Strategies to Combat Antibiotic Resistance

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Strategies to Combat Antibiotic Resistance

I. Introduction:

Antibiotics are the drugs that are used for treatment of infections caused by bacteria. Administration of antibiotics is currently the most commonly used method for combating infections in modern medicine. The use of antibiotics has not only saved patients’ lives, but they have also played a major role in other advances in medicine and surgery. This widespread use of antibiotics has led to a new problem termed as “antibiotic resistance.” Antibiotic resistance develops primarily due to overuse and misuse of antibiotics, which leads to proliferation of bacteria that do not respond to treatment with antibiotics. In other words, these bacteria are “resistant” to antibiotics.

1 See Combating Antibiotic Resistance, Food and Drug Administration, http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm092810.htm (“FDA article on Combating Antibiotic Resistance”) (last visited Nov. 30, 2016); see also Lecia Bushak, A Brief History of Antibiotic Resistance: How a Medical Miracle Turned into the Biggest Public Health Danger of Our Time, Medical Daily (Feb. 17, 2016), http://www.medicaldaily.com/antibiotic-resistance-history-373773 (“Bushak 2016”) (“The term “antibiotic” has an extremely broad definition, describing the activity of any compound or chemical that can be applied to kill or inhibit bacteria that cause infectious diseases.”) (last visited Nov. 30, 2016).

2 See Lee Ventola, The Antibiotic Resistance Crisis, Part I: Causes and Threats, 40 PHARMACY & THERAPEUTICS, 277, 278 (2015) (“Ventola 2015”) (“They have successfully prevented or treated infections that can occur in patients who are receiving chemotherapy treatments; who have chronic diseases such as diabetes, end-stage renal disease, or rheumatoid arthritis; or who have had complex surgeries such as organ transplants, joint replacements, or cardiac surgery.”).

3 Id. at p. 277.

4 See FDA article on Combating Antibiotic Resistance, supra note 1.
Antibiotic resistance is a growing public health concern not only in United States, but worldwide.\textsuperscript{5} According to the Centers for Disease Control and Prevention (“CDC”), in excess of 2 million patients suffer from antibiotic resistant infections, which leads to about 23,000 deaths.\textsuperscript{6} The ineffectiveness of antibiotics to treat infections leads to use of more and a higher dose of antibiotics and longer and more complicated illnesses. The patients suffering from antibiotic resistant infections may transfer the infections to other people. Moreover, the rate of occurrences of antibiotic resistance bacterial infections, in general, are increasing.\textsuperscript{7} For at least these reasons, antibiotic resistance has become a worldwide public health problem, which should be addressed.

Although the government, through FDA and CDC have taken some steps to address the problem of antibiotic resistance, it is clear that more urgent attention and action is required to combat this problem. This paper will first discuss the primary causes for development antibiotic resistance, and will subsequently discuss some relevant approaches to alleviate this problem. In short, this paper will focus on strategies to curb the human activities leading to proliferation of antibiotic resistance, and some potential solutions to discover new antibiotics that are effective against the resistant strains of bacteria. None of the approaches discussed herein will be exclusively capable of eliminating antibiotic resistance, but through a combination of several interventions, we might be able to develop effective strategies to combat antibiotic resistance.


\textsuperscript{6} See Antibiotic/ Antimicrobial Resistance, Centers for Disease Control and Prevention, https://www.cdc.gov/ (“CDC Antimicrobial Resistance”)

\textsuperscript{7} See Brian Krans, Few New Drugs: Why The Antibiotic Pipeline Is Running Dry, Healthline (July 22, 2014) http://www.health-line.com/health/antibiotics/why-pipeline-running-dry (“Healthline 2014”) (“The resistance rates we saw in the ‘90s were at 10 to 15 percent. Now it’s up to 60 percent in hospitals”) (last visited Nov. 30, 2016)
II. **Background**

The earliest believed use of antibiotics was in between 350 – 550 C.E, where tetracycline was used in Egypt.\(^8\) However, the modern era of antibiotics started in the first half of the 20\(^{th}\) century, when Sir Alexander Fleming first discovered that blue-green mold prevented the growth of *staphylococcus* in a petri dish.\(^9\) A mycologist (mis)identified the mold as Penicillum rubrum, and subsequently Sir Alexander Fleming named the broth filtrate as penicillin.\(^10\) The term “antibiotic” was first coined by Selman Waksman to describe “any small molecule made by a microbe that antagonizes the growth of other microbes.”\(^11\) Penicillin was a very popular drug, primarily because of its ability to treat the infections quickly.\(^12\) Penicillin was heavily used by the Allied Troops during the World War-II.\(^13\) In addition to being useful in treatment of infections, antibiotics were also responsible for major advantages in medical science, primarily by reducing the risk of infection following surgical procedures.\(^14\) Moreover, soon after discovering that antibiotics were effective in treatment of diseases, food scientists also discovered that

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\(^8\) See Bushak 2016, *supra* note 1.


\(^10\) Id.


\(^12\) See Bushak 2016, *supra* note 1.

\(^13\) Id.

\(^14\) Budi Setiawan, *The role of prophylactic antibiotics in preventing perioperative infection*, 43 ACTA MED INDONES J INTERNAL MED, 262, 262 (2011) (“Antibiotic prophylaxis is one of important modalities in preventing surgical site infection. Antibiotic prophylaxis administration significantly reduces the incidence of surgical site infection up to four-fold of decrease.”)
administration of antibiotics to livestock, especially chicken, increased their growth rate.\(^\text{15}\) This discovery led to the wide-scale use of antibiotics in agriculture.

