiller. Though the painkiller may provide significant benefits over existing painkillers, it will be in competition with them. Additionally, if a drug is the first to address a specific problem, it is likely that follow-on drugs will arise that take advantage of other aspects of the treated condition to achieve similar results, perhaps even with better clinical profiles. See generally Silvio Garattini, Are Me-Too Drugs Justified?, 10(6) J NEPHROLOGY 283-94 (1997).

76 See Kevin Outterson, Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets, 5 YALE J. HEALTH POL’Y, L. & ETHICS 193, 193-286 (2005); Kristina M. Lybecker, Parallel Imports or Imposters: The Economics of Reimportation and Counterfeit Pharmaceuticals, 16(3) J. PHARM’CAL
regulate imports of the patent-holder, even one patent gives the patent-holder the power to segment the world market between the nation covered by the patent, and the rest of the world. In this simple example, the patent-holder could keep prices high in one market, while competing on price in all others.

When the patent-holder has access to several patents, it can potentially carve the world up into many independent markets, and cover all economically significant nations and regions. Based on the ability of the populace in each market to afford the product, the patent-holder can charge whatever price will maximize profit. Normally, in a situation analogous to water finding its own level, a lower price in one region will stimulate arbitrage whereby consumers in a higher price region purchase the product from suppliers in the lower price region. However, the patent right allows the patent-holder to wall off the different regions and prevent arbitrage.

In the world of pharmaceuticals, even though drug-makers may possess patents allowing them to price the drugs at monopoly prices, in practice drugs tend to be fairly inexpensive in some markets that could support much higher prices. For instance, in 2003, a basket of the thirty most prescribed medicines cost up to fifty percent less in Canada, the United Kingdom and France, than the United States. These price differentials are related to several diverse factors, including price controls, bulk purchasing power exercised by various national health care systems, stronger legal tools for compulsory licensing, differentials in purchasing power, and societal differences with regard to health care.

**B. Parallel Imports**

Parallel imports, or gray-market goods, are imported copies of a product protected by some class of intellectual property, which are legitimately and legally purchased in a foreign jurisdiction.

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Mkt'g & Mgmt. 81, 81-100 (2004).

77 Id.

78 Gerard F. Anderson et al., Doughnut Holes and Price Controls, Health Aff. Web Exclusive W4-397 (July 2004).

79 See Outterson, supra note 76, at 195.

80 Parallel imported goods are not restricted to patented goods, but rather any good protected in any realm of intellectual property can be the subject of parallel imports.
This activity is, obviously, in direct conflict with the patent holder’s exclusive right to control imports. In the United States, the responsibility to restrict and regulate parallel imports rests with the Department of Homeland Security, Immigration and Customs Enforcement.  

The goal of parallel imports is to allow purchasers of a protected good to obtain the good at the lowest price globally available. With respect to the United States, consumers would presumably be able to take advantage of the purchasing powers and legal restrictions other countries have, to avoid some of the patent premium which exists domestically. With respect to developing nations, consumers and health boards would be able to purchase the goods at the lowest global prices, without worrying about the patent-holder restricting imports. 

In the short term, this policy may benefit consumers in the United States. It is hard to see how the developing world would benefit, however, as the prices they may have to pay, which may already be above their ability to pay, could rise even higher. This rise in prices could stem from manufacturers refusing to supply smaller, less prosperous economies, for fear of driving down prices elsewhere, or from outside buyers bidding up the limited supply that is provided to such markets. 

Another complication caused by parallel imports is the potential diminution in drug research and development. Since private drug research and development is funded in large part by the monopoly revenue extracted from the sales of currently protected products, working to diminish that monopoly revenue will necessarily lower the funds available for new drug discovery. Several methods have been suggested to avoid or remedy this problem, including transferring the responsibility for

83 Id.
84 Solutions to this may include, perhaps, export restrictions limiting the parallel trade leaving disadvantaged nations.
85 See Maskus, supra note 82, at 41.
86 Id.
research funding to the public sector, requiring all drug manufacturers to pay into a research and development fund, and increasing the drug patent term.\textsuperscript{87}

\textbf{C. Drug Subsidization Measures}

Drug subsidization measures include any program, measure, or device by which the true cost of drugs, as charged by the supplier, is shielded from the consumer. Drug subsidization, unlike parallel imports, is generally directed only toward the poor, and may, through bulk purchasing, be directed toward developing countries. One of the most visible programs of drug subsidization for developing countries is the subsidization of AIDS drugs.\textsuperscript{88}

\textbf{D. Consequences}

Though they take advantage of differing methods, both parallel imports and drug subsidies function by lowering the cost of drugs to consumers. By holding drug prices at a lower level, it is hoped that people with less means will have the opportunity to share in the technological advances that medical research has brought to the marketplace. For many drugs, lowering the price is unlikely to present significant unforeseen consequences for the drugs themselves. As mentioned above, the impacts on drug research, though present, may be manageable by creative research funding.

