ANTIBIOTIC DEVELOPMENT AND THE PHARMACEUTICAL INDUSTRY: AN EXAMINATION OF THE 2012 GENERATING ANTIBIOTIC INCENTIVES NOW ACT, THE COUNTERINTUITIVE MARKET FOR ANTIBIOTICS RESEARCH AND DEVELOPMENT AND THE NEED FOR PROFIT-MAXIMIZING POLICY SOLUTIONS

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ABSTRACT

There is growing concern within the public health community that the rapid decline of new antibiotics over the last two decades, coupled with the adaptive nature of bacterial infections, could lead to widespread disease without effective treatments. It is difficult for pharmaceutical companies to recoup the billions of dollars invested in the research and development (R&D) of new antibiotics because bacterial infections are treated with older antibiotics first *and* for short dosage periods to stymie antibiotic resistance. Without a means to recoup their R&D costs and enduring shareholder demands for profit-maximizing endeavors, many companies shut down their antibiotics labs in favor of more profitable medications, like those for chronic illnesses that require continual administration for extended periods. In an effort to stimulate more antibiotic R&D, the United States passed the *Generating Antibiotic Incentives Now* (GAIN) Act in 2012 to motivate companies to bring more antibiotic treatments to market. This paper aims to explain the supply and demand problems of the current market for antibiotics and analyze GAIN's impact on R&D investment. After examining the amount of antibiotics in clinical trials before and after the GAIN Act, there was insufficient statistical evidence to support the hypothesis that GAIN altered the behavior of companies. This Act does not offer enough incentives to counteract the unique market anomaly antibiotics present. Without a continual robust antibiotic pipeline, bacterial infections, including new strains of antibiotic-resistant infections, will be untreatable. This study has public health significance because it highlights the urgent nature of providing additional incentives to companies that invest in antibiotics R&D, without which, there will be few options to treat bacterial infections in the future.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I would like to express my sincerest gratitude to Dr. Beaufort Longest, Dr. Jeremy Martinson, and Dr. Nicholas Castle for their time and assistance in completing this research project. I would also like to extend thanks for the suggestions, debates and help with the development of this research project to Dr. John Crilly and Dr. Lan Chi Luu. Gratitude is also extended to Liana Verzella, Allison Raithel, Jessica Dornin, Lillie Crilly and Sean Young for your continued support. And finally, I want to thank my family, most especially, Ann Marie Crilly who has continually supported my educational endeavors.

1.0 INTRODUCTION

The 1928 discovery of the first antibiotic, penicillin, transformed healthcare by curing infections that previously, were often fatal illnesses.[1] As more antibiotics were discovered and successful treatment of infections became routine, pharmaceutical companies shifted investment from short-term use medications, like antibiotics, to more long-term use medications, like those for chronic illnesses.[2] This modification in research goals benefited public health and allowed companies to be more profitable. However it overlooked the evolving nature of bacterial infections, which requires a consistent and robust antibiotic pipeline to effectively fight infections. Given the previously stated shift in drug development, the current antibiotic pipeline is small. From 1983 to 1987, 16 new antibiotics gained FDA approval.[3] From 1993-1997, 10 antibiotics received FDA approval.[4] Further declines occurred from 2003 to 2007, when only five antibiotics received FDA approval and from 2007-2012, only two were approved.[5] Pharmaceutical companies need more federal incentives to motivate them to re-invest in a product that does not follow standard supply and demand principles.

This paper aims to analyze the current industry trends and issues facing the antibiotics market and evaluate the 2012 GAIN Act. While it is critical that antibiotics are developed for antibiotic-resistant strains of bacteria, this research project focuses on the need for additional government incentives to create a robust antibiotic pipeline. Currently, the 2012 GAIN Act (and to a much smaller extent, the 1983 Orphan Drug Act) incentivizes R&D for antibiotics for specific *Qualified Infectious Disease Products* (QIDP). The main objective is to determine if there was a measurable difference in the behaviors of companies' antibiotics pipelines since the introduction of GAIN. Given GAIN's small incentives for QIDP's, I hypothesized that there would be a small change in industry behavior, but found that there was not a statistically significant change. Armed with this information, policymakers and governmental agencies can make informed decisions regarding future incentive programs to stimulate antibiotic pipelines.

The antibiotics industry operates within the profit-driven pharmaceutical industry. Despite that, the antibiotics industry does not follow the typical supply-demand structure of other medications. In a typical market, when demand rises, more manufacturers enter the market in hopes of gaining a profit. Demand is intensifying for new antibiotics. A marked increase in antibiotic-resistant infections indicates that current antibiotics are not as effective as in the past. In theory, fiercely competitive pharmaceutical companies should respond to market demands and invest in antibiotic R&D. However, unlike typical supply-demand market trends, the antibiotics market does not reward companies—even when demand is high and supply is low. This counterintuitive structure lies with the treatment of bacterial infections, which are treated with older antibiotics first for short periods of time.[6] While this prescribing method is beneficial for society, it is not appealing to companies. It is not profitable for pharmaceutical companies to invest billions of dollars into R&D for new antibiotics if they cannot recover the investment. Encouraging companies to re-invest in antibiotics is imperative and can only be done with some legislative interventions in a timely manner.

Policies can encourage R&D for unmet medical needs by offering incentives. The 1983 Orphan Drug Act (ODA) was the first to do so, offering incentives to companies that bring therapeutic treatments to market for diseases that affect 200,000 individuals or less.[7] Companies have obtained *orphan drug status* for antibiotics that target new strains of antibiotic-resistant bacterial infections.[8] Another policy is GAIN, which provides certain incentives to those bringing *qualified infectious disease products* (QIDP) to market. However, it does not offer enough protection to offset the risks taken when developing medications or the need to replenish antibiotics for more common bacterial infections. The GAIN Act relies too heavily on traditional tools used to stimulate R&D for an untraditional market. Given the counterintuitive nature of the antibiotics market, new policies should offer incentives that balance the risks.

2.0 LITERATURE REVIEW

The brand-name antibiotic industry is nestled within the larger framework of the pharmaceutical industry. The pharmaceutical industry is inherently profit-driven because their survival rests on the high-risk decisions made in the development of new medications. Companies take enormous risks when developing drugs that are safe, effective, and innovative. They must recoup their losses from compounds that failed to be brought to market, often due to safety and efficacy concerns. To balance this risk, they are rewarded with sole market privileges for the protected compound during patent exclusivity periods (typically 20 years).[9]

The development process begins with New Molecular Entities (NME), which are newly discovered compounds that have potential to lead to therapeutic treatments.[10] Once a compound is discovered, the manufacturer must decide if it has a realistic chance of coming to market. The right decision is crucial to a company's well being. Only 8% of drugs that go through phase I trials are approved for use.[11] It was estimated that in the year 2014, a company could spend nearly $2.6 billion to bring a drug to market—this estimate includes the failed attempts to bring other drugs to market.[12] If too many NME do not receive approval, investment capital will be drained.

Companies create thousands of molecular compounds from drug discovery research.[13] The industry lobbying group Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that of the 5,000-10,000 compounds from drug discovery, only 250 will enter pre-clinical testing to determine potential.[14] Of those estimated 250 compounds, only 5 will undergo clinical trials.[15] Each NME within any given pharmaceutical manufacturer is required to undergo the same stages of clinical trials on humans to be eligible for FDA approval.[16]

Phase I Trials: A small group of healthy human subjects will take the trial drug to test for safety. Phase I trial size ranges from 20-100 volunteers.[17]

Phase II Trials: Efficacy and further safety testing occur in this phase with a sample size

that is larger than phase I. This group should have the condition for which the medication is meant to treat. Phase II trial size ranges 100-500 volunteers.[18]

Phase III Trials: These clinical trials have large sample sizes. This phase is meant to test the efficacy of the medication against the placebo and pinpoint side effects to the medication. Phase III trial size ranges from 1,000-5,000 volunteers.[19]

Clinical trials typically take 6-7 years to complete.[20] The failure rate is extremely high and failure in late stage development is extremely costly. Only one of five drugs that enter clinical trials will receive FDA approval. Depending on the type of medication being developed, the clinical research phases may be much longer. For example, medications that treat chronic illnesses require larger sample sizes and longer trials to establish long-term efficacy and side effects. While longer development time does require additional resources, the manufacturer can expect patients to take their drug throughout their patent protection period, and the price will reflect this longer trial phase. Once the medication has undergone all safety and efficacy testing, the company will apply for FDA final approval and bring the medication to market.

2.1 ANTIBIOTICS INDUSTRY

The antibiotics industry, in its current state, is relatively small, resulting in a steady decline of antibiotic medications brought to market. At its peak, in the 1940's-1950's, there were 11 major pharmaceutical companies actively participating in R&D for antibiotics. Today, there is only a handful, and most of them have just recently re-entered the market in the last few years.[21] The result has been a steadily declining pipeline, from 11 major antibiotics discoveries from 1940-1960 to only 4 from 1960-2003.[22]

The antibiotics industry operates under the same assumptions and regulations as the larger pharmaceutical industry. The demand is building to create new medications to treat bacterial infections, which are always evolving to become resistant to antibiotics. The market has not rewarded companies who develop strong medications, because "best practice" treatment of bacterial infections dictates that healthcare providers prescribe the older antibiotics first *and* for the shortest time possible.[23] Research supports this practice as an effective way to decrease

antibiotic resistance. Other factors of increasing antibiotic resistance include, inappropriate prescribing and widespread use of antibiotics in livestock.

Recently, there are been several cases of gram-negative antibiotic resistant "superbugs" that have returned attention to this issue.[24] As these bacteria continue to evolve and impact healthcare systems, the antibiotics industry will be under increasing pressure to produce new antibiotics. Antibiotics are distinctly different from other medications because they are developed to fight and kill bacterial infections. Bacterial infections do not discriminate—affecting both young and older individuals. They can evolve by modifying existing proteins to develop antibiotic resistance, a practice known as bacterial metabolism.[25]. This distinction makes antibiotic medications unlike those for chronic illnesses, as they need to continually develop new drugs to fight constantly adapting bacteria.

The development of antibiotics marked a pivotal point in medical history because they were able to cure bacterial infections that were once considered fatal. After their conception in 1908, the medical community marveled at their capabilities and considered them a worthwhile investment. Today, health experts argue that perhaps antibiotics have been too successful—leading people to undervalue them because the devastation of common infections has been forgotten. Along with this form of "pseudo-amnesia", many antibiotics have surpassed their patent protection periods. Therefore, the pricing of the most used antibiotics are the least expensive. Patients have become accustomed to these low prices—leading them to further distance the actual value of a medication from its benefits.

2.1.1 INAPPROPRIATE PRESCRIBING PATTERNS

A rapidly diminishing antibiotics pipeline is further complicated by their overuse. Patient misconceptions about the role of antibiotics (i.e. bacterial and viral infections) increase pressure on physicians to inappropriately prescribe antibiotics because it is more manageable to prescribe than to educate a patient during a ten-minute office visit. This practice harms the industry by providing the bacteria with an opportunity to modify their protein structure—assisting bacteria in becoming resistant to antibiotics. If a patient has a viral infection, like a cold, it cannot be fought with antibiotics. Patients often ask for an antibiotic to help. Conversely, physicians feel pressure

to stay on schedule within their ten-minute visit and prescribe the antibiotic inappropriately because it takes less time than explaining the differences between bacterial and viral infections. The introduction of an antibiotic to a person's system aids in antibiotic resistance because it allows more opportunities for bacteria to adapt to the antibiotic. The CDC estimates that 50% of antibiotic prescriptions are inappropriately prescribed. [26]

2.1.2 ANTIBIOTIC USE IN LIVESTOCK

An estimated 80% of antibiotics sold in the U.S. are used by the meat industry.[27] Livestock live in close quarters, providing a breeding ground for bacteria to grow. While there have not been any studies that link antibiotic use in livestock to growing antibiotic resistance, many public health experts suspect that this is happening.[28] Antibiotic use in livestock is largely unregulated, although some antibiotics are being monitored because overuse occurred when farmers discovered that it helped livestock grow faster.[29] The widespread use in livestock affects the market for new antibiotics because experts suspect it provides opportunities for bacteria to modify to build resistance to antibiotics.