The problem with antibiotic resistance started soon after the discovery of antibiotics themselves. Penicillin was widely used and it was successful in containing bacterial infections of World War II soldiers.\(^\text{16}\) However, soon scientists discovered that penicillin-resistant antibacterial infections had become a substantial clinical problem.\(^\text{17}\) Even Sir Alexander Fleming, in his Nobel Prize acceptance speech, recognized the problem of antibiotic resistance, and warned against the problem of development of resistant bacteria as a result of under-dosing penicillin.\(^\text{18}\) The primary reason for rapid development of antibiotic resistance is the ability of bacteria to “transfer genes horizontally — from one bacteria to another immediately — its ability to share resistance.”\(^\text{19}\) The rates of resistant *staphylococcus* infections in hospitals rose by 14% from 1946 to 1948.\(^\text{20}\)

After the discovery of penicillin-resistant bacteria, in an effort to defeat penicillin-resistant strains, scientists developed another antibiotic, methicillin. Methicillin was initially successful in treatment of penicillin resistant infections, but within a year, strains resistant to methicillin were also discovered – methicillin resistant *Staphylococcus aureus* (“MRSA”).\(^\text{21}\) Yet another class of

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\(^{15}\) Bushak 2016, *supra* note 1.

\(^{16}\) See Ventola 2015, *supra* note 2, at p. 277.

\(^{17}\) *Id.*


\(^{19}\) Bushak 2016, *supra* note 1.

\(^{20}\) *Id.* (“According to Harvard Magazine, resistant staph infections in hospitals had risen from 14 percent in 1946 to 59 percent in 1948.”).

\(^{21}\) *Id.* (“But within a year, bacterial strains developed resistance to methicillin too — eventually called MRSA, methicillin-resistant Staphylococcus aureus, or S. aureus. Now, MRSA can resist most antibiotics,
antibiotics known as beta-lactams were developed as an agent effective against antibiotic resistant bacteria.\textsuperscript{22} These beta-lactams were deployed clinically with good results.\textsuperscript{23} However, beta-lactam resistant infections were soon discovered both in the UK and USA.\textsuperscript{24} In 1972, vancomycin, a newly developed antibiotic, was introduced for treatment of the previously known antibiotic resistant infections.\textsuperscript{25} It was initially thought that it would be hard to develop resistance to vancomycin, but by 1979, there were reports of infections resistant to vancomycin.\textsuperscript{26} From 1950 – 1970s, many new antibiotics were developed for treatment of infections including, endocarditis, plague, respiratory tract infections, and meningitis.\textsuperscript{27} The new antibiotics were made available to the public readily, which eventually paved the way for development of antibiotic resistance. With time, some bacteria also became resistant to multiple antibiotics, these bacteria cause multi-drug resistant (MDR) infections.

During the 1990s, MDR MRSA began to infect healthy people in the United States. By 2005, “over 100,000 Americans were stricken with MRSA infections and some 20,000 died, more than the amount of people who were dying from HIV and tuberculosis combined.”\textsuperscript{28} Previously, help in combating antibiotic-resistant infections was provided by discovery of new antibiotics. For

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\footnotesize
See Ventola 2015, \textit{supra} note 2, at p. 277.
\[22\]
See id.
\[23\]
See id.
\[24\]
See id.
\[25\]
See id., p. 278.
\[26\]
See Bushak 2016, \textit{supra} note 1.
\[27\]
Id.
\[28\]
\end{flushright}
example, starting in the 1960’s the pharmaceutical industry introduced a variety of antibiotics, including, *inter alia*, streptomycin, chloramphenicol, and tetracycline, to combat the problem of antibiotic resistance.\(^{29}\) However, in the past few years, the pipeline of antibiotics has begun to dry. From 2009 to 2014, the FDA has approved only two systemic antibiotics, which is a 88% drop from mid-1980s.\(^{30}\) The major reason for the reduction in number of new antibiotics developed by the pharmaceutical industry is the lack of return on investment on developing a drug which might lose efficacy shortly after getting approved.\(^{31}\)

### III. Causes of Antibiotic Resistance:

As discussed above, development of antibiotic resistance is the inevitable outcome of using antibiotics. However, as discussed below, through careless use of antibiotics, humans have contributed in the acceleration of development of antibiotic resistance. Although there might be additional reasons for development of antibiotic resistance, the primary causes recognized by the scientific community are discussed in this paper.

1. **Over-prescription of antibiotics:**

Over-prescription of antibiotics is one of the primary causes of development of antibiotic resistance. As discussed above, the fundamental effect of administration of antibiotics is that it stops the growth of bacteria that are sensitive to the antibiotic, whereas it has no effect on the growth of bacteria that are insensitive or resistant to the antibiotic.\(^{32}\) Thus, administration of


\(^{31}\) Id.

\(^{32}\) *Get Smart: Know When The Antibiotics Work*, Centers for Disease Control and Prevention, http://www.cdc.gov/getsmart/-community/about/antibiotic-resistance-faqs.html (“Every time a person takes antibiotics, sensitive bacteria (bacteria that antibiotics can still attack) are killed, but resistant bacteria
antibiotics to treat any infection leads to a preferred selection for the growth of bacteria resistant to antibiotic over the sensitive bacteria. As the use of antibiotics increases, it will inevitably lead to more instances of growth of resistant bacteria, resulting in development of antibiotic resistance. According to CDC, approximately half of antibiotics administered to humans are “unnecessary and inappropriate and make everyone less safe.”33

In modern medicine, physicians rely heavily on antibiotics to treat infections.34 However, recent studies have demonstrated that “at least 30 percent of antibiotics prescribed in the United States are unnecessary.”35 Specifically, one study found that “most of these unnecessary antibiotics are prescribed for respiratory conditions caused by viruses – including common colds, viral sore throats, bronchitis, and sinus and ear infections – which do not respond to antibiotics.”36 Moreover, this trend of needless prescription of antibiotics is also observed in countries other than the United States. For example, in the United Kingdom, a majority of primary care antibiotic prescriptions are for the treatment of respiratory tract infections.37 The efficacy of antibiotics for

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33 About Antimicrobial resistance, Centers for Disease Control and Prevention (September 8, 2015), https://www.cdc.gov/drugresistance/about.html (“[u]p to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe.”) (last visited Nov. 30, 2016)

34 See Carl Llor and Lars Bjerrum, Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem, 5 THERAPEUTIC ADVANCES IN DRUG SAFETY, 229, 230 (2014) (“Llor 2014”) (“Most of the antibiotics used in medicine are prescribed by general practitioners (GP”).


