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The Relationship Between Patient Education and Adherence to Antibiotic Regimens: Exploring Profiles of Adherent Groups

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THE RELATIONSHIP BETWEEN PATIENT EDUCATION AND ADHERENCE TO ANTIBIOTIC REGIMENS: EXPLORING PROFILES OF ADHERENT GROUPS

by

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ABSTRACT

Objective:

Currently, there does not exist a cohesive and predictive set of criteria that can be used to identify patients that are at risk of being non-adherent to antibiotic regimens. In this study, we sought to answer the question of whether patients' knowledge of the scientific background of antibiotic resistance is related to their likelihood to adhere to antibiotic regimens. Additionally, we explored other facets of the profiles of adherent and non-adherent subjects.

Methods:

All responses were collected via questionnaire. Subjects were split into two groups (adherent and non-adherent) based upon four patient-behavior questions. These two groups of subjects were compared in a variety of ways to test for significant differences in categories such as science knowledge, age, and self-reported understanding of the problem of antibiotic resistance.

Results:

It was determined that the adherent group of subjects had significantly higher science scores (mean=5.46, n=384) than the non-adherent subjects (mean=4.99, n=460); $t(842)= -2.73$, $p=0.0064$. Subjects majoring in STEM were more likely to be adherent than biology or non-STEM majors. There were no differences in adherence or science scores across age groups. About 26% of subjects had not previously heard of the problem of antibiotic resistance.

Discussion:

Increasing patient education on the topic of antibiotic resistance could increase patient adherence, which could in turn lead to a reduction in the rate at which bacteria develop resistance. Initiatives to educate patients and health care professionals have the potential to increase understanding and improve rates of adherence.

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CHAPTER 1: INTRODUCTION

Objective

Currently, there does not exist a cohesive and predictive set of criteria that can be used to identify patients that are at risk of being non-adherent to antibiotic regimens. Non-adherence to prescribed regimens of antibiotic treatment is a problem that has been demonstrated to have potentially life threatening downstream effects on individual patients and the health of the community at large. In this study, we sought to answer the question of how patients' knowledge of the scientific background of antibiotic resistance is related to their likelihood to adhere to antibiotic regimens. In addition to collecting information on the respondents' (i) likelihood to adhere and (ii) scientific knowledge, we collected responses to a variety of questions related to antibiotics and demographics in order to enhance the understanding of differences between the profiles of adherent and non-adherent patients.

The golden era of medicine

The term "antimicrobial" refers to any compound whose action kills or stops the growth of microorganisms. For the purposes of this study, the term "antibiotics" will be used to refer to drug treatments that are prescribed by doctors with the intent of killing or inhibiting bacteria (and not viruses or other parasites) that are causing a disease state in patients.[1]

Antibiotics have not always been available to medical practitioners. Prior to the early 1900s, infections were treated according to anecdotal accounts, and medicinal folklore. In some cases, these folk recipes contained components which are known today to have legitimate antimicrobial properties, such as active ingredients from various species of molds. The vast

majority of such ancient recipes, however, have been found to exhibit minimal antimicrobial activity.[2] In the 1920s and 1930s, bacteriophage therapy was used as a treatment for bacterial infections, but the mechanisms by which it was successful were poorly understood.[3] Excitement at phage therapy's potential led to careless applications, which led to uncertain results and a general decline of favorability as other treatments (e.g. antibiotics) became available in the years to follow.[3]

Louis Pasteur observed the ways that microorganisms kill each other in the late 19th century. He commented on the apparent potential to harness the microbes' capacity to kill other microbes.[4] In 1928, Alexander Fleming, a Scottish biologist and pharmacologist, noticed that fungi of the genus *Penicillium* were capable of killing a number of bacteria growing in petri dishes. Fleming carried out studies on other molds, and found one particular characteristic of *Penicillium* that made it stand out from the others; the broth in which the *Penicillium* grew contained antibiotic properties itself. His efforts to extract crude preparations from the molds and use them to treat infections proved unsuccessful without the aid of more experienced chemists.[5]

Fleming named the active compound from the mold "penicillin" – a term that is familiar and standard in modern times. Although he didn't know it at the time, penicillin exerts its bactericidal effects by inhibiting the production of peptidoglycan – a molecular component that is critical in the construction of bacterial cell walls.[6] Penicillin is actually a broad group of antibacterial compounds that all exhibit this mode of action, and contain a common structural motif, the β-lactam ring.[6]