2.2 ECONOMIC ANALYSIS OF ANTIBIOTICS INDUSTRY

There are around 90,000 hospital-acquired infections per year in the U.S., and 70% of them are from antibiotic-resistant bacteria.[30] Another common infection that is often difficult to treat because it is highly resistant to current antibiotic treatments is Methicillin-resistant *Staphylococcus aureus* (MRSA). In the U.S., there are around 100,000 cases, leading to approximately 20,000 deaths per year.[31]

The costs of drug-resistant bacteria are very high, accounting for $200 million per year.[32] Many people require hospitalization while they are fighting these types of infections. If hospital costs for patients with drug-resistant infections are added, the overall cost of treating these infections rises to approximately $30 billion per year.[33] As the number of these infections (and their associated costs) rise, more groups will begin to call for antibiotic research. This attention

will benefit the antibiotics industry because information regarding the poor reimbursement system for novel treatments will highlight the dwindling options available to healthcare providers to fight infection. Many public health officials suspect that this will lead to policy options that aim to incentivize companies to produce new antibiotics to the market.

There are many barriers to entry within this industry. Companies interested in entering the pharmaceutical market face enormous costs. There is a very high risk when investing in research options. Decisions to continue research of a NME has a direct impact on the company's stability 10 to 15 years into the future. If a company does not invest in the right research (i.e. a NME that is able to successfully be brought to market), they face huge economic repercussions from lost R&D. Behind every blockbuster medication, there are hundreds of failed drugs that haven't been brought to market because they are not safe or effective.[34]

New antibiotics entering the market are reserved for the sickest patients as a last-resort option, to preserve the medication's efficacy.[35] Industry leaders know that it is very difficult to regain the high costs of R&D, because the restricted use of the medication limit returns on investment. It is during this time that the manufacturers work to regain the hundreds of millions of dollars that were spent in the research and development of the medication.

Drug manufacturers argue that the costs of R&D justify the high price tag of brand products. There are several aspects that factor into drug pricing. (1) The likelihood of failure (2) The type of drug: an antibiotic will have shorter clinical trials than an antipsychotic medication (3) Whether or not the drug contains a new molecular entity (NME).[36] The nature of the pharmaceutical industry is to continue to seek a successful and lucrative pipeline of drugs coming to market, each with a patent. Once the patent expires—a company loses profits almost immediately because a cheaper generic product will replace the brand product. A company's portfolio must balance future products on the market with the conclusion of patent exclusivity for their current drugs on the market. The risks involved with drug discovery, coupled with the safety and efficacy hurdles, are quite large. Portfolio decisions made today have a direct impact on the future of the company 10+ years from now. Today, most commonly used antibiotics have surpassed their patent protection periods. Therefore, the pricing of the most used antibiotics are the least expensive. Two policies that provide a platform to ease these economic concerns are the ODA and GAIN.

2.3 USE OF H.R.5238: ORPHAN DRUG ACT OF 1983

Historically, incentivizing pharmaceutical companies to invest in less profitable areas of research has been done through the Orphan Drug Act. Medications for rare diseases became increasingly scarce after safety and efficacy legislation emerged following the thalidomide scandals in the 1950's-60's.[37] Thalidomide was prescribed to pregnant women around the world to lessen symptoms of morning sickness.[38] If the medication was taken within the first trimester, significant birth defects occurred.[39] While the FDA never approved this drug, it lacked the regulatory power to require companies to disclose side effects that arose in clinical trials and prove effectiveness before it began large-scale clinical trials.[40] The *Kefauver Harris Amendment* to the Federal Food Drug and Cosmetic Act in 1962 transformed the drug approval processes by requiring more information be disclosed to the FDA about adverse reactions and efficacy.[41] The Kefauver Harris Amendment resulted in dramatically safer drug approval practices. Another, perhaps unintended consequence was much higher R&D costs to ensure that drug approval applicants were successful. For example, to successfully demonstrate a product's safety and efficacy, clinical trials needed to be larger and required informed consent of participants. The higher costs lead companies to look for ways to recoup their higher R&D expenses. One such way was to investigate new medications for illnesses that were common, which increases the number of potential users. If the illness was both a chronic illness and common, companies could hope to maximize their profits by selling to a larger market for a long period of time. People suffering from rare diseases began lobbying their elected representatives for legislation that would encourage pharmaceutical companies to invest some of their resources into rare illnesses. The Orphan Drug Act was designed with this mindset.

The ODA grants "orphan drug status" to qualified applicants—it does not give approval to a particular medication. When a New Drug Applicant (NDA) receives orphan drug status, it qualifies for several benefits, varying by how far the NDA makes it in the drug approval process. The regulatory pathway to approval is the same as any other medication, however, federal intervention occurs throughout the process to incentivize manufacturers to continue development.[42] These incentives include direct and indirect financial benefits. The pool of potential volunteers for clinical trials is much smaller for rare diseases compared to more common diseases. The number of patients required for clinical trials for orphan drugs is smaller

than those for more common diseases. Additionally, tax incentives allow the company to allocate more capital to orphan drug development.[43] Other benefits include extension of exclusivity rights, typically an extension of 7 years of protections from any other competition for that particular medication—which extends profit-earning opportunities by that timeframe.[44] Subsidies for research are also available. Historically, these benefits have proven to be motivating for the pharmaceutical industry. Many orphan drugs have been developed; including several that became blockbuster drugs, meaning they generated revenues in excess of a $1 billion.[45] These drugs include Humira, Abilify, Enbrel, Cialis and Topamax.[46]

The most crucial requirement to receiving orphan drug status is providing credible documentation that a sponsor's NDA is meant to treat a disease that affects less than 200,000 people and that there is a reasonable expectation that a company will be unable to recoup R&D costs without federal assistance.[47] One can think of the market potential for antibiotics in very much the same way that policymakers thought about rare diseases when creating the Orphan Drug Act. According to HR 5238, §316.1, antibiotics are mentioned as a candidate for submission.

> "(a) This part implements sections 525, 526, 527, and 528 of the act and provides procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics. This part sets forth the procedures and requirements for:
>
> (1) Submissions to FDA of:
>
> (i) Requests for recommendations for investigations of drugs for rare diseases or conditions;
>
> (ii) Requests for designation of a drug for a rare disease or condition; and
>
> (iii) Requests for gaining exclusive approval for a drug for a rare disease or condition." [48]

Although antibiotic medications are only mentioned once throughout the legislation, its inclusion allows for companies to petition for orphan drug status. A 2013 report from the Centers for Disease Control and Prevention (CDC) states that approximately 2 million people a year are infected with an infection that is resistant to at least one current antibiotic.[49] The most serious antibiotic resistant infections kill around 23,000 people a year.[50] Pharmaceutical companies can make a case that current antibiotics focused on infections that are currently infecting less than 200,000 people qualify for orphan drug status.[51]

2.4 2012 GAIN ACT: GENERATING ANTIBIOTIC INCENTIVES NOW

The 2012 GAIN Act is part of the larger Food and Drug Administration Safety and Innovation Act.[52] Its existence indicates Congress is aware of the growing need for antibiotics. The Act gives incentives to companies that develop *QIDP's*. The following criteria for a QIDP designation are:

"(1) QUALIFIED INFECTIOUS DISEASE PRODUCT.—The term 'qualified infectious disease product' means an antibiotic drug for treating, detecting, preventing, or identifying a qualifying pathogen.

(2) QUALIFYING PATHOGEN.—The term 'qualifying pathogen' means—

(A) resistant gram positive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Staphylococcus aureus (VRSA), and vancomycin-resistant enterococcus (VRE);

(B) multi-drug resistant gram negative bacteria, including Acinetobacter, Klebsiella, Pseudomonas, and E. coli species;

(C) multi-drug resistant tuberculosis; or

(D) any other infectious pathogen identified for purposes of this section by the Secretary."[53]

Among the incentives is the extension of exclusivity rights of 2-5 years (in addition to any other exclusivity, such as that from Orphan Drug status) and fast tracking the regulatory approval process for new antibiotic therapies.[54] An expedited approval process allows antibiotics to enter the market and be used much faster, allowing companies to begin recouping their costs of drug development.[55]

Unfortunately, these incentives do not address the core issue with antibiotics—the market. It provides benefits, but they are not enough to motivate companies to re-enter the market. If an antibiotic targets a common infection, it will not meet the criteria for orphan drug status or the GAIN Act—leaving the R&D cost burden on the pharmaceutical developer. Exclusivity is much more appealing when a drug will be used by many people and for longer periods of time—allowing companies to gain profits. Older antibiotics will continue to be

prescribed first. Many new antibiotics will be saved for the sickest patients with antibiotic-resistant infections. This practice weakens the appeal of extended exclusivity rights. However, this Act is most flawed because it does not provide incentives to defray the upfront costs of R&D.

The unmet need for incentives is briefly mentioned within the law.

"Study on incentives for qualified infectious disease biological products (a) In general.—The Comptroller General of the United States shall— (1) Conduct a study on the need for incentives to encourage the research, development, and marketing of qualified infectious disease biological products; and (2) Not later than 1 year after the date of the enactment of this Act, submit a report to the Congress on the results of such study, including any recommendations of the Comptroller General on appropriate incentives for addressing such need."[56]

I have been unable to find any report to Congress citing the results of such a study. The President's Council of Advisors on Science and Technology (PCAST), an advisory group that councils the president on science and technology issues, released a report in 2014 with recommendations to increase the antibiotic pipeline. While the report covered a number of issues surrounding the growing antibiotic crisis, it highlighted the need for additional R&D incentives. Among their most feasible recommendations is the development of an *Antibiotic Incentive Fund* to supplement the costs of development through economic push-pull mechanisms.[57] Federal funding could take the shape of large subsidies to defray the costs of drug development (economic push mechanism) or delinking antibiotic usage from the revenue companies receive by offering a large financial reward (economic pull mechanism).[58] Most likely, given the seemingly sustained uncompromising political climate, these economic measures are likely to be unpopular, as they directly benefit the pharmaceutical industry. Federal incentives were created to counteract an unmet need in the market, and it is important to examine if the GAIN Act is truly impacting the pipeline for antibiotics

3.0 METHODS

For the purposes of this analysis, it is important to quantitatively assess if the 2012 GAIN Act provided enough incentives for pharmaceutical companies to place more experimental antibiotic treatments into clinical trials. Given the nature of the antibiotics market (an anomaly of normal market principles) and the minor incentives offered in GAIN, I suspected that there would be some change in antibiotics in clinical trials since this law was enacted. GAIN offers incentives to specific types of antibiotics—new incentives would therefore increase the overall numbers of antibiotics in clinical trials.

Null Hypothesis: There is no difference in the level of antibiotics placed into clinical trials before and after the implementation of the GAIN Act (H_0: $\mu 1 = \mu 2$)

Alternative Hypothesis: There is a difference in the level of antibiotics placed into clinical trials before and after the implementation of the GAIN Act. (H_a: $\mu 1 \neq \mu 2$)

Although GAIN only provides benefits to companies who create antibiotics with QIDP designations, this analysis was designed to determine if pharmaceutical companies were investing in clinical trials for any new antibiotics before and after GAIN. Data collection began by reviewing all companies that had an antibiotic in clinical trials from 1/1/2000-12/31/2011. Clinicaltrials.gov, company websites (including past pipeline data), the PEW Research Institute's list of current antibiotics in clinical trials, and academic journal articles listing new antibiotics in company pipelines were used.

From 2000-2011, a spreadsheet was created (Appendix A) to track antibiotic R&D using the following categories: antibiotic name, company name, date of clinical trials, continued development, and a link to the antibiotic on clinicaltrials.gov. Another spreadsheet was created for 2012-2015 (Appendix B). More information was available for drugs created after 2012 because of GAIN. The following categories were expanded to include: antibiotic name, the company developing it, potential activity against Gram-Negative ESKAPE Pathogens, QIDP

designation, any expected activity against a CDC urgent pathogen, potential indications, development phase, continued development, and the link to the antibiotic on Clinicaltrials.gov. The following exclusion criteria were used to standardize the data search.

Inclusion Criteria for 2000-2015

- Clinical Trials done in the United States
- Any new antibiotic treatment targeting any type of bacterial infection, including, but not limited to, Methicillin-resistant Staphylococcus aureus (MRSA) infection, acne, Bacterial Vaginosis, etc.
- New combinations of old antibiotics
- Any attempt to begin clinical trials—-examining if a company is willing to invest in an antibiotic compound when only 1 in 5 will actually be approved

Exclusion Criteria for 2000-2015

- Clinical trials not conducted within the United States
- Old antibiotics (developed before 2000) with new delivery methods (i.e. Amikacin inhalation (NKTR-061)—Amikacin is an old antibiotic with a new delivery method)
- New vaccines
- Tests for risk factors (found in clinicaltrials.gov)
- Devices
- New antibiotics not within the study time-period of 2000-2010

After information gathering, a third Excel spreadsheet was created (Appendix C) to condense the data needed to answer the research question. I decided to look at companies that made any attempt to begin developing an antibiotic (that met the inclusion criteria) by beginning clinical trial on a new antibiotic, which a very expensive undertaking. The data were combined and duplicates were eliminated. Each duplicate was re-checked to ensure that it was counted in the correct category. The number of medications that each company had in their pipeline in the year 2010 and year 2015 was then counted. Those time-points were chosen for the following differences:

2010: This year provided a marker for a pre-GAIN Act assessment. The GAIN Act was drafted in 2011. Companies could not be sure that a law giving extra incentives would pass through Congress. By 2010, there were growing concerns about antibiotics pipelines from the public. The public health community was very aware of the problem. Despite all of these factors, 2010 marks a point in time when antibiotic development was not very profitable and there were very few incentives.