36 Id., see also Llor 2014, supra, note 34 at p. 229 (“Antibiotic overprescribing is a particular problem in primary care, where viruses cause most infections.”).

37 See Llor 2014, supra, note 34 at p. 230 (“In fact, primary care accounts for 80–90% of all antibiotic prescriptions in Europe and most antibiotics are prescribed for respiratory tract infections.”).
treatment of respiratory tract infections, even if they are bacterial, is modest in the best case scenario.\textsuperscript{38} Research in Europe has demonstrated that the incidence of antibiotic resistance in a country depends on the amount of antibiotics consumed in that country.\textsuperscript{39} Thus, unnecessary prescription of antibiotics will lead to rise in the cases of antibiotic resistance.

In addition to contributing to development of antibiotic resistance, unnecessary prescription of antibiotics can have other unintended health and economic consequences. For example, it can lead to substantial over-expenditure in managing uncomplicated illnesses.\textsuperscript{40} Moreover, over-prescription can also lead to “increased risk of adverse effects, more frequent re-attendance and increased medicalization of self-limiting conditions.”\textsuperscript{41} In an effort to reduce the problem of, \textit{inter alia}, over-prescription, CDC issued guidelines for treatment of upper respiratory tract infections.\textsuperscript{42} However, in spite of such guidelines, the incidences of over prescription of antibiotics for treating uncomplicated upper respiratory tract infections remains prevalent.\textsuperscript{43}

\textsuperscript{38} Id. at p. 231 (“The benefits of antibiotic therapy for most respiratory tract infections are modest in the best-case scenario.”).

\textsuperscript{39} Id. at p. 230 (“Countries with a higher consumption of antibiotics show higher rates of resistance.”).

\textsuperscript{40} Xu et al., \textit{Over-prescribing of antibiotics and imaging in the management of uncomplicated URIs in emergency departments}, 13 BMC EMERGING MEDICINE, 13, 13 (2013) (“Xu 2013”) (“Inappropriate testing and treatments can lead to substantial over-expenditure in managing uncomplicated illnesses.”).

\textsuperscript{41} Llor 2014, \textit{supra} note 34 at p. 229.


\textsuperscript{43} Xu 2013, \textit{supra} note 40 at p. 13 (“Despite the recommendations and campaign efforts by the CDC and many medical associations, the prescribing of antibiotics in treating uncomplicated URIs in the EDs remains prevalent.”).
2. **Use of antibiotics in soaps, detergents, and other household cleaners:**

The use of antibiotics in household products, such as soaps, detergents and cleaners has increased substantially in the past few years. Some of the newer products where antibiotics are present now include window cleaners, chopsticks, plastic silverware, and mattresses. A study published in 2001 showed that antibacterial agents were present in at least 76% of liquid soaps and 29% of bar soaps available in the United States. Numerous studies have demonstrated that there is little to no benefit of the presence of antibiotics in these household products. Moreover, research shows that use of antibiotics like triclosan in soaps contributed to increase in antibiotic resistance in lab experiments.

After decades of research showing that antibiotics in household cleaners are potentially harmful, in 2013, FDA proposed a rule to “require manufacturers of antibacterial hand soaps and body washes to demonstrate that their products are safe for long-term daily use and more effective

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44 Stuart B. Levy, *Antibacterial Household Products: Cause for Concern*, 7 EMERGING INFECTIOUS DISEASES, suppl. 3, 512, 512 (2001) (“Levy 2001”) (“Seven years ago, only a few dozen products containing antibacterial agents were being marketed for the home. Now more than 700 are available. The public is being bombarded with ads for cleansers, soaps, toothbrushes, dishwashing detergents, and hand lotions, all containing antibacterial agents.”).

45 Id. (“Among the newer products in the antibacterial craze are antibacterial window cleaner and antibacterial chopsticks. Antibacterial agents are now in plastic food storage containers in England. In Italy, antibacterial products are touted in public laundries. In the Boston area, you can purchase a mattress completely impregnated with an antibacterial agent. Whole bathrooms and bedrooms can be outfitted with products containing triclosan (a common antibacterial agent), including pillows, sheets, towels, and slippers.”).


47 Aiello et al, *Consumer Antibacterial Soaps: Effective or Just Risky?*, 45 CLINICAL INFECTIOUS DISEASES., S137, S137 (2007) (“Aiello 2007”) (“Soaps containing triclosan within the range of concentrations commonly used in the community setting (0.1%–0.45% wt/vol) were no more effective than plain soap at preventing infectious illness symptoms and reducing bacterial levels on the hands”).