What has previously been neglected is the impact that policies which lower prices, such as those embracing parallel imports and drug subsidies, will have on antimicrobial resistance. Measures such as parallel imports, which seek to increase access and lower price, will have the effect of increasing consumption of affected drugs.\textsuperscript{89} With most drugs, this is of little concern, and is indeed desired. Except where the consumption of a drug leads to some


\textsuperscript{89} See Sarah Fisher Ellison et al., Characteristics of Demand for pharmaceutical products: an examination of four cephalosporins, 28(3) RAND J. ECON 426, 426-46 (1997) (demonstrating the demand elasticity of pharmaceutical products on the dispensary side, as opposed to the prescription side, of drug prescriptions).
acute detrimental personal effects, such as addiction or other harms to the user, increased drug consumption is by itself unlikely to have negative social consequences.\textsuperscript{90} Misuse of antimicrobials, however, is of concern to the entire community, as one user’s misuse is unlikely to cause significant harm to that user, but on the aggregate such misuse will contribute to hastening the obsolescence of the misused antimicrobial.

There are two separate avenues where parallel imports and other price mitigation measures can create and enhance problems for antibiotic resistance. The first avenue is in the retardation of research efforts, and the second is in the direct stimulation of resistance by increasing consumption.

1. Research Effects

Retardation of research efforts is the worst possible effect when new medicines need to come out to fight newly resistant strains. Antibiotics, antivirals and other antimicrobials are an extremely complicated class of medications. Currently, there are many antibiotics available, but there are only about twelve classes of antibiotics.\textsuperscript{91} Resistance to one member of a class does occasionally indicate resistance to all members of that class, but this is not always the case, and certain classes are more susceptible to such deactivation.\textsuperscript{92} However, resistance to one member of a class is often a harbinger of other related resistances, as slight modifications of the resistance-conferring gene may grant resistance to more than one, or all members of a class.\textsuperscript{93}

In antimicrobials, like all drugs, it is easier to build on past research. That is, perhaps, one reason why there are so few classes of antibiotics while there are hundreds of individual

\textsuperscript{90} With the most common drugs that are taken, such as acid-reflux medication, cholesterol medication, and blood-pressure medication, addiction is not much of a concern.

\textsuperscript{91} Sulfa antibiotics, β-Lactams (Penicillin), Tetracyclines, Macrolides (Erythromycin, also includes the Lincosamides and Streptogramins), Aminoglycosides, Quinolones (Cipro), Glycopeptides (Vancomycin), Rifampin, Nitroimidazoles (Flagyl), Oxazolidinones (Linezolid-Zyvox), Cycloserine, and Aminocyclitols. See Wikipedia, http://en.wikipedia.org/wiki/Antibiotic#endnote_antibiotics-classes-table.


\textsuperscript{93} Class resistance is a notable problem for β-lactams and the macrolides.
antibiotics. The most recently approved new class of antibiotics, the Oxazolidinones, was approved in 2000.\(^4\) It is the only new antibiotic class to be introduced into a clinical setting in thirty years.\(^5\) By 2001, clinical resistance was observed.\(^6\) Within one year of its introduction, the most advanced, cutting edge antibiotic, had shown resistance.

Considering the historically slow speed of innovation in this sector, and with antibiotic resistances arising so fast, any policy which may have a negative impact on the speed of research in this area must be carefully considered. Perhaps a total rethinking of how antibiotic funding is handled is in order, similar to those modifications proposed by James Love.\(^7\)

### 2. Effects of Misuse

Though the negative effects on research which may result from policies promoting equitable distribution may be substantial, they present particularly difficult political and economic problems. Additionally, they are likely not as severe as effects of misuse, which are more tractable. If our ability to bring an antimicrobial to clinical use is slowed from thirty to thirty-five years, it makes little difference if the former antibiotics have been rendered impotent in ten years.