2015: By this time, GAIN has been active for three years. Companies had time to explore options for brining potential antibiotic compounds into trials knowing the incentives offered in GAIN. It is also the most current point that had available for research.

If a company was developing antibiotics, they were included in the data. If any of those companies had an antibiotic in trials (phase I, II, or III) in 2010 that met the inclusion criteria, they were counted in 2010. The same was done for 2015 *however* they needed to be new/different antibiotics than those in the pipeline in 2010.

The pharmaceutical industry rapidly changes through mergers and acquisitions. As the 2010 and 2015 data were examined, there were several companies from 2010 that were purchased or merged with other companies by 2015. Excluding these mergers and acquisitions outright would skew the data and deliver false results. Additionally, the inclusion of small companies, whose sole purpose is to discover compounds and sell them to larger companies could also skew the data. The following procedure was used to alleviate these issues:

Any mergers or acquisitions were placed under the purchasing company (ex. Scherling-Plough merged with Merck&Co. in 2009 under Merck&Co.'s name, therefore, their antibiotic pipeline was placed under Merck&Co.)

Smaller companies who create compounds (sometimes beginning phase I trials) only to sell them to larger companies presented a special challenge. Ultimately, I decided to place each compound under the larger company that purchased the compound. These smaller companies are inherently different from larger ones that want to bring a medication to market and should not be treated in the same way.

A paired t-test using STATA package 14.0 was used to compare the means of antibiotics in clinical trials for each company at the two time points. The paired t-test only allows the interpretation of industry behavior by comparing averages of antibiotics in clinical trials before and after a law, to get a sense of whether GAIN made any impact on antibiotic development.

4.0 DISCUSSION AND RESULTS

The data indicates that there is not a statistically significant difference in antibiotics in clinical trials after GAIN was enacted (p-value of 0.0657 at a significance level of 0.05). Table 1 shows the number of companies studied (n=59) and the mean antibiotics in clinical trials in year 2010 and year 2015.

Table 1. Results of Paired T-Test with Merck&Co. Data

Year	Companies with Antibiotics in Clinical Trials	Mean Antibiotics in Clinical Trials
2010	59	0.88
2015	59	0.58

Merck&Co. was an outlier with high residual value and moderate leverage (see Appendix D). After studying the boxplots (see Figure 1) and looking into Merck&Co. further, they presented as different from the other data because it is an extremely large company who has purchased the rights to many antibiotics. Merck is different because they are able to sustain more failed clinical trials. While that is a benefit for more antibiotic development, it does not accurately convey the needs or complications of development of the industry as a whole. Even with Merck&Co. removed from the data, there continued to be no statistically significant difference in antibiotics in clinical trials after the GAIN Act (P-value of 0.1084 at a significance level of 0.05). Figure 2 shows the number of companies studied (n=58) and the mean antibiotics in clinical trials in year 2010 and year 2015 when Merck&Co was removed from the data.

Table 2. Results of Paired T-Test without Merck&Co. Data

Year	Companies with Antibiotics in Clinical Trials	Mean Antibiotics in Clinical Trials
2010	58	0.81
2015	58	0.55

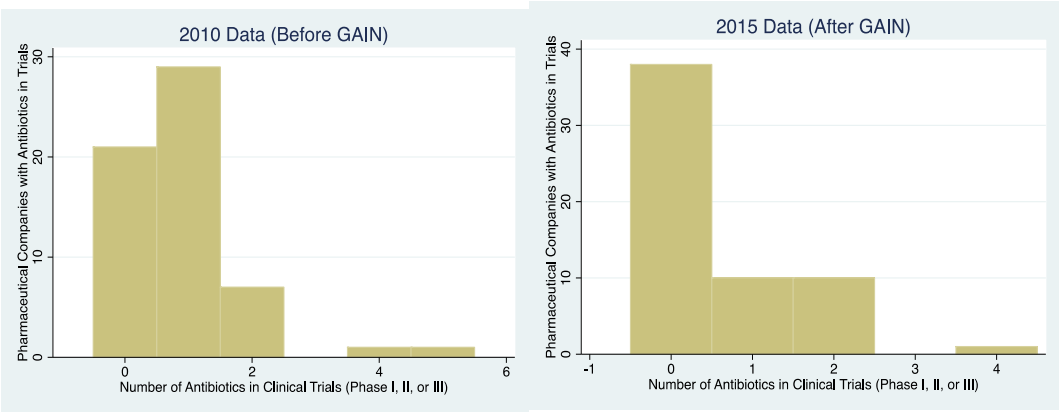


Figure 1. 2010 and 2015 Boxplots of Antibiotics in Clinical Trials

The years 2010 and 2015 were chosen because they represented two distinctly different time-points in antibiotic development legislation. The GAIN Act was not yet in draft form in 2010. 2010 was a politically tumultuous year. President Barack Obama used much of his political capital (along with Democratic majorities in the House of Representatives and the Senate) to push through his healthcare overhaul, known as the Patient Protection and Affordable Care Act (ACA). The ACA received much attention because it radically changed the healthcare landscape in the US by prohibiting insurers from denying coverage to individuals with pre-existing health conditions, requiring insurance of most individuals (without which a fee would be collected based on one's income), and standardizing basic health insurance plans.[59] These provisions were just a few of the many changes the law made to improve healthcare coverage and care in the US. It was also extremely controversial. Many felt that the new requirements were too restrictive, unnecessary and did not cut costs in the right way. At the time, the pharmaceutical industry received many incentives in exchange for their support of the bill; however, antibiotics incentives were not part of the ACA. These factors meant that 2010 was late enough for public health officials to be very concerned about the need for antibiotics, but not for

the pharmaceutical industry to be sure that enticing incentives were coming. Any research or development costs would carry the same risks as developing any other medication, but reimbursement to recoup costs was still very low. The only hope of earning higher revenues would be through use of the Orphan Drug Act—if the antibiotic treated an infection that affected less than 200,000 people. 2010 offered certainty about the need for antibiotics but uncertainty about the reimbursement that companies needed to fully invest in antibiotic development.

The year 2015 offers an example of the post-GAIN Act behaviors. GAIN had been in affect since 2012, but it was introduced in Congress in 2011.[60] . Companies have many new compounds that they decide not to develop for reasons varying from reimbursement to likelihood of success in clinical trials. Since GAIN only offered incentives specific antibiotics (those with QIDP status), the hope was that the number of antibiotics in clinical trials would increase, even if it was only by those with QIDP status.

The need for additional incentives is highlighted in the results of the statistical analysis. The industry's resistance to developing new antibiotic development continues, even three years after GAIN. Companies had time to begin developing antibiotics that may meet the criteria to qualify for GAIN's benefits, but many chose to continue past behaviors.

There are two exceptions to these findings. Compared to other companies interested in antibiotic development, Merck&Co. and Pfizer had large numbers of antibiotics in clinical trials during 2011 and 2015. These companies are unique in their drug output and size and are among the world's largest pharmaceutical revenue earners.[61] GAIN may have had some impact on their antibiotics pipelines, but their high revenues allow them to pursue more risky ventures.

This analysis has several limitations. It only looks at two years and there could be differences in statistical significance if different years were chosen. This analysis looks at 2015 as a year to measure the impact of GAIN. While three years gives pharmaceutical companies time to bring antibiotic compounds into clinical trials, it may not have been enough time. The data collection that was used to complete the statistical analysis has been made available for future studies on this subject (Appendix D).

Policymakers have several options going forward. PCAST has suggested the following options: much higher reimbursement, uncoupling antibiotic use from the revenues received from companies, tradable vouchers to extend patent life or market exclusivity of other drugs, and antibiotic usage fee to generate funds for any of these programs.[62] Each of these options will be

costly and likely unpopular with the public. I believe that the most appealing of these options to the industry is the tradable vouchers to extend patent life or market exclusivity and an antibiotic usage fee to fund the extension of patent life. This solution offers pharmaceutical companies the option to continue charging full price for their blockbuster medications. The industry is predictable, in that they like stability of patent protections. A patent extension voucher can give them a sense of security in a very risky business by offsetting the costs of antibiotic development. There is a longstanding tradition within the industry to extend patents, especially those for blockbuster drugs, for as long as possible. This incentive allows them to choose what to extend—which is very tempting.

5.0 CONCLUSION

The counterintuitive nature of the antibiotics market is not easily persuaded by typical incentives. Unlike most medications on the market, novel antibiotics are prescribed for short dosage times and after older (often generic) versions fail to treat a bacterial infection. This practice continues because antibiotics strip the body of both beneficial and harmful bacteria—making shorter prescribing times necessary. Additionally, antibiotics are treating bacteria that are continually modifying themselves to become unaffected by once-effective antibiotics, eventually leaving antibiotics useless to fight the newly modified bacteria. This results in a demand for new antibiotics but with very little return on investments. Typical incentives, like those used for medications that follow normal market behaviors do not work for antibiotics. For example, a common incentive that is used to stimulate R&D is patent extensions—however, patent extensions do not have the same appeal when you are extending the exclusivity of a drug that is not used often.

The lack of incentives for new antibiotics coupled with the overuse of antibiotics in medical practice and livestock has lead to an urgent need for more antibiotics—requiring policymakers to create incentives beyond those of the ODA and GAIN Act. When looking at the amount of antibiotics in clinical trials, both before the enactment of GAIN (2010 data; Appendix A) and after (2015 data; Appendix B), there has not been a statistically significant difference in the amount of antibiotics in trials. GAIN has not done enough to incentivize the industry to create more antibiotics. The policy options proposed by PCAST will help balance the risks and benefits of antibiotic R&D, but each will be very expensive and be unpopular the public because they will be seen as more beneficial to the pharmaceutical industry.

It is imperative that this is resolved quickly because medications take several years to fully develop and antibiotic resistance is rising daily. If the status quo continues, antibiotics will no longer work for common bacterial infections, like strep throat, and infection rates will

dramatically increase. Knowing which health policies are effective is an important component of public health. If federal funds will be used to create incentives for antibiotics R&D, it is important that those incentives are appropriate. The GAIN Act is only the beginning of a much-needed financial foundation for antibiotics. Without which, there will be dire consequences and massive disease outbreak that will take many years to resolve.