The first commercially available antibiotic was not penicillin, however. Prontosil, a sulfonamide prodrug drug developed in 1932 by a team led by Gerhard Domagk, was the first drug to open the field of medicine to the golden era of antibiotics.[7] Prontosil was found to have effective potential versus Gram positive organisms, especially *Streptococci*.[7]

It was not until the 1940s that penicillin was able to be mass produced and used to treat and prevent infections. In the years leading up to that time, research teams were having difficulty acquiring yields large enough to provide significant returns on the investment of their time and resources. The United States determined that having a large supply of antibiotics would be a critical tool to have at the Allies' disposal during World War II. In 1943, the War Production Board detailed a plan that was centric about the ability of the Allied forces throughout Europe to be supplied by a source of penicillin.[8] Luckily, as a result of research into corn steep liquor (a by-product of corn wet-milling), methods for mass culture of *Penicillium* were discovered and implemented, allowing the U.S. to supply the Allies with an impressive 2.3 million doses of penicillin for the war.[9] This availability of medicine reduced casualties from battlefield infections, providing the Allies with a tactical edge. Microorganisms' influence on battlefield outcomes was thus curbed in the 20th century as a result of the utilization of antibiotics derived from naturally occurring sources.

An urban legend states that in 1968, the US Surgeon General, Dr. William H. Stewart, declared that "It is time to close the book on infectious diseases, and declare the war against pestilence won." Although it appears as though he never made such a statement, that belief was certainly held by some academics at the time.[10] The practice of medicine since the implementation of antibiotics began to rest upon the assumption that infections would largely be

treatable with antibiotics, and researchers began to allocate their resources in other directions. Notably, a 1968 US government report said

> *"The emphasis of epidemiologic investigation has shifted markedly in the last two decades. A decline in interest in the infectious diseases and increase in concern with the noninfectious diseases have resulted from the change in relative importance of these categories of disease in many parts of the world, including the United States. It is also recognized that, although major tasks still remain in the improvement of control over the infectious diseases, the contribution of epidemiology to the development of control methods is largely past —new advances are being made predominantly as the result of work in the experimental laboratory and through the better application of existing knowledge. On the other hand, the identification of cigarette smoking as the major cause of this century's epidemic of lung cancer has clearly demonstrated the potential contribution of epidemiologic research at the present stage of knowledge of those chronic diseases that now constitute the predominant health problems in this country."*[9]

At the time, it seemed as though modern scientific research had become dominant over the threat of infection and that it was time to move on to conquering other questions of the biomedical sciences.

Modern trends of antibiotic use

In recent times, researchers have been able to develop new varieties of antibiotics that impact different subclasses of bacteria. In addition to seeking new naturally occurring antimicrobial compounds, today it is possible to synthesize new compounds from scratch and to modify existing compounds to serve our specific needs. Large scale drug screens that test the bactericidal potential of hundreds of thousands of compounds at a time can be used to rapidly identify potential candidates for future therapies.

Unfortunately, today we find ourselves in a time when many of the simplest, most readily developed antibiotics have been researched and produced. Drug screens often return hits of compounds that are already thoroughly investigated and employed, and new candidate

compounds are fewer and further in between. Only about 0.1% of drugs even make it to the stage where they are tested in human clinical trials.[11]

The resulting slow-down in production of novel antibiotics would not be a problem were it not for the development of antibiotic resistance. Bacteria are remarkably well adapted to evolve to be resistant to antibiotic compounds. Even mutations at a single base pair of the genome (single nucleotide polymorphisms, or SNPs), can cause the development of a resistant strain. Prokaryotic genomic innovation is facilitated by mechanisms such as horizontal gene transfer, which allows for bacteria to transfer plasmids containing genetic information to neighboring bacteria (sometimes of different genera), bucking the classically understood rule of the downward generational movement of genetic material.[12] This horizontal gene transfer is especially important to the topic of antibiotic resistance because genes encoding anti-antibiotic elements can be quickly passed from one member of the bacterial community to another. Conjugative plasmids (a form of horizontal gene transfer) often contain such information, allowing organisms to quickly adapt *en masse* to life inside a new host environment.[12]

Thus, as soon as a single organism comes across (via a mutation event or otherwise) a gene conferring antibiotic resistance, there is a potential for that gene to quickly spread among neighboring organisms. It is not only the progeny of that originating mother cell, but also any neighboring cells that might be able to receive a protective plasmid from the mother.

This capacity to share plasmids among bacteria has led to the consideration of bacterial communities of genes. It is not reasonable to assume that a bacterium will only have access to the deoxyribonucleic acid (DNA) that it was given when it split off from its mother cell.