48 See id. at S137.
than plain soap and water in preventing illness and the spread of certain infections." Under this proposed rule, if companies are not able to demonstrate the efficacy of antibiotics present in the product, those products will need to be reformulated. On September 2, 2016 FDA issued a rule to ban marketing of over-the-counter (OTC) products containing certain antibiotics including, *inter alia*, triclosan and triclocarban. This new rule from FDA was specifically directed to products intended to be used with water. However, this rule did not affect products such as “hand ‘sanitizers’, wipes, or antibacterial products used in healthcare settings.” According to this rule, products such as toothpastes, shaving creams, cosmetics, hand sanitizers, and wipes containing antibiotics can still be marketed. For example, a list of products containing triclosan, which is banned in soaps, includes, *inter alia*, deodorants and body spray. The presence of antibiotics in these household products without any proven benefit may accelerate the development of antibiotic resistance.

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50 *See id.*

51 *See FDA issues final rule to determine safety and effectiveness of antibacterial soaps*, FDA News Release (Sept. 2, 2016), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm517478.htm ("FDA Press Release Sept. 2, 2016") ("This final rule applies to consumer antiseptic wash products containing one or more of 19 specific active ingredients, including the most commonly used ingredients – triclosan and triclocarban.") (last visited Nov. 30, 2016).

52 *Id.*

3. Use of Antibiotics in Agriculture and Poultry

In 1948, Robert Stokstad and Thomas Jukes discovered that poultry that had been fed broth with antibiotics in them grew 24% more than the poultry not receiving these antibiotics.54 “This discovery jumpstarted the process of routinely injecting antibiotics into animals.”55 Since then, “[a]ntibiotics are widely used in food-producing animals.”56 Most of the antibiotics used in livestock are not used as veterinary medicine, but rather in sub-therapeutic doses for increasing growth of farmed animals.57 Today, around 13 million kilograms of antibiotics are administered to livestock, which amounts to approximately 80% of all antibiotics used in the United States.58

As discussed above, administration of sub-therapeutic doses of antibiotics leads to development of antibiotic-resistant bacteria. Thus, it is not unsurprising that administration of subtherapeutic doses of antibiotics to livestock has been connected with development of antibiotic resistance.59 As the sub-therapeutic doses of antibiotics are administered to the animals, it kills the bacteria sensitive to the administered antibiotic, whereas the resistant bacteria continue to thrive.60 For example, in 2013, “a Consumer Reports investigation showed that over half of ground

54 See Bushak 2016, supra note 1.
55 Id.
58 See id. at p. 240.
59 Chang 2015, supra note 57 at p. 240; see also Mathew A.G. et al., Antibiotic Resistance in bacteria, 4 FOODBORNE PATHOGEN DISEASES 2, 115, 115 (2007) (“However, use of antibiotics for agricultural purposes, particularly for growth enhancement, has come under much scrutiny, as it has been shown to contribute to the increased prevalence of antibiotic-resistant bacteria of human significance.”).
60 See CDC NARMS 2016, supra note 56.
turkey meat sold in the U.S. contained strains of drug-resistant bacteria.” The resistant bacteria present in animals can be transferred to humans by simply ingesting the animals. Thus, a resistant bacteria strain may easily be transmitted to humans or other animals in contact with the infected livestock.

In 1996, the government established the National Antimicrobial Resistance Monitoring System (NARMS) to increase collaboration amongst CDC, FDA, the U.S. Department of Agriculture (USDA), and state and local public health departments. An important objective for NARMS was to track antibiotic resistance in bacteria commonly transmitted through food. In 2013, FDA announced that it was “implementing a voluntary plan with industry to phase out the use of certain antibiotics for enhanced food production.” One of the goals of FDA is to phase out the use of “medically important” drugs (used for treatment in humans) in the livestock feed. The underlying rationale is that if the animals are not provided the “medically important” drugs, the bacteria in livestock are unlikely to develop resistance to such antibiotics. In 2015, FDA issued further regulations directed to collecting the sales data for antibiotics to be used in livestock feed. In a detailed study to evaluate the economic impact of use of antibiotics in livestock feed, the

61 Bushak 2016, supra note 1.
62 See CDC NARMS 2016, supra note 56.
63 See id.
64 See id.
66 See id.
authors concluded: “the efficacy of antibiotics in increasing farm-level productivity has decreased . . . European countries that have stopped using growth-promoting antimicrobials, U.S. producers are likely to adopt alternative practices in place of antibiotics for production purposes.”

4. Non-adherence to medical advice

Non-adherence (also known as non-compliance) is defined as: “any deviation by a patient from a doctor’s instructions.” Non-adherence to prescribed doses could occur when the patients forget to take the prescribed dose of medication or prematurely discontinue the medication when they start feeling better while recovering from an infection or illness. Another form of misuse of antibiotics is self-medication using antibiotics. Self-medication involves administering antibiotics without any direction from a physician. In most of the cases, self-medication leads to: “unnecessary, inadequate, and ill-timed dosing.” The problem of self-medication with antibiotics is more prevalent in developing nations, where antibiotics are readily available without a prescription.

The problem of suboptimal dosing was predicted by Sir Alexander Fleming, who discussed the potential development of antibiotic resistance due to suboptimal dosing of antibiotics in his


71 Id.

72 See id.
Nobel acceptance speech.\textsuperscript{73} Non-adherence to prescribed doses is not advisable for patients. Non-adherence to prescribed doses is one of the main reasons for the failure of short-term antibiotic treatment leading to ineffective management of the disease.\textsuperscript{74} More importantly, “[n]on-adherence to antibiotic therapies may result in antibiotic resistance, as suboptimal doses of antibiotic therapy can result in insufficient antibiotic exposure for eradicating infectious bacteria and potentially create an environment that promotes antibiotic resistance.”\textsuperscript{75} If there is suboptimal dosing of antibiotic for treatment of an infection, bacteria that are developing resistance to antibiotics will continue to proliferate, leading to development of antibiotic resistance. In an effort to combat the problem of non-adherence to prescribed dosing, CDC has encouraged pharmacies where antibiotic prescriptions are filled to post flyers demonstrating, the importance of completing the prescribed dose of antibiotics.\textsuperscript{76}