APPENDIX A: 2000-2011 DATA ON ANTIBIOTICS R&D

1	Drug Name	Company	Year	Expected Activity against a CDC urgent pathogen?	Potential Indications* (in latest stage listed)	Development Phase	Still in Development?	Clinicaltrials.gov	notes
2	Teflaro (Ceftaroline fosamil)	Forest Laboratories (under Takeda licsense)	2007-present	yes	Bacterial Pneumonia, MRSA	Phase 1/2/3 complete	Approved-2010	https://www.clinicaltrials.gov/ct2/results?term=Ceftaroline&pg=1	continues to be tested for new indications
3	linezolid (Zyvox)	Pfizer	2001-present	yes	Pneumonia, Pneumococcal Community Acquired Infections Gram-positive Bacterial Infections	Phase 1/2/3 complete	Approved-2000	https://www.clinicaltrials.gov/ct2/results?term=linezolid&Search=Search	continues to be tested for new indications
4	Tigecycline (Imipenem)	Pfizer	2004-present	yes	bacterial infections, complicated skin and structure infections, complicated intra-abdominal infections community-acquired bacterial pneumonia	Phase 1/2/3 complete	Approved-2005	https://www.clinicaltrials.gov/ct2/results?term=tigecycline&pg=1	continues to be tested for new indications
5	Daptomycin	Cubist Pharmacueticals	2003-present	yes	bacterial infections, skin and skin structure infections caused by Gram-positive infections, *S. aureus* bacteraemia, and right-sided *S. aureus* endocarditis	Phase 1/2/3 complete	Approved--2003	https://www.clinicaltrials.gov/ct2/results?term=daptomycin&pg=1&submit_fld_opt=	continues to be tested for new indications
6	TD-6424 (Telavancin) (Vibativ)	Theravance Inc.	2009-present	yes	complicated skin and skin structure infections, hospital-acquired and ventilator-associated bacterial pneumonia caused by Staphylococcus aureus	Phase 1/2/3 complete	Approved-2009	https://www.clinicaltrials.gov/ct2/results?term=Telavancin&Search=Search	continues to be tested for new indications
7	Atuna Racemosa	Mayo Clinic	2006	possibly	bacterial infections	phase 1 complete	Terminated	https://www.clinicaltrials.gov/ct2/show/NCT00318344?term=Atuna+Racemosa&rank=1	
8	Fidaxomicin (PAR-101/OPT-80)	Cubist Pharmacueticals	2011	yes	Clostridium difficile-associated diarrhea	Phase 1/2/3 complete	Approved-2011	https://www.clinicaltrials.gov/ct2/results?term=PAR-101%2FOPT-80&Search=Search	http://www.drugdevelopment-technology.com/projects/fidaxomicin/
9	GS-CDA1	Bristol-Myers Squibb (Medarex)	2006-2010	yes	Clostridium Infections	Phase 1/2 complete	Terminated	https://www.clinicaltrials.gov/ct2/show/NCT00350298?term=GS-CDA1&rank=1	
10	GSK1322322	GlaxoSmithKline	2009-2012	possibly	bacterial infections	phase 1 complete/phase 2 started	terminated	https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=m&submit_fld_opt=on&term=GSK1322322&show_flds=Y	Emerging GSK1322322 pre-clinical data ID'd potentially reactive metabolites previously not seen that changed the risk: benefit profile and led to a termination
11	sulopenem and PF-03709270	Pfizer	2010	possibly	bacterial infections	phase 1 complete/phase 2 started	terminated	https://www.clinicaltrials.gov/ct2/results?term=sulopenem+and+PF-03709270&Search=Search	listed in 2010 pipeline (phase 2) http://www.pfizer.com/files/research/pipeline/2010_0927/pipeline_2010_0927.pdf
12	Iclaprim	Arpida AG and currently Motif BioSciences	2006-present	possibly	Complicated Skin and Skin Structure Infection	Phase 1/2 complete--phase 3 terminated	terminated--denied FDA approval but Motif is still developing it	https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=m&submit_fld_opt=on&term=iclaprim&show_flds=Y	
13	Ertapenem (Invanz)	Merck	2001	yes	gram-negative and gram positive bacterial infections	Phase 1/2/3 complete	Approved (2001)	https://www.clinicaltrials.gov/ct2/results?term=Ertapenem&Search=Search	http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021337s038lbl.pdf

14	Doripenem (Finibax)	Johnson&Johnson	2007		complicated intra-abdominal infections, complicated urinary tract infections, including pyelonephritis	Phase 1/2/3 complete	Approved (2007)	https://www.clinicaltrials.gov/ct2/results?term=Doripenem&Search=Search	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022106s012lbl.pdf
15	Tebipenem pivoxil						not in US	nothing in clinicaltrials.gov	currently used in Japan (not approved in the U.S.--**is it being developed here?** http://www.ncbi.nlm.nih.gov/pubmed/19122338 and http://www.eurekaselect.com/86843/article
16	Ceftobiprole medocaril	Basilea Pharmaceutica (developed by Johnson&Johnson)	2008	yes	community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections	Phase 1/2/3 complete	Terminated--not given approval by FDA	https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=m&submit_fld_opt=on&term=Ceftobiprole+medocaril&show_flds=Y	--however FDA did not approve bc of issues with clinical trials) looks like they are restarting
17	Retapamulin	GlaxoSmithKline	2007	possibly	impetigo due to Staphylococcus aureus (methicillin-susceptible only) or Streptococcus pyogenes	Phase 1/2/3 complete	Approved (2007)	https://www.clinicaltrials.gov/ct2/results?term=Retapamulin&Search=Search	
18	Prulifloxacin	Optimer Pharmaceuticals	2004		bacterial infections		Terminated	https://www.clinicaltrials.gov/ct2/results?term=Prulifloxacin&Search=Search	patented in the US in 1989 but never received FDA approval, patent expired--available in other countries, like Japan
19	Pazufloxacin							no trials listed in 2000-2011 timeframe	not counted--not available in US (only Japan)
20	Balofloxacin							no trials listed in 2000-2011 timeframe	not counted--not available in US (only in Korea)
21	Gemifloxacin	Vasen Pharma						no trials listed in 2000-2011 timeframe	not counted--not available in US (only in Korea)
22	Garenoxacin	Schering-Plough	2006	yes	Gram-positive and Gram-negative bacterial infections		Terminated	no trials listed in 2000-2011 timeframe	available in Japan, China and Korea http://www.drugs.com/nda/garenoxacin_060213.html
23	Sitafloxacin	Daiichi Sankyo						no trials listed in 2000-2011 timeframe	not counted--not available in US (only Japan)
24	Antofloxacin							no trials listed in 2000-2011 timeframe	being tested in China -- http://www.ncbi.nlm.nih.gov/pubmed/18240275
25	Besifloxacin (Besivance)	Bausch & Lomb	2009		bacterial conjunctavitis	Phase 1/2/3 complete	Approved (2009)	https://www.clinicaltrials.gov/ct2/results?term=Besifloxacin&Search=Search	
26	Amadacycline (PTK-0796 and MK-2764) aka Omadacycline	Paratek Pharmaceuticals	2009-present	yes	Bacterial Pneumonia, Community-Acquired Infections, Bacterial Infections, skin Structures and Soft Tissue Infections	Currently listed in phase 3	Terminated but restarted trials in 2015	https://www.clinicaltrials.gov/ct2/results?term=Omadacycline&Search=Search	terminated in 2003 but now restarting clinical trials in 2015
27	Cethromycin (ABT-773) (Restanza)	Advanced Life Sciences Inc	2009		community acquired pneumonia	Phase 1, 2, and 3	Denied but still listed in Pipeline but no trials listed since 2006	https://www.clinicaltrials.gov/ct2/results?term=Cethromycin&Search=Search	FDA found insufficient evidence for cethromycin efficacy in treatment of community acquired pneumonia http://www.drugs.com/nda/restanza_090806.html
28	Plazomicin (ACHN-490)	Achaogen	2009-present		gram-negative bacterial infections	Phase 1/2 complete--phase 3 continues	yes	https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=m&submit_fld_opt=on&term=Plazomicin+%28ACHN-490%29&show_flds=Y	http://www.achaogen.com/plazomicin/
29	BC-3781	Nabriva Therapeutics AG	2010-present		bacterial infections, Community Acquired Pneumonia	Phase 1/2 complete--phase 3 continues	yes	https://www.clinicaltrials.gov/ct2/results?term=BC-3781&Search=Search	
30	Eravacycline (TP-434)	Tetraphase Pharmaceuticals	2010-2014		Complicated Urinary Tract Infections (cUTI), Complicated Intra-abdominal Infections	Phase 1, 2, and 3	yes	https://www.clinicaltrials.gov/ct2/results?term=TP-434&Search=Search	not currently listed in pipeline (already on other spreadsheet--count in 2010)
31	Solithromycin (CEM-101)	Cempra	2011-present		Community-acquired Bacterial Pneumonia, Uncomplicated Urogenital Gonorrhea,	Phase 1, 2, and 3	yes	https://www.clinicaltrials.gov/ct2/results?term=Solithromycin+AND+CEM-101	

32	Zerbaxa (CXA-101 and FR264205)	Cubist Pharmaceuticals LLC	2009-2014		Nosocomial Pneumonia, Cystic Fibrosis, Cystic Fibrosis Pulmonary Exacerbation, Pseudomonas Aeruginosa Infection	Phase 1, 2, and 3	Approved 2014	https://www.clinicaltrials.gov/ct2/results?term=CXA-101+and+FR264205&Search=Search	
33	Brilacidin (PMX-30063)	Polymedex	2010-2014		Acute Bacterial Skin and Skin-structure Infection(ABSSSI) Due to Staphylococcus Aureus (MSSA); (Susceptible or Methicillin Resistant)	phase 1 and 2	yes	https://www.clinicaltrials.gov/ct2/results?term=PMX-30063&Search=Search	https://en.wikipedia.org/wiki/Brilacidin#History
34	NVC-422	NovaBay Pharmaceuticals, Inc.	2008-2013		Bacterial Conjunctivitis	only phase 2 listed	Terminated	https://www.clinicaltrials.gov/ct2/results?term=NVC-422&Search=Search	the company doesn't plan to pursue further research after failure to get results in phase 2 trials--may look for other inidcations--http://novabay.com/pressrelease/novabay-announces-results-nvc-422-phase-2-viral-conjunctivitis
35	Bedaquiline (TMC207 AND R207910)	Janssen Pharmaceutica	2007-present		multi-drug resistant TB	Phase 1/2/3 complete	Approved	https://www.clinicaltrials.gov/ct2/results?term=Bedaquiline+%28TMC207+AND+R207910%29&pg=1	approved 12/12
36	SQ109	Sequella Inc.	2007		multi-drug resistant TB	Phase 1 (completed), Phase 2 ongoing	yes	https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=m&submit_fld_opt=on&term=SQ109&show_flds=Y	received orphan drug status in 2007, listed in company's pipeline in phase 2http://www.sequella.com/pipeline/index.html
37	OPC-67683	Otsuka Pharmaceutical Development & Commercialization, Inc.	2002-present?		multi-drug resistant TB	Phase 1, 2, and 3	yes	https://www.clinicaltrials.gov/ct2/results?term=OPC-67683&Search=Search	not being tested in the u.s
38	Pretomanid (PA-824)	Global Alliance for TB Drug Development	2007-present		multi-drug resistant TB	Phase 1, 2, and 3	yes?	https://www.clinicaltrials.gov/ct2/results?term=PA-824&Search=Search	not currently listed in pipeline but new studies in clinicaltrials.gov
39	Delafloxacin (RX-3341 and ABT-492)	Melinta Therapeutics, Inc.	2008-2013		Skin and Subcutaneous Tissue Bacterial Infections	Phase 1, 2, and 3	yes	https://www.clinicaltrials.gov/ct2/results?term=Delafloxacin+%28RX-3341+and+ABT-492%29&Search=Search	currently listed in phase 3 trials on website http://melinta.com/pipeline/baxdela/
40	Finafloxacin (BAY 35-3377)	MerLion Pharmaceuticals GmbH	2007-2014		Urinary Tract Infections; Acute Pyelonephritis	Phase 1, 2, and 3	Approved (2014)	https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=Finafloxacin&show_flds=Y	currently approved for acute otitis externa only in 2014, in trials for more indications (http://www.merlionpharma.com/?q=node/16)
41	Zabofloxacin (PB-101 AND DW-224a)	IASO Pharma Inc.	2010		Community Acquired Pneumonia	phase 2 listed	terminated (financial issues)	https://www.clinicaltrials.gov/ct2/results?term=Zabofloxacin+%28PB-101+AND+DW-224a%29&Search=Search	IASO (formally Pacific Beach BioSciences, Inc.)
42	Nemonoxacin (TG-873870)	TaiGen Biotechnology Company,	2008-present				yes	https://www.clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=Nemonoxacin+%28TG-873870%29&show_flds=Y	don't count...no us study sites
43	BC-7013	Nabriva Therapeutics AG	2007-present?		Gram-positive infections, including uncomplicated skin and skin structure infections (uSSIs).	phase 1	yes	not listed in clinicaltrials.gov but is listed on company website	http://www.nabriva.com/programs/development/
44	BC-3205	Nabriva Therapeutics AG					Terminated	nothing in clinicaltrials.gov	not listed on company's current pipeline
45	Lotilibcin (WAP-8294A (2))	aRigen	2011		MRSA	phase 1	Terminated	nothing in clinicaltrials.gov	being tested in Korea http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=235245
46	AZD5847	AstraZeneca	2009		TB	phase 1	Terminated	https://www.clinicaltrials.gov/ct2/results?term=AZD5847&Search=Search	https://www.astrazeneca.com/our-science/pipeline.html