Microorganisms can even bypass the need to have a particular antibiotic resistance gene at all through the implementation of nanotubes; there is evidence to suggest that bacteria growing in biofilms are capable of using nanotubes to share small molecules, proteins, and nucleic acids in a direct fashion. These proteins can include enzymes that confer antibiotic resistance.[13]

One example of an enzyme that can confer resistance to antibiotics can be found in bacteria that have a β-lactamase. The penicillin class of drugs contains a β –lactam ring and inhibits cell wall synthesis, causing bacterial cell death. These drugs are readily inactivated by β -lactamase enzymes, which cleave the β-lactam ring of the antibiotic compounds, rendering them ineffective.[14] Over time, as patients are prescribed penicillin, the bacterial strains that are susceptible to the drugs are killed, leaving the bacteria that can produce β-lactamase to survive in the resulting ecological niche. When β-lactam drugs are prescribed today, they are often coupled with β-lactamase inhibitors, compounds that stop bacteria from cleaving the β-lactam ring in penicillin. This is regarded as the most successful strategy to gain control over β-lactam resistant bacteria.[15] The fact that such drug cocktails are necessary is a testament to the rapidity with which bacterial agents have come to circumvent interventions.

In some countries around the world, such as Jordan, antibiotics are available over the counter without a prescription.[16] This contrasts with systems where antibiotics are only available by prescription from a physician. The rationale behind the prescription-based system is to reduce the incidence rate of the use of antibiotics without sufficient cause. Antibiotics are often disruptive to commensal gut flora.[17] These commensal organisms are beneficial to their host's health and capacity to digest food. For example, the normal intestinal bacteria in humans produce vitamin K2.[18] Vitamin K is essential to several human processes, notably the production of

clotting factors.[19] In the absence of clotting factors, there is an increased risk of abnormal blood loss resulting from injuries.

The end of an era

The consistent use of antibiotics over the last 70 years has applied a relentless selective pressure to the microbes capable of infecting humans. As a result, the artificial selection of antibiotic-resistant bacteria has been a constantly looming threat. This is a simple form of an evolutionary process where those bacteria that are capable of surviving the antibiotics are the only ones capable of reproducing, thus exponentially expanding the impact of their antibiotic-resistant genes. When antibiotic resistance develops, it tends to first be observed in hospital environments, and then spread to the community.[20]

The rate at which antibiotic resistant strains of bacteria emerge is hastened by increased bacterial exposure to antibiotics, such as with human therapeutic treatment. This effect is magnified when non-adherent patients stop taking their doses partway through a regimen; stopping early gives surviving bacteria a chance to replicate that they might not have otherwise had, promoting the possibility of the propagation of resistant genes.[21]

The development of resistance to antibiotic compounds, however, is not a uniquely modern phenomenon. An analysis of DNA from 30,000 year old Beringian permafrost revealed genes encoding resistance to β-lactam, tetracycline, and glycopeptide antibiotics.[22] It is apparent that the development of antibiotic resistance is an inevitability.[21]

In 1942, penicillin resistance was demonstrated in a lab setting, where it was induced by slowly increasing the concentration of penicillin in which bacteria were grown.[23] For example,

the initial medium in which the bacteria were grown had only a very low concentration of penicillin. When it was time to give the bacteria a fresh supply of growth medium, slightly more penicillin was added to the mix. This gradual process selected for the bacteria that were best able to survive.

The mass production of penicillin began in 1943. Penicillin resistance was reported in a clinical Australian strain of *Streptococcus pneumoniae* in 1967.[24] In 1974, a case of resistance was reported in the United States.[24] By 1980, it was estimated that approximately 3-5% of all *S. pneumoniae* were resistant to penicillin, and by 1998, 34% of a sample of *S. pneumoniae* were found to be resistant.[25] A 2014 study on the prevalence of antibiotic resistance genes among clinical *Streptococcal* isolates from pregnant women revealed that 97.6% of the isolates contained the *tetM* gene, which encodes a soluble protein that helps to shield the bacterial cell's ribosomes from the otherwise inhibitory action of tetracycline antibiotics.[26, 27] The product of *tetM* acts in conjunction with the product of several other genes (*tetQ* and *OtrA*) to protect the bacterial ribosomes form the effect of tetracycline. In 2013, the number of *S. pneumoniae* that were found to be resistant to at least one drug was around 30%.[28] Some regions of the United States have seen proportions of penicillin resistant *S. pneumoniae* as high as 40-50%.[29]

Mycobacterium tuberculosis (*Mtb*) is another example of a tremendously dangerous pathogen that has come to present staunch resilience against antibiotic treatments. One in three people in the world have tuberculosis (TB), and *Mtb* ranks as the second most deadly infectious agent in the world (in terms of deaths per year), falling behind only HIV/AIDS.[30] It was long thought that treating *Mtb* with chemotherapy would not be possible, due to its lipid-rich cell wall.