IV. Strategies for combating antibiotic resistance

The development of antibiotic resistance is a natural effect of the administration of antibiotics. Although antibiotics have been around for centuries, human (mis)use of antibiotics after discovery of penicillin, has been responsible in accelerating the development of antibiotic resistance. In order to combat the problem of antibiotic resistance there are two primary

\textsuperscript{73} Fleming Nobel Acceptance Speech, \textit{supra}, note 18 (“Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

\textsuperscript{74} See Kardas 2002, \textit{supra} note 69 at p. 897.


approaches: preventative measures and remedial measures. The preventative measures are
directed to decelerate the rate of development of antibiotic resistance, especially due to factors
related to human involvement. The remedial measures are focused on developing new lines of
treatments for patients who are currently or in future might suffer from infections caused by
antibiotic resistant bacteria. These two approaches should be developed in conjunction with each
other to combat the threat of antibiotic resistance.

1. Preventative Solutions:

The essence of developing preventative solutions is to curb the human use (or misuse) of
antibiotics, which is the primary cause of development of antibiotic resistance. According to Dr.
Marc Sprenger, Director of the WHO’s secretariat for antimicrobial resistance, “. . . we are
speeding up the process [of development of antibiotic resistance] dramatically by using antibiotics
too much and often in the wrong contexts. We need to slow down the development and spread of
resistance so that the antibiotics we have continue to work for as long as possible.”

In the past few years, some of the policies promulgated by the government, in conjunction
with CDC and FDA, have tried to reduce the misuse of antibiotics by humans. The approaches
undertaken by the FDA include, inter alia,: (i) prohibiting the use of antibiotics in some household
cleaning products without demonstrated efficacy; (ii) promoting patient adherence to the
prescribed dosing regimen; and (iii) discouraging the use of antibiotics in livestock except in cases
of medical necessity.

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77 Marc Sprenger, *How to stop antibiotic resistance? Here's a WHO prescription*, World Health
Organization (Nov. 20, 2015), http://www.who.int/mediacentre/commentaries/stop-antibiotic-

78 See id.
products, the FDA banned the use of antibiotics in soaps unless the companies demonstrate the utility of these antibiotics in the cleaning products.\textsuperscript{79} The government has also issued directives to prevent the use of antibiotics in livestock feed, except as required by medical necessity.\textsuperscript{80} Although these efforts to slow down the development of antibiotic resistance are crucial, this paper primarily discusses approaches to reduce the misuse of antibiotics in medical settings, \textit{i.e.}, antibiotics prescribed by physicians.

As discussed in detail above, over-prescription of antibiotics in medical settings is one of the primary reasons for development of antibiotic resistance. Antibiotics are often unnecessarily prescribed by physicians for treatment of diseases that cannot be treated by antibiotics. In addition to administration of antibiotics for diseases not treatable by antibiotics, due to lack of information about the infection(s), physicians often prescribe “powerful antibiotics that should ideally be kept in reserve, just in case their infection is caused by a drug-resistant strain that would not be cured by older medicines.”\textsuperscript{81} The fundamental problem is that the physicians often do not have sufficient information to prescribe the right drug to the right patient at the right time.\textsuperscript{82}

In many instances, physicians prescribe antibiotics for treatment of conditions that are not treatable by administration of antibiotics. In an effort to reduce the over-prescription of antibiotics,
there are stewardship programs counseling physicians and patients for prudent use of antibiotics.\textsuperscript{83} In 2010, the CDC launched a campaign known as “Get Smart for Healthcare,” focusing on improving the prescription of antibiotics in healthcare settings.\textsuperscript{84} In France, a similar campaign to educate physicians about the proper use of antibiotics in community settings led to a 25% decrease in the use of antibiotics.\textsuperscript{85} However, despite these efforts, the misuse of antibiotics in healthcare settings is prevalent, and it continues to be the leading cause of development of antibiotic resistance.\textsuperscript{86}

Even if a patient is suffering from a bacterial infection, the problem of misuse of antibiotics is exacerbated by physicians often being unable to determine the identity of the bacteria prior to prescribing antibiotics for that infection. In most of the cases, the antibiotics are prescribed by physicians lacking specialized training in dealing with infectious diseases.\textsuperscript{87} The approach that physicians currently employ to prescribe antibiotics is based on their practical experience by assessment of patients’ symptoms.\textsuperscript{88} Such an approach for treatment using antibiotics is one of the major reasons for misuse of antibiotics, which leads to development of antibiotic resistance.

\textsuperscript{83} Id. at p. 1 (“Stewardship programmes to change the prescribing habits of doctors and the expectations of patients can go some way towards addressing the issues of overuse.”).


\textsuperscript{85} See Louis B. Rice, Rapid Diagnostic and Appropriate Antibiotic Use 52 CLINICAL INFECTIOUS DISEASES S4, S357, S359 (2011) (“Rice 2011”).

\textsuperscript{86} See Brian J. Ogrin and Michael E. Klepser, Rapid Diagnostic Tests and Antibiotic Prescribing, 4 PHARMACEUTICA ANALYTICA ACTA, 1, 1 (2013) (“Allowing clinicians to use diagnostic tools directly has demonstrated significant benefits for a variety of infectious diseases”) (“Ogrin 2013”).

\textsuperscript{87} See Rice 2011, supra note 85 at p. S357.