47	GSK2251052 (AN3365)	GlaxoSmithKline/Anacor	2010-2012		Community-acquired Infection	Phase 1, Phase 2 terminated	Terminated	https://www.clinicaltrials.gov/ct2/results?term=GSK2251052&Search=Search	not listed in current pipeline http://investor.anacor.com/releasedetail.cfm?ReleaseID=711456 //placed under Anacor bc they had it first	
48	AZD9742	AstraZeneca	2009-2011		unknown	phase 1	Terminated	https://www.clinicaltrials.gov/ct2/results?term=AZD9742&Search=Search	https://www.astrazeneca.com/our-science/pipeline.html	
49	PNU-100480 (formerly PF-2341272)	Sequella Inc. (and Pfizer)	2009-present		drug-resistant and sensative TB	phase 1 and 2 (not started yet?)	terminated	https://www.clinicaltrials.gov/ct2/results?term=PNU-100480&Search=Search	not listed in company's (or Pfizers) current pipeline, however listed in http://www.newtbdrugs.org/project.php?id=135 //count under sequella	
50	AFN-1252 (now called Debio 1452)	Affinium (now Debiopharm)	2012-2014		MRSA		terminated	https://www.clinicaltrials.gov/ct2/results?term=Debio+1452&Search=Search	not listed in company's current pipeline	
51	FAB-001	FAB Pharmaceuticals	2009		MRSA		terminated	nothing in clinicaltrials.gov	not listed in company's current pipeline	
52	CG400549	CrystalGenomics, Inc.	2010-present				yes	https://www.clinicaltrials.gov/ct2/results?term=CG400549&Search=Search	Listed in current pipeline : http://www.crystalgenomics.com/en/clinical/antibiotic.html?ckattempt=1	
53	Biapenem	Rempex	2012-2013		bacterial infections				not counted bc not in us	not counted bc not in us
54	Amikacin inhalation (NKTR-061)	Bayer (partered with Nektar)	2009-present		adjunctive treatment for intubated and mechanically ventilated patients with Gram-negative pneumonia	Phase 1/2 complete, currently in phase 3	yes	https://clinicaltrials.gov/ct2/results?term=amikacin&Search=Search	http://www.nektar.com/product_pipeline/anti-infectives_nktr-061.html //Don't count--old antibiotic	
55	AN0128	Anacor Pharmaceuticals	2006-2011		acne	phase 1 complete, phase 2	Terminated	nothing in clinicaltrials.gov	http://investor.anacor.com/releasedetail.cfm?ReleaseID=285061// not currently listed in company's pipeline	
56	Anthrasil (anthrax immune globulin)	Cangene (later bought by Biomedical Advanced Research and Development Authority (BARDA))	2007-2015		inhulation anthrax	Phase 1/2/3 complete	Approved in 2015	https://clinicaltrials.gov/ct2/show/NCT00448253?term=Anthrasil&rank=1		
57	ARD-3100	Aradigm	2009-2010		cystic fibrosis-associated respiratory tract infections, non-cystic fibrosis bronchietctasis	phase 1 and 2	yes	https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=ARD-3100&show_flds=Y	still listed in company's current pipeline// http://www.aradigm.com/products_pipeline.html //does not meet criteria--liposomal ciprofloxacin--cipro=old drug	does not meet criteria--liposomal ciprofloxacin--cipro=old drug
58	ARD-3150	Aradigm				Phase 1/2 complete--phase 3 continues	yes	https://clinicaltrials.gov/ct2/results?term=ARD-3150&Search=Search	still listed in company's current pipeline// http://www.aradigm.com/products_pipeline.html does not meet criteria--liposomal ciprofloxacin--cipro=old drug	does not meet criteria--liposomal ciprofloxacin--cipro=old drug
59	Arikace	Insmed (Transave)			brochiectiasis, cystic fibrosis-associated respiratory tract infections, mycobacterial infections	phase 1 and 2		https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=Amikacin&show_flds=Y	does not meet criteria--old drug	does not meet criteria--old drug
60	BLI-489	Pfizer	2009		bacterial infections	phase 1	terminated	https://clinicaltrials.gov/ct2/results?term=bli-489&Search=Search	no longer listed in company's pipeline	
61	CB- 182,804	Cubist Pharmaceuticals LL	2010		gram-negative bacterial infections	phase 1	Terminated	nothing in clinicaltrials.gov	not listed in company's current pipeline	
62	DX-619	Daiichi Sankyo	2006		bacterial infections	phase 1	Terminated	nothing in clinicaltrials.gov	http://www.daiichisankyo.com/rd/pipeline/products/index.html //no longer listed in company's pipeline	
63	EDP-322	Enanta Pharmaceuticals	2009-2014		bacterial infections, methicillin-resistant Staphylococcus aureus infections	phase 1	Terminated	https://clinicaltrials.gov/ct2/results?term=edp-322&Search=Search	not currently listed in pipeline //http://www.enanta.com/research/enanta-pipeline/	
64	EDP-420	Enanta Pharmaceuticals	2005		community acquired pneumonia	phase 2	Terminated	https://clinicaltrials.gov/ct2/results?term=edp-420&Search=Search	not currently listed in pipeline //http://www.enanta.com/research/enanta-pipeline/	

65	Anthim (obiltoxaximab) (ETI-204)	Elusys Therapeutics	2009-present		prevention and treatment of anthrax	phase 1, 2 and 3 (ongoing)	yes	https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=ETI-204&show_flds=Y	(company website undergoing transitions) http://www.prnewswire.com/news-releases/elusys-completes-commercial-manufacturing-process-validation-for-anthrax-antitoxin-eti-204-254348861.html
66	GS 9310/11 (tobramycin/fosfomycin	Gilead Sciences (now developed by Curx Pharmaceuticals)	2008-present		brochiectiasis, cystic fibrosis-associated respiratory tract infections	phase 2	yes	not listed in clinicaltrials.gov but is listed on company website	http://curxpharma.com/fti.html
67	GSK-580416	GlaxoSmithKline	2007-2008		bacterial infections	phase 1	Terminated	https://clinicaltrials.gov/ct2/results?term=gsk580416&Search=Search	not currently listed in pipeline //http://gsk.com/media/850046/product-pipeline-november-2015.pdf
68	GSK-945238	GlaxoSmithKline	2007-2009		bacterial infections	phase 1	Terminated	https://clinicaltrials.gov/ct2/results?term=GSK-945237	not currently listed in pipeline //http://gsk.com/media/850046/product-pipeline-november-2015.pdf
69	IDP-107	Valeant Pharmaceuticals	2008-2010		acne	phase 2	Terminated	https://clinicaltrials.gov/ct2/results?term=idp-107&Search=Search	not currently listed in pipeline//http://ir.valeant.com/~/media/Files/V/Valeant-IR/reports-and-presentations/893698-final-ar-2015-v001-x21nf3.pdf
70	MK-1682	Merck	2006		bacterial infections	phase 1	Terminated	nothing in clinicaltrials.gov	not listed on company's current pipeline // http://www.biospace.com/News/merck-co-inc-ends-development-of-arena/31094
71	MK-3415A	Merck	2010-2012		Clostridium difficile-associated diarrhea	phase 2	Terminated	https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=MK-3415A&show_flds=Y	no longer listed in company's pipeline (http://www.fiercebiotech.com/story/one-win-one-loss-mercks-phili-double-header-c-diff/2015-09-21)
72	MP-601205	Mpex Pharmaceuticals (sold to Rempex then aquired by the Medicines Company)	2005-2011		cystic fibrosis-associated respiratory tract infections	phase 1	terminated	nothing in clinicaltrials.gov	not listed in company's current pipeline //http://www.themedicinescompany.com/pipeline
73	NB-003	NanoBio	2010		acne	phase 1	terminated	nothing in clinicaltrials.gov	not listed on company's current pipeline
74	NXL103	AstraZeneca (acquired from Novexel)	2008-2009		community-acquired infections, skin and soft tissue infections	phase 2	Terminated	https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=NXL103&show_flds=Y	not listed on company's current pipeline // https://www.astrazeneca.com/our-science/pipeline.html
75	Pagibaximab	Biosynexus and GSK	2008-2011		prevention of staphylococcal infections	phase 2 and 3	yes	https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=Pagibaximab&show_flds=Y	not listed in gsk or biosynexus websites but still active studies going on with a google search
76	SAR279356	Alopexx Pharmaceuticals and Sanofi-aventis	2011		bacterial infections	phase 2 listed	Terminated	https://clinicaltrials.gov/ct2/results?term=SAR279356&Search=Search	not listed in sanofi or alopexx pipelines // http://www.alopexx.com/alopexx-pipeline-2/ // http://en.sanofi.com/Images/40641_RD_Portfolio_PharmaVaccines_2016-02-09.pdf

77	ShigamAbs	Thallion Pharmaceuticals	2010		shinga-toxigenic Escherichia coli infections	phase 2 listed	yes	https://clinicaltrials.gov/ct2/results?term=Shigamabs&Search=Search	http://www.marketwired.com/press-release/thallion-and-lfb-terminate-shigamabs-collaboration-tsx-venture-tln-1758841.htm //not counted bc not in us
78	SPRC-AB01	Naryx Pharma	2007-2013		sinusitis	phase 2	Terminated	https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=SPRC-AB01&show_flds=Y	http://adisinsight.springer.com/drugs/800021543
79	talactoferrin alfa	Agennix	2008-2011		severe sepsis, nosocomial infections in infants	phase 2	Terminated	https://clinicaltrials.gov/ct2/results/displayOpt?flds=a&flds=b&flds=f&flds=c&flds=m&submit_fld_opt=on&term=talactoferrin+alfa&show_flds=Y	http://adisinsight.springer.com/drugs/800004715
80	Ushercell (cellulose sulfate)	Polydex Pharmaceuticals and CONRAD	2005		bacterial vaginosis	phase 2	Terminated	https://clinicaltrials.gov/ct2/results?term=cellulose+sulfate&Search=Search	tested in 1 location within the US // http://adisinsight.springer.com/drugs/800012049
81	Valortim (anthrax mAb) (mdx-1303)	PharmAthene	2009-present		prevention and treatment of anthrax	phase 1,2,3	yes	https://clinicaltrials.gov/ct2/results?term=valortim&Search=Search	http://www.pharmathene.com/welcome
82	Xifaxan (rifaximin)	Salix Pharmaceuticals	2010		Clostridium Infections	phase 3	Approved (2010)	https://clinicaltrials.gov/ct2/results?term=rifaximin&Search=Search	http://www.salix.com/products/xifaxan550
83	AZD5099	AstraZeneca	2011		bacterial infections	phase 1	Terminated	https://clinicaltrials.gov/ct2/results?term=AZD5099&Search=Search	
84	LFF571	Novartis	2010-		C.difficile associated diarrhea	phase 1 and 2	Terminated	https://clinicaltrials.gov/ct2/show/NCT01232595	

Key:
No longer in Trials
Approved by FDA
Still in Trials
not counted bc no trials in US
Old antibiotic--not counted

APPENDIX B: 2012-2015 DATA ON ANTIBIOTIC R&D

1	Drug Name	Company	Potential Activity Against Gram-Negative ESKAPE Pathogens?	QIDP Designation ?	Expected Activity against a CDC urgent pathogen?	Potential Indications	Development Phase	Still in Development?	Clinicaltrials.gov	notes
2	Oritavancin (orbactiv)	The Medicines Company	no	yes	no	acute bacterial skin and skin structure infections	NDA submitted and approved Aug. 6,2014	**approved**--acute bacterial skin and skin structure infections caused by Gram-Positive bacteria, including MRSA		will go in 2010 bc it was being developed then
3	Dalbavancin (Dalvance)	Durata Therapeutics	no	yes	no	acute bacterial skin and skin structure infections	NDA submitted and approved May 23, 2014	**approved**--acute bacterial skin and skin structure infections--*other potential indications: community aquired bacterial pneumonia*		
4	Tedizolid	Cubist Pharmacueticals	no	yes		acute bacterial skin and skin structure infections, hospital aquired bacterial pneumonia/ventilator aquired bacterial pneumonia	NDA Submitted and approved June 20, 2014	**approved**--acute bacterial skin and skin structure infections--*other potential indications hospital aquired bacterial pneumonia/ventilator aquired bacterial pneumonia*		
5	ACHN-975	Achaogen	yes			bacterial infections	Phase 1	terminated	https://clinicaltrials.gov/ct2/show/study/NCT01597947	
6	AFN-1720///Debio-1450	Affinium Pharmaceuticals///Debiopharm Group				acute bacterial skin and skin structure infections (staphylococcal-specific)	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/show/NCT01519492 **or** https://clinicaltrials.gov/ct2/results?term=Debio+1450&Search=Search for DEBIO	this is AFN-12520000 No more information on AFN-1720. It is on the company website: and changed to DEBIO-1450 recruiting for Phase 2, Debiopharm International SA
7	AZD-0914	AstraZeneca	yes	yes		gonococcal infections (uncomplicated gonorrhea)	Phase 1 complete/ Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=AZD-0914&Search=Search	
8	Aztreonam+Avbactam (ATN	AstraZeneca/ Forest Laboratories	yes		yes	bacterial infections	Phase 1	yes	https://clinicaltrials.gov/ct2/results?term=Aztreonam%2BAvibactam	Avibactam is a new beta-lactamase inhibitor being tested in conjunction with 3 individual antibiotics--all 3 are listed separately. **No US study sites?**
9	BAL30072	Basilea Pharmaceutica	yes		yes	multidrug-resistant gram-negative infections	phase 1	yes	no study listed	http://www.basilea.com/Portfolio/BAL30072/ //count in 2010