Parallel imports are likely to increase the improper use of antimicrobials by increasing both unnecessary consumption and underconsumption. Unnecessary consumption will be increased simply as a price effect and as medications can be shipped across borders, due to the inherently designed lack of enforcement of import controls.\(^8\) Underconsumption may increase as a secondary effect of price, however, as underconsumption is likely a result of patient capriciousness and the medications themselves; any effect

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\(^7\) See Love & Finn, *supra* note 87, and accompanying text.

\(^8\) See, e.g., Ellison et al., *supra* note 89.
from parallel imports is likely minor.

a. Unnecessary Consumption

Unnecessary consumption of antibiotics will only increase as prices fall. Today, many antimicrobial drugs can be taken orally, and so are relatively benign to take.\(^99\) Many powerful ones, like Cipro and ketokonazole (an anti-fungal), are effective after only one to three doses of medication.\(^100\) If a patient approaches a doctor with an illness that looks—at least to the patient—like an antimicrobial will help, then the patient may request antibiotics.\(^101\) It can often be more costly, in terms of patient time, reputation, and perceived liability for a doctor to deny an unnecessary antimicrobial.\(^102\) If the costs go down, then the balance of power shifts more toward the requesting patient.

Another, more substantial, concern that parallel imports raise is the ability of patients to order medications from pharmacies and suppliers located outside their nation.\(^103\) Today, one can reach nearly every business by either international telephone, or, more likely, by the Internet.\(^104\) For example, Great Britain allows pharmacies to ship medications to individuals located outside of Great Britain and who are not British citizens.\(^105\) Some opponents of parallel imports have attacked parallel imports on this front by

\(^99\) In an interview with the New York Times, Alexander Flemming explicitly mentioned the problem that oral medications could eventually cause: “But the public will demand a preparation which can be taken by mouth, and doubtless they will get it. Then will begin an era of self-medication with penicillin, with all its abuses.” Penicillin’s Finder Assays Its Future, N.Y. TIMES, June 26, 1945, at 21.


\(^102\) See id. at 137 (stating that a medical practitioner may spend more time to dissuade a patient from antibiotics).


\(^104\) See, e.g., Quality Health Inc.: Medicines for the Modern Mainstream, http://www.qhi.co.uk.

\(^105\) For example, Quality Health Incorporated will sell several prescription drugs (though none are antibiotics in this case) to overseas customers without prescription. See id.
claiming that foreign drugs or suppliers are somehow unsafe. However, considering that the manufacturing of most on-patent drugs are tightly controlled by their manufacturer, this argument loses some credibility. A possible countervailing solution could include labels containing different warnings, depending on the rules of the regulatory apparatus of the jurisdiction from which the drugs are purchased. Although some warnings and directions are not written in English, this is easily remedied by the patient’s access to the Internet.

These two concerns need to be addressed separately, though each is simple to address. To address the potential increase in improper prescriptions issued by medical practitioners, countries that allow parallel imports of antibiotics should implement stronger policies regulating the prescription of all antibiotics, instead of regulating the cutting edge antibiotics as is common practice today.

Research has shown that educating both medical practitioners and the public can help to stem this problem. Education of both groups, as well as institutional regulations—with appropriate sanctions for unobservant doctors—should help to minimize improper prescription of antibiotics. Fortunately, as both of these methods are in place, at least in the United States and Europe, merely extending these policies by linking them with policy of parallel imports should be sufficient to rein in this category of misuse.

More complicated, however, is the purchasing of drugs from overseas pharmacies, when the exporting jurisdiction does not require a prescription for the export, or where the pharmacies can easily avoid what regulations do exist. In these cases, parallel importing jurisdictions should require that all imported medication

106 See, e.g., Meadows, supra note 103.


109 See Avorn & Solomon, supra note 63, at 128.

110 Id. at 130-33.

111 See, e.g., Quality Health, Inc., supra note 104.
be screened by the respective border control agency, and every prescription drug matched with a valid prescription. If an individual attempts to obtain a drug from a foreign jurisdiction, particularly an antimicrobial, without a valid prescription, then the offending materials should be seized and, perhaps, donated to medical dispensaries that serve poorer communities.\textsuperscript{112} With today's computer technology, this should not be a complicated task. Smuggling may be an issue. However, since these are not addictive drugs, the leakage through the black market should be minimal as long as the hassles imposed on the black market are sufficient to raise those prices significantly above the legal market.

Tracking imported medications may also result in other benefits. The risk of unsafe medications from foreign sources, particularly Canada and the European Union, is hard to estimate.\textsuperscript{113} If a particular foreign dispensary is found to be distributing a contaminated batch of medication, antimicrobial or otherwise, potential victims could be quickly discovered, and medications in transit could be intercepted prior to affecting the purchaser.