Indeed, when penicillin and the sulfonamides were first developed, it was found that they had no action against *Mtb*. Eventually, however, drugs such as isoniazid were developed. In the early 1950s, isoniazid therapy was tested on a Navajo population that was heavily affected by TB. In those trials, the first ray of hope for an antibiotic treatment for TB emerged.[31] Since those early days of treatment, *Mtb* has developed a multitude of resistances. The terms for classification of the various levels of resistance in *Mtb* allude to the severity of the problem at hand: multidrug-resistant (MDR), extensively drug-resistant (XDR), totally drug-resistant (TDR), and pan drug-resistant (PDR) tuberculosis.[32]

The treatment course for TB now consists of 6 months of therapy during which patients take a combination of four drugs (isoniazid, rifampin, pyrazinamide, ethionaminde) for the first two months, and take just rifampin and isoniazid for the remaining four months.[32] The particularly extended length of this therapy has led to issues stemming from patient non-adherence, which has been shown by models to play a role in the evolution of drug resistance.[33] Those same models suggest that the rate at which the bacteria are killed is more important than the mutation rate, in terms of predicting the relative rates of development of resistant mutants.[33]

Although we have not yet come to the absolute end of the era of antibiotics, it is certain that there is a race between the development of new drugs and pathogens' capacity to become resistant to old drugs. Unfortunately, there has been a recent stagnation in the development of new antibiotics. In the four years between 1983 and 1987, the U.S. Food and Drug Administration (FDA) approved sixteen antibiotics for human use. In the four years between 2008 and 2012, only two systemic drugs were approved.[34] In the last 40 years, there have been zero new antibiotics for the treatment of Gram-negative bacilli.[34] There are currently drugs in the

pipeline of clinical trials, but the development of new drugs alone is not a suitable solution for the problem of resistance. Slowing the rate at which resistant bacteria spread is critical to maintaining antibiotics' medical efficacy. Another solution might involve the development of a method to suppress bacterial virulence without killing the organisms, thus avoiding artificial selection, but for now it seems that the use of effective antibiotics offers patients the greatest chance at achieving positive outcomes.

Part of what hastens the development of antibiotic resistance is the fact that farmers often feed antibiotics to their livestock.[35] In fact, the amount of antibiotics given to animals is about four times that given to humans each year; in 2009, animal use constituted 80% of all antibiotics consumed in the United States, and human use made up the other 20%.[36] This is especially problematic if the same drugs that are used for human patients are regularly fed to animals – a common occurrence. About 61% of antibiotics sold for farm animals in 2009 were a type that is also medically important for humans.[36]

Farmers have been giving antibiotics to animals since World War II, after they observed that their livestock were growing larger while under the effects of the drugs. Animals taking antibiotics provide more environments for the development of antibiotic resistant strains of bacteria, thus encouraging the rate at which resistant strains emerge.

Antibiotic resistance has made its way to popular attention in recent years. With online article titles such as "Are you ready for a world without antibiotics?" and "7 scary facts about superbugs," it seems as though the public is taking an interest in the issue.[37, 38] A Google Trends insight suggests that the public's interest in the topic is cyclical, with more search queries in the

winter months and fewer in the summer months.[39] Although interest is seasonal, it appears that overall, interest in the issue is on the rise.

The Centers for Disease Control's (CDC) announcement in the Summer of 2013 named antibiotic resistant *Clostridium difficile*, Carbapenem-resistant Enterobacteriaceae, and *Neisseria gonorrhea* as being "Threat level: Urgent." There are strains of pathogens which are capable of overcoming every antibacterial agent that is currently in widespread use. Carbapenem-resistant Enterobacteriaceae (CRE) is resistant to carbapenem, which is often used as an antibacterial agent of last resort. There are about 9,300 CRE infections per year, with 600 resulting deaths.[28] Slightly less than one fifth of long-term stay hospitals in the United States had a patient with a severe CRE infection during the first half of 2012.[40] Increasing trends of resistance, especially in the hospital setting, are alarming to researchers and medical professionals, and have implications reaching into the lives of the entire population. In 2005, methicillin resistant *Staphylococcus aureus* caused 94,000 infections and about 14,000 deaths in the United States alone.[28, 40]