10	Carbavance (RPX709+mero	Rempex Pharmaceuticals/the Medicines Company	yes	yes	yes	complicated urinary tract infections, complicated intra-abdominal infections, hospital aquired pneumonia, febrile neutropenia, bacteremia, acute pyelonephritis (some indications specifically target infections caused by carbapenem-resistant Enterobacteriacae)	Phase 1 completed, Phase 2 completed?, Phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Carbavance&Search=Search	advanced development--potential to treat gram-negative bacilli
11	CRS-3123	Crestone, Inc.	no		yes	C.difficile infection	phase 1	yes	https://clinicaltrials.gov/ct2/results?term=CRS-3123&Search=Search	
12	EDP-788	Enanta Pharmaceuticals				bacterial infections	Phase 1	terminated	https://clinicaltrials.gov/ct2/results?term=EDP-788&Search=Search	
13	S-649266 (GSK-2696266)	now developed by Shionogi GlaxoSmithKline (partnered product)				bacterial infections	Phase 1	terminated	no study listed	http://www.glaxosmithkline.de/docs-pdf/forschung/GSK-product-pipeline-Feb-2013.pdf // count under Shinogi
14	LCB01-0371	LegoChem Biosciences (S.Korea)	no		no	bacterial infections	Phase 1	yes	https://clinicaltrials.gov/ct2/results?term=LCB01-0371&Search=Search	no US study sites
15	MRX-I	MicuRx Pharmaceuticals	no		no	acute bacterial skin and skin structure infections	Phase 1 completed, Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/show/NCT02269319?term=MRX-I&rank=1	
16	POL7070 (RG7929)	Polyphor (Roche licensee)	yes		no	ventilator associated bacterial pneumonia (caused by Pseudonomnas aeruginosa), lower repiratory infections, bronchiectasis	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=POL7080&Search=Search	no US study sites
17	TD-1607	Theravance, Inc.	no		no		phase 1	yes	https://clinicaltrials.gov/ct2/results?term=TD-1607&Search=Search	completed phase 1 but no movement since 2014? Still listed on website, so saying it is still in development http://www.theravance.com/programs
18	WCK 2349	Wockhardt	no	yes	no	bacterial infections	Phase 1	yes	https://clinicaltrials.gov/ct2/results?term=WCK+2349&Search=Search	
19	WCK 771	Wockhardt	no	yes	no	bacterial infections	Phase 1	yes?	https://clinicaltrials.gov/ct2/show/NCT01875939?term=WCK+771&rank=1	one phase 1 trial completed, but no movement since 2013
20	AFN-1252///Debio 1452	Affinium Pharmaceuticals///Debiopharm Group	no	yes	no	acute bacterial skin and skin structure infections (staphylococcal-specific)	Phase 1 (completed), Phase 2 ongoing	yes?	https://clinicaltrials.gov/ct2/show/NCT01519492?term=AFN-1252&rank=1	check bc it is not listed in their current (active) pipeline. https://www.debiopharm.com/medias/press-release/item/3445-preclinical-pharmacokinetics-and-efficacy-of-debio-1450-previously-afn-1720-a-prodrug-of-the-staphylococcocal-specific-antibiotic-debio-1452-previously-afn-1252.html
21	Avarofloxacin (JNJ-3272946	Furiex Pharmaceuticals-->Actavis-->Allergan plc	no		no	community-aquired bacterial pneumonia, acute bacterial skin structure infections	Phase 1 (completed), Phase 2 ongoing	yes	can't find this in clinicaltrials.gov	counted for 2010
22	Brilacidin	Cellceutix Corp	no		no	acute bacterial skin and skin structure infections	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/show/record/NCT02052388?term=Brilacidin&rank=2	also being tested to treat throat cancer

23	Ceftaroline+Avibactam	AstraZeneca/ Forest Laboratories	yes		yes	complicated urinary tract infections	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Ceftaroline%2BAvibactam&Search=Search	
24	CG-400549	CrystalGenomics, Inc.	no		no	acute bacterial skin and skin structure infections, osteomyelitis	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=CG-400549&Search=Search	on other spreadsheet
25	Finafloxacin	MerLion Pharmaceuticals	yes		possibly	complicated urinary tract infections, acute pyelonephritis (kidney infection), complicated intra-abdominal infections, acute bacterial skin and skin structure infections	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Finafloxacin&pg=1	col e explaination--look to Pew Dec. 2015
26	GSK-1322322	GlaxoSmithKline				acute bacterial skin and skin structure infections	Terminated in Phase 2	terminated	https://clinicaltrials.gov/ct2/results?term=GSK-1322322&Search=Search	not in pipeline after dec 2015, counted bc in pipeline at first of year in 2015
27	GSK-2140944 (Gepotidacin)	GlaxoSmithKline	no		yes	respiratory tract infections, acute bacterial skin and skin structure infections, uncomplicated urogenital gononorrhea	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=GSK-2140944&pg=1	
28	Lefamulin (BC-3781)	Nabriva Therapeutics	no		no	acute bacterial skin and skin structure infections, community-aquired bacterial pneumonia, hospital-aquired bacterial pneumonia/ventilator associated bacterial	phase 1 and 2 (completed), phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=BC-3781&Search=Search	
29	LFF571	Novartis				C.difficile associated diarrhea	phase 1 completed/ phase 2 completed	terminated	https://clinicaltrials.gov/ct2/show/NCT01232595?term=LFF571&rank=1	2010
30	MK-7655+ (imipenem/cilast	Merk & Co.	yes	yes	yes	complicated urinary tract infections, acute pyelonephritis (kidney infection), complicated intra-abdominal infections,hospital-aquired pneumonia/ventilator-associated bacterial pneumonia	phase 1 and 2 (completed), phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/show/NCT02452047	no US study sites
31	Nemonoxacin	TaiGen Biotechnology	no	yes	no	community-aquired bacterial pneumonia, acute bacterial skin structure infections, diabetic foot infection	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Nemonoxacin&pg=1	study sites in China and Taiwan only
32	Omadacycline	Paratek Pharmaceuticals	yes	yes	possibly	community-aquired bacterial pneumonia, acute bacterial skin structure infections, complicated urinary tract infections	Phase 1 (completed), Phase 2 (terminated?), Phase 3 (on-going)	yes	https://clinicaltrials.gov/ct2/results?term=Omadacycline&Search=Search	
33	Radezolid	Melinta Pharmaceuticals	no	yes	no	acute bacterial skin and skin structure infections, community-aquired bacterial pneumonia	Phase 1 (completed), Phase 2 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Radezolid&Search=Search	study results available for phase 2
34	Ramoplanin	Nanotherapeutics	no		yes	C.difficile relapse prevention	Phase 1 (completed), Phase 2 ongoing	yes	http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm257024.htm	not listed in clinicaltrials.gov but approved by FDA in 2011
35	Taksta (Fusidic acid)	Cempra Pharmaceuticals	no		no	prosthetic joint infections, acute bacterial skin and skin structure infections	Phase 1 (completed), Phase 2 (completed), Phase 3 (on-going)	yes	https://clinicaltrials.gov/ct2/results?term=Fusidic+acid&Search=Search	http://www.cempra.com/products/taksta-cem-102/ (CEM-102) trade name
36	TD-1792	Theravance, Inc.				complicated skin and soft tissues infections (cSSSI), caused by gram-positive bacteria	phase 1 and 2 (completed), phase 3 terminated	yes	http://www.theravance.com/bacterial	currently listed in company's pipeline//mentioned that they partnerned with R-PHARM but no current info on their website // count in 2010

37	Zabofloxacin	Dong Wha Pharmaceutical	no		no	community-aquired bacterial pneumonia	Phase 1 completed, Phase 2 ongoing?	terminated	https://clinicaltrials.gov/ct2/show/NCT01081964?term=Zabofloxacin&rank=1	terminated for financial reasons...look into this
38	Cadazolid	Actelion Pharmaceuticals	no	yes	yes	C.difficile associated diarrhea	phase 1 and 2 (completed), phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Cadazolid&Search=Search	2010-present
39	Ceftazidime+Avibactam (CA	AstraZeneca/ Forest Laboratories	yes	yes	yes	complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis *other possible indications: hospital-aquired bacterial pneumonia/ventilator-associated bacterial pneumonia, bactermia*	Phase 1,2,3 completed	**approved**--complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis	https://clinicaltrials.gov/ct2/results?term=Ceftazidime%2BAvibactam+%28CAZ-AVI%29&Search=Search	
40	Ceftolozane+Tazobactam (Z	Cubist Pharmacueticals	yes	yes	no	approved for: complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infections)//*other potential indications: hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, bactermia*	Phase 1,2,3 completed	**approved for:** complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infections)	https://clinicaltrials.gov/ct2/results?term=Ceftolozane%2BTazobactam&Search=Search	
41	Delafloxacin	Melinta Pharmaceuticals	possibly	yes	possibly	acute bacterial skin and skin structure infections, hospital-aquired bacterial pneumonia, complicated urinary tract infections, complicated intra-abdominal infections	phase 1 and 2 (completed), phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Delafloxacin&Search=Search	
42	Eravacycline	Tetraphase Pharmaceuticals	yes	yes	yes	complicated intra-abdominal infections, complicated urninary tract infections, hospital-acquired bacterial pneumonia	phase 1 and 2 (completed), phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Eravacycline&Search=Search	counted for 2010
43	Plazomicin	Achaogen	yes		yes	complicated urniary tract infections, catheter-related bloodstream infections, hospital-acquired pneumonia/ventilator-associated pneumonia, complicated intra-abdominal infections, acute pyelonephritis (kidney infections) (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae)	Phase 1 (completed), Phase 2 (completed), Phase 3 (on-going)	yes	https://clinicaltrials.gov/ct2/results?term=Plazomicin&Search=Search	
44	Solithromycin	Cempra Pharmaceuticals	no	yes	yes	community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhea, urethritis	phase 1 and 2 (completed), phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Solithromycin&Search=Search	
45	Surotomycin (CB-183,315)	Cubist Pharmacueticals	no	yes	yes	C.difficile associated diarrhea	phase 1 and 2 (completed), phase 3 ongoing	yes	https://clinicaltrials.gov/ct2/results?term=Surotomycin&Search=Search	
46	Ceftobiprole	Basilea Pharmaceutica	yes			Hospital-aquired bacterial pneumonia, community-acquired bacterial pneumonia	phase 1 and 2 (completed), phase 3 (terminated)	terminated	https://clinicaltrials.gov/ct2/results?term=Ceftobiprole&Search=Search	**has been approved in Europe for hospital and community-acquired bacterial pneumonia. **in june 2014, Basilia announced it would no pursue this med use in USA further until they find a partner**
47	OP0595 (RG 6080)	Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc. (Roche licensee)	possibly		possibly	bacterial infections	phase 1	yes	https://clinicaltrials.gov/ct2/show/NCT02134834?term=OP0595&rank=1	**no US study sites**
48	XF-73	Destiny Pharma	2012-present			post-surgical Staphylococcal infection	phase 1 (within the US)	yes	https://www.clinicaltrials.gov/ct2/results?term=xf-73&Search=Search	2012-present :phase 1 and 2 completed in UK...currently in phase 1in US http://www.destinypharma.com/xf73.shtml