\textsuperscript{88} See Chris Lo, Antibiotic resistance: could rapid tests prevent disaster?, Pharmaceutical Technology (Jul. 4, 2016), http://www.pharmaceutical-technology.com/features/featureantibiotic-resistance-could-rapid-
Recently, there has been a push to explore the application of rapid point-of-care diagnostic tests to determine the type of infection prior to administration of antibiotics. Rapid diagnostic tests (RDTs) are defined as “a type of point-of-care diagnostic, meaning that these assays are intended to provide diagnostic results conveniently and immediately to the patient while still at the health facility, screening site, or other health care provider.” In addition to providing results to the patients, RDTs will also provide critical information about the infection to the physicians treating the patient. This information has demonstrated to be useful. For example, the diagnostic tests performed on HIV-1 patients enabled physicians to diagnose HIV-1 strain resistance and prescribe effective antiviral drugs. A recent study conducted for critically ill patients in the ICU demonstrated that RDT provides rapid pathogen identification (6 hours). As noted by CDC, in excess of 10 rapid influenza diagnostic tests (RIDTs) have been approved by the FDA.

In spite of research demonstrating the usefulness of RDT methods for diagnosis of infections, and their undeniable medical and economic value, such tests have not been widely

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89 See Ogrin 2013, supra note 86 at p. 1.


91 See Caliendo et al., Better Tests, Better Care: Improved Diagnostics for Infectious Diseases, 57 CLINICAL INFECTIOUS DISEASES, S3, S139, S144 (2013) (“Caliendo 2013”).


adopted in the healthcare system.\textsuperscript{94} In general, the high cost of implementation of RDTs have been widely cited as the reason for absence of commonplace application of such tests.\textsuperscript{95} A second concern often raised is the cost-effectiveness of RDTs in patient-management, i.e., whether RDT in question has sufficient “clinical value” to be implemented.\textsuperscript{96} The factors analyzed in determining clinical value often involve, inter alia, whether the RDT will improve the understanding of the patient’s medical condition, whether there is a cheaper option available, and whether the condition is manageable without ordering the RDT.\textsuperscript{97} Healthcare providers also consider whether insurance companies will reimburse the cost of conducting RDTs.\textsuperscript{98} Finally, lack of investment in developing new RDTs is also limiting nationwide implementation of these tests in treatment of diseases.\textsuperscript{99}

Prescribing antibiotics without first conducting RDTs is generally less expensive. Thus, for hospitals, doctors, and pharmacists, the diagnostic test is likely to be perceived as an unnecessary cost for healthcare facilities that may already be strained financially.\textsuperscript{100} However, this is a very narrow view on the issue of costs. As discussed above, drug-resistant infections place a large drain on the healthcare system in the long run. For example, a recent study showed that “a


\textsuperscript{95} See id.

\textsuperscript{96} See id.

\textsuperscript{97} See id.


\textsuperscript{99} See Rapid Diagnostics Review, supra note 81 at p. 19.

\textsuperscript{100} See id. at p. 13.
resistant infection costs between 18,588 USD and 29,069 USD per patient. First, even if RDTs are employed even at a fraction of this cost per patient, it would lead to significantly higher savings later during the course of treatment. RDTs would likely reduce the misuse of antibiotics, which in turn would slow the development of antibiotic resistance, thus reducing the overall cost of healthcare. Second, if RDTs are used routinely, it would significantly reduce the amount of antibiotics prescribed, reducing the cost of healthcare by not paying for the antibiotics. Third, even the patients who are likely to shoulder the initial cost of implementation of RDTs either directly in their personal healthcare expenditure, or indirectly by higher cost of insurance, will benefit by a reduced likelihood of suffering from infections pursuant to antibiotic resistant bacteria. These advantages, even if they do not completely offset the immediate cost of implementation of RDTs, should provide a compelling reason for implementation of RDTs.

In the past few years, the technology for detection and analysis of bacteria infecting the patients has advanced significantly. The newly developed techniques are increasing the specificity, sensitivity, and the speed of detection of microbial infections, as well as reducing the costs of implementing such tests. Specifically, the advent of techniques such as polymeric chain reaction (PCR) and nucleic acid-based technologies (NAATs) that enable genetic sequencing of pathogens has been immensely helpful in diagnosis of infections as well as development of new drugs. These technologies have enhanced the diagnosis of bacterial and viral infections. In the more recent advances for RDTs, the development of nanotechnology based tests that do not require

\[101\] Id.

\[102\] Caliendo 2013, supra note 91 at S 143 (“Recently, new technologies have brought great advances in infectious diseases diagnostics.”).

\[103\] See id. at S144.
addition of various reagents, has resulted in the use of such tests in the point of care for clinical
treatment. Indeed, in 2011 and 2012, FDA approved numerous molecular diagnostic tests for
detection of strains of bacteria.

The development and implementation of new RDTs will be an invaluable tool in combating
the misuse of antibiotics. In an ideal setting, the RDT will primarily answer the following
questions: (i) Is the infection bacterial or viral; and (ii) If the infection is bacterial, what kind of
bacteria is causing the infection. This information will be crucial for physicians to design an
efficient treatment for the patients. In an Executive Order issued on September 18, 2014, President
Obama announced a strategy to combat antibiotic resistance by, inter alia, “develop[ing] and
[promoting] the use of new, rapid diagnostic technologies.” A prize of up to $20 million was
also announced for: “the first group(s) to develop a rapid, point-of-care diagnostic test to be used
by health care providers to identify highly resistant bacterial infections.” Although these
initiatives would be undoubtedly helpful to spur innovation in developing new RDT to be used in