The economic burden caused by resistance to antibiotics has been estimated at $55 billion per year in the United States.[41] Prospective estimates at the impact of complete antibiotic resistance reveal a frightening future. Currently, antibiotics are given prophylactically for patients undergoing hip replacement. The infection rate is about 0.5-2%, and most patients who do get infected can be properly treated. It has been estimated that in the absence of prophylactic antibiotics, infection rates would increase to roughly 40-50%, and that about 30% of those patients infected would die.[42] Before antibiotic treatments were available, death rates from bacteremia caused by *Staphylococcus aureus* were around 80%.[43]

Indeed, the threat of infection would quickly present a terrifying deterrent to those considering spending time at a health care institution. This would lead to a decrease in treatments for non-life threatening disease states with high infection rates, which would increase the burden of various morbidities.

The current use of prophylactic antibiotics for mothers undergoing cesarean section reduces the incidence of wound infection and serious complications by 60-70%.[44] In a world without antibiotics, child birth would be considerably more dangerous.

The question of how to reduce the negative impacts that resistant bacteria will have upon our medical system is simple. We can strive to increase the rate at which we produce novel antibiotics and we can strive to reduce the rate at which bacteria are developing antibiotic resistance. In order to reduce the rate at which bacteria are developing antibiotic resistance, it would be helpful to gain an understanding of why patients do not adhere to their antibiotic drug regimens.

Patient behaviors and mentalities

A study conducted in an urban hospital environment suggested that patients often desire to be prescribed antibiotics, regardless of the cause of their illness. Patients seem to weigh their own potential benefit from antibiotic use more heavily than the possible negative side effects that may come about.[45]

Moreover, when patients are prescribed antibiotics, they occasionally display patterns of non-adherence. This most often manifests in the form of patients forgetting to take their pills or intentionally stopping taking the antibiotics before they have completed their regimen. The most

common reasons for stopping their regimen are improved health state, forgetfulness, and negative side effects.[46, 47]

A study investigating patients' understanding of antibiotic resistance discovered a dominant theme of the thought that antibiotic resistance is a characteristic of a "resistant human body," which is incorrect.[48] The patients did not understand that it was the bacteria that were becoming resistant to the antibiotics. It has been suggested that this barrier in communication could be lessened by a label transformation away from "antibiotic resistance," and toward a term that includes a direct reference to the bacteria themselves.[49]

A prior study of factors that are associated with adherence to antiretroviral therapy found several lifestyle elements that are associated with proper adherence. These included having source of support from others (such as friends and family), having an intrinsic or extrinsic reason to adhere, and having a system for maintaining motivation.[50] The belief that God was in control of the patient's health status was found to be negatively associated with adherence.[50]

It could be beneficial to increase our understanding of patterns that are associated with non-adherence. Given sufficient insight into the underlying causes of non-adherence, physicians and clinical staff will be able to consult with their patients in a manner that will encourage optimal cooperation.

Patient adherence to other sorts of medical programs (such as endocrine therapy for breast cancer and lifestyle changes for cardiac patients) has been shown to be positively affected by an educational intervention providing enhanced information to patients.[51, 52] It would seem as

though enhanced education on the topic of antibiotic resistance could also lead to increased patient adherence to drug regimens.

This study seeks to identify patterns that are associated with non-adherent subjects. Importantly, we will explore knowledge of basic biology related to antibiotic resistance as a potential distinguishing feature between the profiles of non-adherent and adherent patients.

CHAPTER 2: METHODS

A survey containing three sets of questions was used to gather the responses for this study. Participants were students at the University of Central Florida from a variety of academic majors. Respondents were recruited via UCF's SONA Research Participation System. All participation was carried out online. The three sections of the survey were i) adherence questions, ii) science questions, and iii) demographic and miscellaneous questions.

The combination of a previously developed[53] adherence questionnaire, original science questions, and demographic information obtained was utilized to find associations with predicted non-adherence.

The exclusion criteria were: (1) Being under the age of 18; (2) Choosing "I want to withdraw from this study" as a response at any point in the survey; (3) Failing at least one of the two questions designed to identify those who were not reading the questions; (4) Submitting an incomplete set of responses; (5) Repeated submissions from the same subject (Spam).