APPENDIX C: ACUMULATIVE DATA FOR ANTIBIOTICS IN CLINICAL TRIALS IN 2010 AND 2015

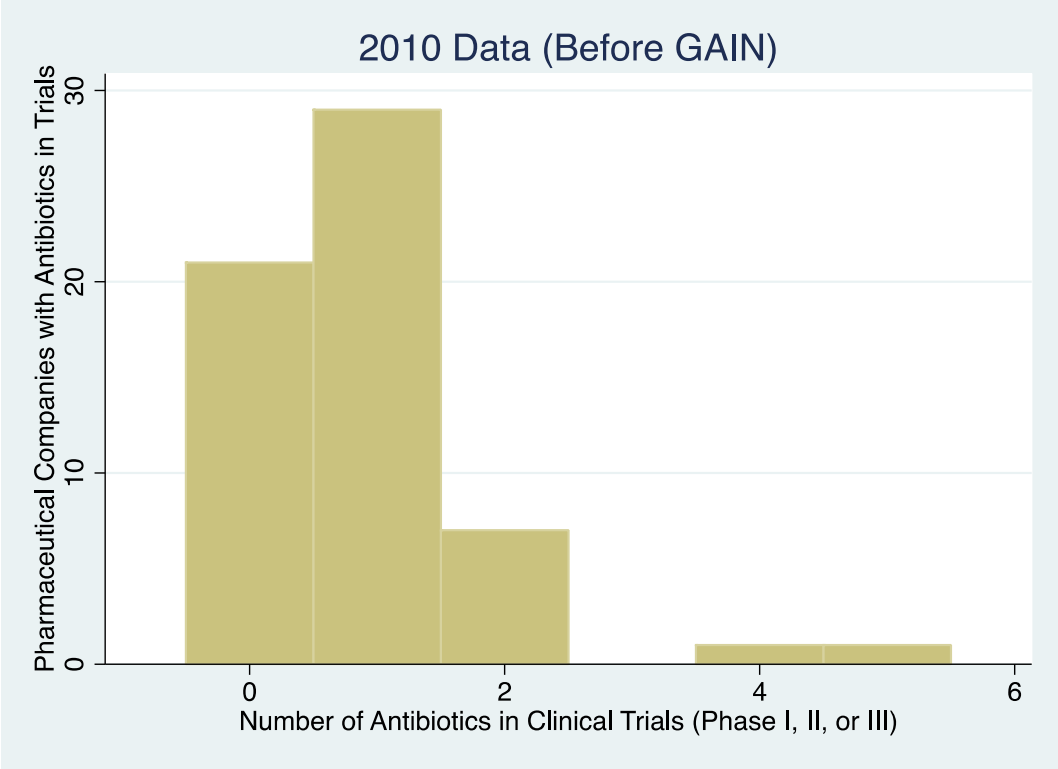
1	Company	X	(y1) YR:2010	(y2) YR:2015	Difference
2	Achaogen	1	1	1	0
3	Actelion Pharmaceuticals	2	1	1	0
4	Advanced Life Sciences Inc	3	1	0	-1
5	Affinium (now Debiopharm)	4	0	2	2
6	Agennix	5	1	0	-1
7	Alopexx Pharmaceuticals and Sanofi-aventis	6	0	0	0
8	Anacor Pharmaceuticals	7	2	0	-2
9	Aradigm	8	0	0	0
10	aRigen	9	0	0	0
11	Arpida AG and currently Motif BioSciences	10	1	0	-1
12	AstraZeneca	11	1	2	1
13	Basilea Pharmaceutica	12	0	2	2
14	Bausch & Lomb	13	0	0	0
15	Bayer (partered with Nektar)	14	0	0	0
16	Biomedical Advanced Research and Development Authority	15	1	0	-1
17	Cellceutix Corp	16	0	1	1
18	Cempra Pharmaceuticals	17	0	2	2
19	Crestone, Inc.	18	0	1	1
20	CrystalGenomics, Inc.	19	1	0	-1
21	Daiichi Sankyo	20	1	0	-1
22	Destiny Pharma	21	0	1	1
23	Dong Wha Pharmaceutical	22	0	1	1
24	Durata Therapeutics	23	0	1	1
25	Elusys Therapeutics	24	1	0	-1
26	Enanta Pharmaceuticals	25	1	0	0
27	FAB Pharmaceuticals	26	0	0	0
28	Allergen	27	2	4	2
29	CURx Pharmaceuticals	28	1	0	-1
30	GlaxoSmithKline	29	2	2	0

31	Global Alliance for TB Drug Development	30	1	0	-1
32	IASO Pharma Inc.	31	1	0	-1
33	Janssen Pharmaceutica	32	1	0	-1
34	Johnson&Johnson	33	0	0	0
35	Melinta Pharmaceuticals	34	1	2	1
36	Merck & Co.	35	5	2	-3
37	MerLion Pharmaceuticals	36	1	0	-1
38	MicuRx Pharmaceuticals	37	0	1	1
39	Nabriva Therapeutics	38	2	0	-2
40	NanoBio	39	1	0	-1
41	Nanotherapeutics	40	1	0	-1
42	Naryx Pharma	41	1	0	-1
43	NovaBay Pharmaceuticals, Inc.	42	1	0	-1
44	Novartis	43	1	0	-1
45	Optimer Pharmaceuticals	44	0	0	0
46	Paratek Pharmaceuticals	45	0	2	2
47	Pfizer	46	4	0	-4
48	PharmAthene	47	1	0	-1
49	Polydex Pharmaceuticals	48	0	0	0
50	Polymedex	49	1	0	-1
51	Salix Pharmaceuticals	50	1	0	-1
52	Sequella Inc.	51	2	0	-2
53	Shionogi	52	0	1	1
54	Tetraphase Pharmaceuticals	53	1	0	-1
55	The Medicines Company	54	2	1	-1
56	Theravance Inc.	55	2	2	0
57	Insmed	56	1	0	-1
58	Bristol-Myers Squibb	57	1	0	-1
59	Valeant Pharmaceuticals	58	1	0	-1
60	Wockhardt	59	0	2	2
61			**52**	**34**	

APPENDIX D: STATA 14.0 OUTPUT

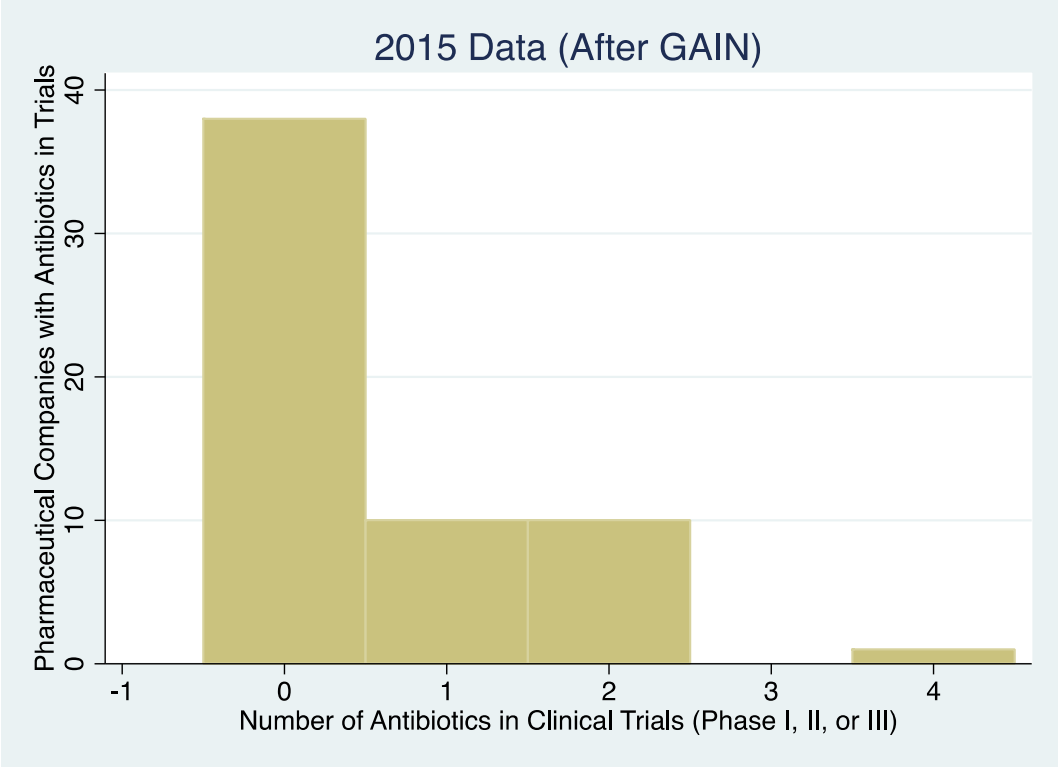
1. I felt a paired t-test would be an appropriate approach when comparing the means of two time points of pairs. The pharmaceutical industry (my "test subjects") makes a small pool (n), which gets significantly smaller when it is narrowed to those creating antibiotics. I wanted a test that I could comfortably interpret and keep control.

2. After I chose a statistical test that fit the data, I began by plotting the data in several ways, through a histogram, box plot, and examining the frequencies. On each of these, there were outliers that needed further investigation to determine if they were influencing the data so much so that it could cause yield false results.

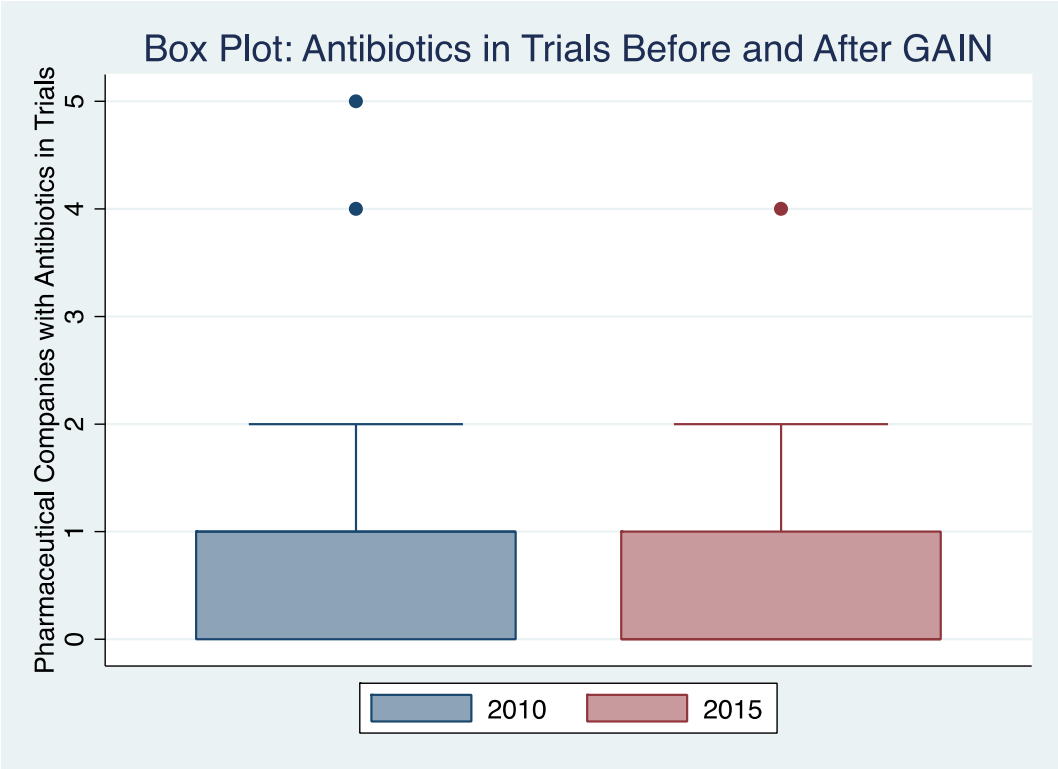


COMMAND:

```
histogram var2, discrete frequency ytitle(Pharmaceutical Companies with Antibiotics in Trials) xtitle(Number of Antibiotics in Clinical Trials (Phase I, II, or III)) title(2010 Data (Before GAIN))
```




```
COMMAND:
histogram var3, discrete frequency ytitle(Pharmaceutical Companies with Antibiotics in Trials) xtitle(Number of Antibiotics in Clinical Trials (Phase I, II, or III)) title(2015 Data (After GAIN))
```



COMMAND:
graph box var2 var3, ytitle(Pharmaceutical Companies with Antibiotics in Trials) title(Box Plot: Antibiotics in Trials Before and After GAIN)

I looked at *studentized residuals* to identify outliers. I used the **predict** command with the **rstudent** to generate the studentized residuals. I named the residuals **r**.

```
. predict r, rstudent
(1 missing value generated)

. stem r

Stem-and-leaf plot for r (Studentized residuals)

r rounded to nearest multiple of .01
plot in units of .01

 -1** | 64
 -1** | 39,35,17,11,10
 -0** | 95,93,90,89,88,87,83,83,80,77,66,65,59,58,55
 -0** | 21,20,18,14,10,09,08,05
  0** | 01,02,03,05,06,11,16,18,19,22,25,27,28,34,35,41,49,49
  0** | 51,57,60,71,83,99
  1** | 00,09,17
  1** | 67
  2** |
  2** |
  3** |
  3** | 56
  4** |
  4** |
  5** | 24
```

*3.56, and 5.24 are most concerning residuals based on the stem and leaf plot (highlighted)

While the stem and leaf plot shows some potential outliers, it does not show which **company** (which observations) are potential outliers. I sorted the data on the residuals to show the 10 biggest and 10 smallest residuals. I referred to my master excel sheet to see which companies corresponded with the observations that stood out the most.

```
. sort r

. list y1 y2 x r in 1/10

     +--------------------------+
     | y1   y2    x           r |
     |--------------------------|
  1. |  0    2   59   -1.642414 |
  2. |  0    2   45    -1.38556 |
  3. |  0    1   52   -1.351735 |
  4. |  0    0   48    -1.16521 |
  5. |  0    1   37   -1.108187 |
     |--------------------------|
  6. |  0    0   44   -1.100971 |
  7. |  0    2   17   -.9508805 |
  8. |  0    0   33    -.932653 |
  9. |  0    1   23   -.9009565 |
 10. |  0    1   22   -.8866526 |
     +--------------------------+

. list y1 y2 x r in -10/l

     +--------------------------+
     | y1   y2    x           r |
     |--------------------------|
 51. |  2    2   55   .7147288 |
 52. |  2    1   54   .8283903 |
 53. |  2    0   51   .9866428 |
 54. |  2    4   27     1.0006 |
 55. |  2    2   29   1.087434 |
     |--------------------------|
 56. |  2    0   38   1.168805 |
 57. |  2    0    7   1.666753 |
 58. |  4    0   46   3.560885 |→Pfizer
 59. |  5    2   35   5.243319 |→Merck&Co.
 60. |  .    .    .          . |
     +--------------------------+
```

I looked further into companies that had a studentized residual that exceed +2 or -2. Residuals that exceeded +2.5 or -2.5 were more concerning and those that that exceed +3 or -3 are most concerning. These results show company 46 (Pfizer) with a studentized residual of 3.56 and company 35 (Merck&Co.) with a studentized residual of 5.24, are most concerning.