104 See id.
105 See id.
106 Rapid Diagnostics Review, supra note 81 at p. 11.
107 Executive Order -- Combating Antibiotic-Resistant Bacteria, The White House, Office of the Press
Secretary (Sept. 18, 2014), https://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-
combating-antibiotic-resistant-bacteria (last visited Nov. 30, 2016).
108 See Francis S. Collins, Statement on Prize for Diagnostic Devices to Identify Antimicrobial Resistant
Bacterial Infections, National Institutes of Health (Sept. 17, 2014), https://www.nih.gov/about-nih/who-
we-are/nih-director/statements/statement-prize-diagnostic-devices-identify-antimicrobial-resistant-
bacterial-infections (last visited Nov. 30, 2016).
In addition to these reward-based innovation approaches, other ideas have also been suggested to accelerate the innovation for development of new RDTs. For example, to ease the concern of high implementation cost, it might be helpful to create a global fund, which will subsidize the cost of implementation of new RDTs for healthcare providers. Another recommended use for the resources of this global fund is to invest in early stage research for new RDTs. This approach is particularly helpful in developing ground-breaking technology, where there is a high risk of failure that the private sector may not be willing to undertake. There have also been recommendations for healthcare providers to play a critical role in development of RDTs by assisting in clinical trials and conducting cost-effectiveness studies. A combination of approaches such as these would indeed be beneficial for the development of new generation of RDTs.

Finally, in addition to development of approaches to curb the needless use of antibiotics, further policy interventions are needed to make sure that the tests already developed are utilized in healthcare, especially prior to prescribing antibiotics. Antibiotics stewardship programs are a step in the right direction, and they should take a stronger role in educating, advocating, and implementing RDTs in the modern healthcare paradigm. As discussed above, with the rapidly

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109 See Rapid Diagnostic Review, supra note 81 at p. 24 (“But to go further the sums involved would need to be larger to truly change the landscape, and for such an intervention lump sum prizes are not our preferred choice.”).
110 See id. at p. 20.
111 See id. at p. 24.
112 See id.
developing technology, a plethora of new RDTs are now available for the physicians to utilize in treatment of patients. FDA, in conjunction with healthcare providers and insurance companies, should promulgate rules and policies which promote the implementation of RDTs that have demonstrated a high sensitivity and specificity in identifying the infections. Government support in funding the initial implementation of the more expensive technologies will be immensely helpful for the increasingly cash-strapped healthcare system. The cost of this initial investment is likely to be offset by the reduced amount time spent by patients receiving treatment for their infections.

RDTs provide one of the most promising avenues to curb the unnecessary use of antibiotics, especially in the healthcare settings. Policies directed towards development of new cost-effective RDTs with high sensitivity and specificity, and successfully implementing them in the modern healthcare paradigm will be crucial in halting the proliferation of antibiotic resistance due to over-prescription. In combination with other policies designed to eradicate the misuse of antibiotics in other areas, such as in household cleaning products and animal feed, would go a long way in at least slowing the development of antibiotic resistance.

2. Remedial Measures:

Remedial measures to combat antibiotic resistance are directed to discovering new tools for treatment of the patients suffering from infections that are resistant to the available antibiotics. This is extremely important in combating antibiotic resistance. There are some multi-drug resistant infections that are slowly becoming resistant to all available antibiotics. For example,
recently the WHO warned that “[w]e are running out of ways to treat gonorrhea.”WHO has released guidelines which recommends physicians to not prescribe an entire class of antibiotics (quinolones) for treatment of gonorrhea due to emergence of resistant strains of gonorrhea.

In general, the best remedial approach to combat antibiotic resistance is to continue to develop novel antibiotics. However, after the initial boom in the development of antibiotics, the pipeline of antibiotics in the pharmaceutical industry is running dry. For example, there was a gap of 38 years between the launch of new (structural) classes of antibiotics. The primary reason for lack of interest from pharmaceutical industry for the development of antibiotics is the low ratio of revenues to cost of development. Antibiotics are generally short-term therapies designed to completely cure the disease. Thus, once the disease is cured, the patient stops the consumption of antibiotics. Moreover, due to development of antibiotic resistance, the newly developed

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114 See id.


117 Healthline 2014, supra note 7 (“On average, pharmaceutical companies spend $5 billion in research and testing for each new drug they bring to market... Pharmaceutical companies can make greater profits on drugs that can be used regularly without losing effectiveness, such as antidepressants, statins, and anti-inflammatory medications.”)

118 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) (“Ironically, antibiotics are victims of their own success; they are less desirable to drug companies and venture capitalists because they are more successful than other drugs.”) (“Spellberg 2008”)
antibiotics lose effectiveness over time. Pharmaceutical companies, often driven by high profits, prefer to develop medicines that do not lose effectiveness, such as drugs for diabetes or depression.

From the early days of development of antibiotics, the primary source of new antibiotics has been the pharmaceutical industry. Thus, the government, in their efforts to develop new antibiotics, designed approaches to motivate the pharmaceutical industry to engage in research and development of new antibiotics. In an effort to boost the development of new antibiotics, the government developed a “National Action Plan For Combating Antibiotic-Resistant Bacteria,” (“NAPCAB”) which proposed a higher degree of collaboration between the NIH and the pharmaceutical industry for development of infrastructure for clinical trials for molecules showing promising antimicrobial activity. NAPCAB also recommended the creation of a “biopharmaceutical incubator,” that brings together researchers, inventors, and start-up companies to develop new antibiotics and non-traditional therapies. In addition, Congress passed “Generating Antibiotic Incentives Now (GAIN)” Act, which was signed into law by President Obama in 2012. GAIN includes a provision for additional five years of exclusivity for the new


122 See id. at p. 48.
“qualified” antibiotics approved by the FDA. The additional exclusivity is in addition to any other applicable exclusivity provision for that particular drug. GAIN also includes a provision for expedited approval of the antibiotics by the FDA. By October 2013, at least 16 antibiotics had been designated as qualified. In 2015, FDA approved two drugs, Avycaz® and Cresemba® under GAIN act. Thus, the approach undertaken by the government to boost the development of antibiotics is generating some positive results.