Of course, such tracking also implicates privacy issues, as knowledge of the medications a particular individual is taking can inform an interested party, or the government of the medical condition of the individual. Such tracking is necessary in order to properly monitor the import traffic in medications, such that no medication enters without a valid prescription. Perhaps the technology can be constructed such that names are concealed from the screening personnel. However, since direct examination of the individual pill bottles may be necessary, individuals wishing to take advantage of parallel import restrictions may be required to accept a potential decrease in privacy to realize the lower prices. If privacy is an overriding issue, then an individual can always purchase the medication from domestic sources.

A third method which would eliminate both the problems inherent in uncontrolled direct-to-consumer purchases of drugs, and the privacy concerns, would be a total ban on direct-to-consumer shipment of medication from foreign sources. If an

\textsuperscript{112} Of course, the recipient organizations must have regulations and good practices to prevent doctor misuse.

\textsuperscript{113} Kristina M. Lybecker, \textit{Economics of Reimportation and Risks of Counterfeit Pharmaceuticals}, 13(3) \textit{Managed Care} 1, 10-14 (2004).
individual wishes to take advantage of parallel import pricing, then the individual would need to approach a domestic dispensary, which would then handle the foreign procurement. All medication shipments would be business-to-business, and therefore domestic controls on dispensaries and pharmacies would be left in place to restrict consumer abuse. Although this solution may be attractive, the privacy of international mail may limit its applicability. An active legal direct-to-consumer market would likely limit all but the most persistent avoiders. This may prove to be the more practicable solution, as government oversight costs and prescription validation can be placed on private industry. Direct-to-consumer sales could still be conducted, with the consumer shopping foreign dispensaries, but the medications are funneled through the foreign dispensary’s domestic affiliate for validation.

Other research on limiting antibiotic overuse focuses on the removal of subsidization for Canadian consumers. However, this policy, which increases the effective price that consumers pay for the medication, significantly reduced consumption. Therefore, it is incompatible with the price reduction purpose of parallel imports.

Another proposed solution involves the grant of long term patent rights over antibiotics, perhaps even permanent rights. Proponents of such a solution urge that antibiotics are akin to depleteable resources, similar to mineral deposits. However, antibiotics may be renewable resources, like trees. By creating a unitary and monopolistic owner over specific antibiotics, the owner has the incentive to rationally and beneficially utilize the resource. In an ideal situation, this may function. However, considering that the current system of limited patent protection is


115 Id. The data in this study show that total prescriptions for fluroquinolones decreased, however, other antibiotics were substituted for the decrease in fluroquinolones, though at a lower rate, resulting in a net decrease in antibiotic use. See id.


117 Id. at 629.

118 Id. at 644-45.
opposed by many in the political and health care industries, the political incentives are arrayed so deeply against this type of system as to render it impracticable.

\[b.\ \text{Underconsumption}\]

When the responsibility for administration of a drug is placed in the hands of the consumer, little can be done about underconsumption. The best hope is to design drugs that are so effective as to provide little chance for misuse. Drugs such as Cipro and Ketoconazole, which require only a few days of dosing, are best. Though side effects may occur, it is likely that the medication will be taken for such a short time.

As resistance mounts, however, longer dosing schedules may be required. If the dosing requirements are such that long term use is required, especially when the drugs have significant side effects, the power to ensure that the medication courses are taken to completion is tremendously lessened. For specific problem diseases, such as multi-drug resistant tuberculosis, measures as strong as observed dosing are used. However these measures are too invasive for the vast majority of uses.

While the price reductions wrought by parallel imports may increase the likelihood that patients will be more willing to discard future courses of antimicrobials, since patients are apparently quite willing to discard future courses now, it is not clear that a price reduction will significantly increase this. The best way to minimize these problems is with education and by designing the drugs to need a minimum of doses, so that consumers are not inclined to skip future doses.

\[\text{IV. Conclusion}\]

The creation of legally sanctioned parallel imports in medications may improve the ability for the poor to afford access to needed medications and lower health care costs for society as a whole. Though most attention to the potential drawbacks of parallel imports focuses on the potential for the retardation of future research, the effects of the policies on microbial resistance cannot be ignored. Because antimicrobial misuse is related, in large part, to patient access to the medications, an increase in non-price based restrictions on the use of antimicrobials incorporated into parallel import policies and legislation may be able to offset
any increase in misuse as well as the concomitant increase in antimicrobial resistance.