I read about another way to get similar output through a user-created ado file, called **hilo**. I downloaded it and ran it on the data as well.

```
. hilo r x
10 lowest and highest observations on r

  +----------------+
  |         r    x |
  |----------------|
  | -1.642414   59 |
  |  -1.38556   45 |
  | -1.351735   52 |
  |  -1.16521   48 |
  | -1.108187   37 |
  |----------------|
  | -1.100971   44 |
  | -.9508805   17 |
  |  -.932653   33 |
  | -.9009565   23 |
  | -.8866526   22 |
  +----------------+

  +---------------+
  |        r    x |
  |---------------|
  | .5967201    3 |
  | .7147288   55 |
  | .8283903   54 |
  | .9866428   51 |
  |   1.0006   27 |
  |---------------|
  | 1.087434   29 |
  | 1.168805   38 |
  | 1.666753    7 |
  | 3.560885   46 |→Pfizer
  | 5.243319   35 |→Merck&Co.
  +---------------+
```

Again, company 46 (Pfizer) and 35 (Merck&Co) are concerning.

```
. list r x y1 y2 if abs(r) > 2

     +-------------------------+
     |        r    x   y1   y2 |
     |-------------------------|
 58. | 3.560885   46    4    0 |
 59. | 5.243319   35    5    2 |
 60. |        .    .    .    . |
     +-------------------------+
```

Above, I wanted to show all variables where the studentized residual exceeds +2 or -2, i.e., where the absolute value of the residual exceeds 2. The data continues to be concerning for the potential outliers identified, Pfizer and Merck&Co. Looking carefully at these 2 observations, I went through the data again to ensure that there was not a data-entry error. I did not find any.

Next, I looked at the leverages to identify observations that could have a potentially large influence.

```
. predict lev, leverage
(1 missing value generated)
. stem lev
Stem-and-leaf plot for lev (Leverage)
lev rounded to nearest multiple of .001
plot in units of .001

0** | 23,24,24,24,24,24,24,25,25,25,26,26,27,27,28,28,29,30,31,31, ... (26)
0** | 40,41,41,43,44,46,48,50,51,52,53,55,56,57
0** | 60,61,61,63,63,63,64,65,68,68,68,69,76,78,78
0** | 95
1** | 03,17
1** |
1** |
1** |
1** |
2** |
2** |
2** |
2** | 70
```

```
. lvr2plot, mlabel(x)
```

Below are the 5 options on the **hilo** command to show just the 5 largest observations—again, we see that Allergen (lev=.270) has a high leverage, followed by Woodhardt (lev= .117).

```
. hilo lev x, show(5) high
5 highest observations on lev

  +---------------+
  |      lev    x |
  |---------------|
  | .0776795   11 |
  | .0945704    4 |
  |   .10334   55 |
  | .1169525   59 |→Woodhardt
  |  .269714   27 |→Allergen
  +---------------+
```

Based on these results, Pfizer and Merck&Co. did have high leverage—however, Allergen had the largest leverage. Because I was interested, I also ran the 10 highest observations, just to be sure the Merck&Co. and Pfizer did not have high leverage that I was missing.

```
. hilo lev x, show(10) high
10 highest observations on lev

  +---------------+
  |      lev    x |
  |---------------|
  |  .067784   17 |
  | .0682544    1 |
  | .0694911    3 |
  | .0757365   12 |
  | .0775336   45 |
  |---------------|
  | .0776795   11 |
  | .0945704    4 |
  |   .10334   55 |→Theravance Inc.
  | .1169525   59 |→Woodhardt
  |  .269714   27 |→Allergen
  +---------------+
```

*Again, Pfizer and Merck&Co. did not come up when I looked at the highest 10 leverage points.

Generally, a point with leverage greater than **(2k+2)/n** should be fully examined. I examine the companies with the highest leverage a bit further.

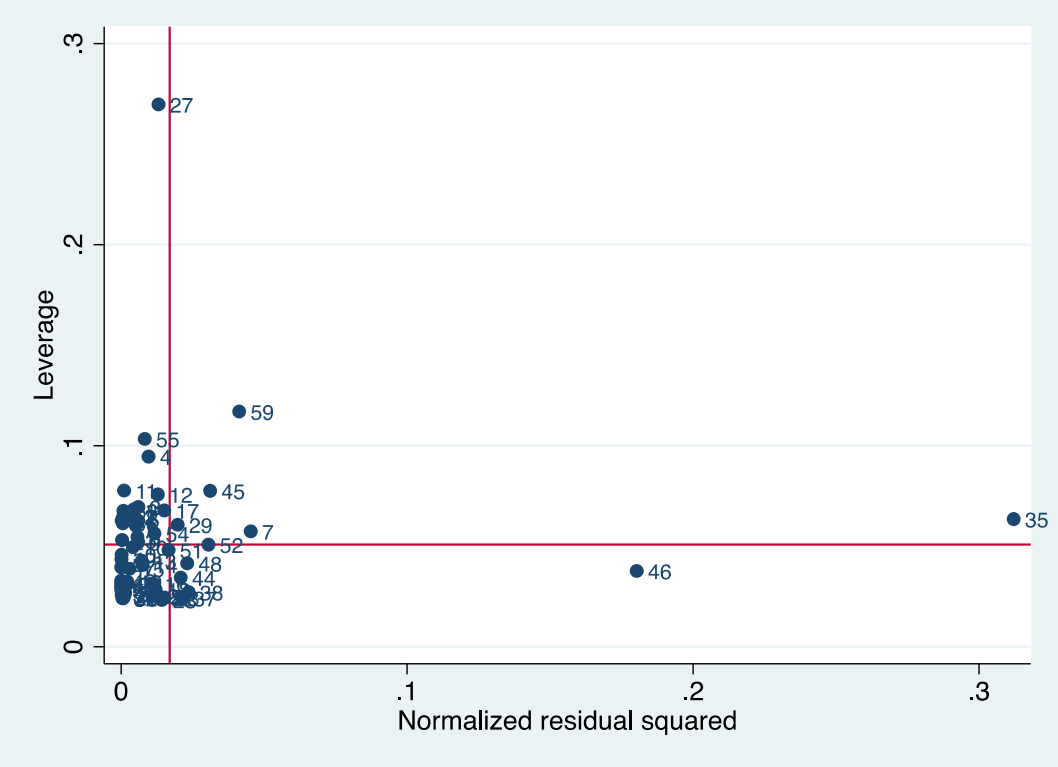
```
* k is the number of predictors and n is the number of observations.
. display (2*2+2)/58
.10344828
. list y1 y2 x lev if lev >.103

     +-------------------------+
     | y1   y2    x        lev |
     |-------------------------|
  1. |  0    2   59   .1169525 |→Wockhardt
 51. |  2    2   55     .10334 |→Theravance Inc.
 54. |  2    4   27    .269714 |→Allergen
 60. |  .    .    .          . |
     +-------------------------+
```

Pfizer and Merck&Co.have large residuals but not large leverage. Conversely, Allergen (along with Theravance and Wockhardt) have small residuals but larger leverage.

Neither have large residuals and large leverage—a combination of the two offers a hint at which points are most influential.

I made a plot that shows the leverage by the residual squared and looked for observations that are jointly high on both of these measures.
I did this by using the **lvr2plot** command (for a leverage versus residual squared plot). Using residual squared instead of residual itself, means that the graph is restricted to the first quadrant and the relative positions of data points are preserved. This is a way of checking potential influential observations and outliers at the same time.



I used a **Cook's D** to combine the information on the residual and leverage.
The lowest value that Cook's D can assume is zero, and the higher the Cook's D is, the more influential the point. The conventional cut-off point is **4/n**.

```
. predict d1, cooksd
(1 missing value generated)

. clist x y1 y2 d1 if d1>4/58, noobs

      x        y1        y2         d1
     27         2         4   .1232539   →Allergen
     35         5         2   .4216602   →Merck&Co.
     46         4         0   .1369645   →Pfizer
     59         0         2   .1155847   →Woodhardt
      .         .         .          .
```

Merk&Co. has consistently been a concern throughout the analysis of the data. I decided to run a paired t-test both with and without them.

Paired T-Test With Merck&Co.

```
. ttest y1== y2

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
      y1 |      59    .8813559    .1234719     .948406       .6342    1.128512
      y2 |      59    .5762712     .116453    .8944925    .3431652    .8093772
---------+--------------------------------------------------------------------
    diff |      59    .3050847    .1626315    1.249196   -.0204575     .630627
------------------------------------------------------------------------------
     mean(diff) = mean(y1 - y2)                                      t =   1.8759
 Ho: mean(diff) = 0                               degrees of freedom =       58

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9671         Pr(|T| > |t|) = 0.0657          Pr(T > t) = 0.0329
```

Paired T-Test Without Merck&Co.

```
. ttest y1_01== y2_01

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   y1_01 |      58    .8103448    .1027654    .7826383    .6045606    1.016129
   y2_01 |      58    .5517241    .1158164    .8820314    .3198058    .7836425
---------+--------------------------------------------------------------------
    diff |      58    .2586207    .1585635    1.207583   -.0588972    .5761386
------------------------------------------------------------------------------
     mean(diff) = mean(y1_01 - y2_01)                                t =   1.6310
 Ho: mean(diff) = 0                               degrees of freedom =       57

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9458         Pr(|T| > |t|) = 0.1084          Pr(T > t) = 0.0542
```

Paired T-Test without Merck and Pfizer

```
. ttest y1_02== y2_02

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   y1_02 |      57     .754386    .0877193    .6622662    .5786631    .9301088
   y2_02 |      57    .5614035     .117454    .8867586    .3261148    .7966922
---------+--------------------------------------------------------------------
    diff |      57    .1929825    .1468948    1.109031   -.1012831     .487248
------------------------------------------------------------------------------
     mean(diff) = mean(y1_02 - y2_02)                                t =   1.3137
 Ho: mean(diff) = 0                               degrees of freedom =       56

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
```

```
 Pr(T < t) = 0.9029         Pr(|T| > |t|) = 0.1943          Pr(T > t) = 0.0971
```

Paired T-Test without Merck, Pfizer, and Allergen

```
. ttest y1_03== y2_03

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   y1_03 |      56    .7321429    .0863813    .6464187    .5590308    .9052549
   y2_03 |      56          .5    .1019294    .7627701    .2957288    .7042712
---------+--------------------------------------------------------------------
    diff |      56    .2321429    .1441299    1.078569   -.0566999    .5209856
------------------------------------------------------------------------------
     mean(diff) = mean(y1_03 - y2_03)                              t =   1.6107
 Ho: mean(diff) = 0                              degrees of freedom =       55

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9435         Pr(|T| > |t|) = 0.1130          Pr(T > t) = 0.0565
```

Conclusions

Research Question: Has the GAIN Act provided enough incentives for Pharmaceutical Company's to place more experimental antibiotic treatments into clinical trials? Given the nature of antibiotics market (an anomaly of regular market princples), I suspect that there has not been much change in the amount of antibiotics in clinical trials since this law was enacted.

Null Hypothesis– H_0: $\mu 1 = \mu 2$

Alternative Hypothesis– H_a: $\mu 1 \neq \mu 2$

Interpretation of Results

The p-value is above O.05 in all three t-tests (all data, data without Merck&Co, and data without Pfizer and Merck&Co.). Therefore, I cannot reject the null hypothesis. The data indicates that there is no statistically significant difference in antibiotics in clinical trials after the GAIN act.

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