The government is trying to provide incentives that may reignite the interest of pharmaceutical companies to develop new antibiotics. However, one of these approaches by the government, i.e., granting additional exclusivity to the newly approved antibiotics, is likely to have an unintended effect of contributing to antibiotic resistance. For example, under a provision of GAIN, the newly developed “qualified” antibiotics might be entitled to additional exclusivity. When a pharmaceutical company is granted exclusivity to market a certain drug for a limited time, it is motivated to maximize the sales of the drugs during that period of exclusivity. This leads to aggressive marketing of the “new” antibiotic to the medical service providers. It is precisely this overuse of these new antibiotics, supposed to be our last-line of defense against infections caused by bacteria resistant to other available antibiotics that leads to development of resistance to these new antibiotics. Thus, such policies, based on granting exclusivity to pharmaceutical companies


124 Id. (“The extra five years of market protection is in addition to any existing exclusivity, including that which may be applicable under Hatch-Waxman (five years or three years), orphan drug (seven years), or pediatric exclusivity (six months).”)
developing a new antibiotic is likely to have the unintended effect of promoting antibiotic resistance.

Thus, a policy motivating the development of new antibiotics without the unintended consequence of promoting antibiotic resistance will overcome the flaw of current policies. To this effect, a policy that gives the pharmaceutical company exclusivity until a certain quantity of drugs is sold, or until a set amount of revenue is generated from the sales of the antibiotic, will still motivate pharmaceutical companies to develop new drugs, but will not push them to aggressively market the new antibiotic. A similar policy has been suggested previously by IDSA, which recommended “federally funded advanced purchase commitments or other ‘promised markets’ for priority antibiotics.”125 A strategy which ensures an innovator pharmaceutical company, which presumably has invested a great deal time and money in developing the new antibiotic, will be able to recoup the investment, does not incentivize the pharmaceutical companies to invest in marketing newly developed antibiotics. Thus, such policies will encourage development of new antibiotics without the unintended consequence of fostering antibiotic resistance.

Another similar proposed strategy is known as “transferable patent extensions,” “wild card patent term extensions,” or “wild card extensions.”126 Under this strategy, after receiving FDA approval for a new antibiotic, a pharmaceutical company would receive 6 months to 2 years of additional exclusivity on any other drug that the pharmaceutical company is marketing.127 Although such a strategy may be considered risky, since it will most likely increase the cost of

125 Spellberg 2008, supra note 118 at p. 160.
126 Id. at p. 161.
127 Id.
other essential drugs, the pharmaceutical industry considers it the most likely to spur research for the development of new antibiotics. Furthermore, “an academic analysis of the transferable patent extension concept has indicated that it likely will result in a net savings of billions of dollars in health care costs by promoting the availability of antibiotics to fight costly multidrug-resistant infections.”

Policies giving pharmaceutical companies enhanced exclusivity or intellectual property protection for a drug of their choice, that they are already marketing, is likely to spur their interest in developing new antibiotics for the treatment of antibiotic-resistant infections. Moreover, carefully designed incentives, such as revenue-based or sales-based exclusivity will ensure that the above-mentioned intellectual property based protections do not lead to inadvertent development of bacteria resistant to the newly developed antibiotic.

Finally, there has been some legislation introduced granting “tax credits” to the pharmaceutical industries engaging in the research and development of, *inter alia*, new antibiotics or diagnostic tools to fight infectious diseases. In addition to the proposed “tax credits,” Congress may also enact legislation that provides deductions for certain qualified research and development expenses directed to development of new antimicrobial drugs. Such deductions would at least motivate pharmaceutical companies to engage in antimicrobial research to lower their tax liability. Moreover, potentially, infrastructure development activities that qualify as tax deductible expenses for development of antibiotics, may also be used for development of other unrelated drugs. Such an approach, might be particularly appealing to the pharmaceutical

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128 *Id.*

129 *See id.* at p. 159.
company constantly looking for ways to lower their tax liability and maximizing their earnings, to engage in research and development associated with development of new antibiotics for fighting antibiotic resistant infections.

V. Conclusion

Antibiotic resistance was highlighted by Sir Alexander Fleming as a potential problem soon after his pivotal discovery of penicillin. Development of antibiotic resistance has now become a modern day healthcare epidemic costing thousands of lives. If we fail to take steps to solve this unprecedented challenge, the ability of healthcare providers to fight bacterial infections will be severely compromised. In an effort to stem the problem of antibiotic resistance, coordinated policies directed at stemming the misuse of antibiotics, especially those prescribed by physicians, need to be advanced. Although there are numerous approaches to tackle this problem, advancing the use of RDTs is likely to reduce the number of antibiotics prescribed by physicians significantly. Thus, policies directed to incentivize the utilization of RDTs prior to prescription of antibiotics will be instrumental in curbing the development of antibiotic resistance.

However, development of resistance amongst bacteria is inevitable upon use of antibiotics. Accordingly, in order to develop new antibiotics, to which the bacteria are sensitive, is important. Policies directed to spur innovation in research and development of new antibiotics by pharmaceutical industries that do not pressurize the innovating company to market the antibiotic aggressively are critical. For example, policies supporting exclusivity till a fixed amount of sales for the newly developed antibiotics are most likely to spur innovation and prevent aggressive marketing of the antibiotics by the pharmaceutical companies. In order to preserve the advances made in the past few decades for the ability of physicians to fight antibacterial infections, policies
directed towards preventive and remedial measures to combat antibiotic resistance should be developed and vigorously advanced.