This study was approved by the University of Central Florida's Institutional Review Board (IRB) as human participant research that is exempt from regulation (IRB Number: SBE-14-10481).

Survey Section 1: Adherence questions

There were four adherence questions given in the first section of the survey. These four questions were developed as a means of predicting whether patients would properly adhere to their antibiotic regimens. The questions are rooted in the World Health Organization's (WHO) 5 dimension adherence model.[54]

For each question, there was only one answer option that was considered to be the "adherent" response. In this study, the total number of the subjects' "adherent" responses were considered to be their "adherent scores." The minimum possible adherence score was zero, and the maximum was four.

A previous study determined that subjects who "adherently" answered only 0, 1, or 2 of these four adherence questions were more likely to be non-adherent with respect to their antibiotic regimens.[53] Subjects who chose the "adherent" response in 3 or 4 of the adherence questions were more likely to be adherent. This system provided good sensitivity, specificity, and total predictive value (80%, 82%, and 81%, respectively) in their sample.[53]

Adherence Question 1: Convenience

"Is taking medicine more than once a day inconvenient?"

(Yes, No)

The "adherent" answer for this question was "No." Patients who do not view taking medicine more than once a day as being inconvenient are considered to be more likely to be adherent.

Adherence Question 2: Uncertainties

"Whom do you consult first if you have any uncertainties about medicine use?"

(Physician/Pharmacist, Not Physician/Pharmacist)

The "adherent" answer for this question was "Physician/Pharmacist." Patients who are likely to consult trained healthcare providers are more likely to be adherent.

Adherence Question 3: Forgetfulness

"Do you ever forget to take medicine if it has been prescribed to you?"

(Yes, No)

The "adherent" answer for this question was "No." Patients who do not forget to take their medicine are less likely to accidentally become non-adherent to an antibiotic regimen.

Adherence Question 4: Health state

"How will you behave if your health state improves after a few days of taking an antibiotic?"

(Continue taking the antibiotic as prescribed, Continue to take the antibiotic at a reduced dosage, Discontinue taking the antibiotic)

The "adherent" answer for this question was "Continue taking the antibiotic as prescribed." Discontinuing taking the antibiotic and taking the antibiotic at a lower dose would increase the chance for a resilient type of bacteria to survive and replicate in the host.

Survey Section 2: Basic biological questions addressed in this study

There were ten science questions given in the second section of the study. Each addressed a topic is related to the topic of bacteria, disease, or antibiotic resistance. The subjects' scores out of ten were considered to be their "science scores."

Some of the questions were framed in relatively colloquial terms in order to avoid alienating non-expert respondents. All questions were in True/False format. A third option, "I do not know," was available for each question, and was considered to be an incorrect response.

Science Question 1: Power of drugs

"Standard doses of penicillin (a type of antibiotic) can kill any bacteria that might be infecting your body."

(True, False)

The correct answer for this question was "False." An analysis of clinical isolates in the United States in 1999-2000 discovered roughly 34% of *S. pneumoniae* isolated from patients to be "penicillin nonsusceptible."[25] Penicillin resistance was observed as early as 1942.[23]

Science Question 2: Antibiotics and viruses

"If you have a virus, taking antibiotics will kill the virus more quickly than your body can on its own"

(True, False)

The correct answer for this question was "False." Antibiotics are uniquely targeted to affect bacteria, which are distinct from viruses. Antibiotics have no effect on viruses.[9]

Science Question 3: Bacterial DNA

"All bacteria have DNA."

(True, False)

The correct answer for this question was "True." If bacteria did not have DNA, they would not successfully reproduce and would have no mechanism for encoding the proteins and ribonucleic acid that give rise to their physical form.[55-57]

Science Question 4: Commensal flora

"It is normal and healthy to have lots of bacteria on your skin and in your body."

(True, False)

The correct answer for this question was "True." Humans live with roughly 10^{13} bacteria in and on them at all times. This is ten times more than the average number of human cells each person has (10^{12}). The microbiome of the gut plays important roles in host digestion and immune function.[58] One square centimeter of human skin can contain roughly 10^{9} bacteria.[59] These commensal bacteria play important roles in outcompeting potentially harmful pathogens.[59]

Science Question 5: The gut

"If you were found to have bacteria inside of your intestines, you should probably take antibiotics as soon as possible."

(True, False)

The correct answer for this question was "False." Bacteria inside the intestines are responsible for the production of vitamin K, which is essential for forming blood clots.[18, 19] The

intestinal flora are also helpful to their human hosts, as they take up environmental niches that deleterious pathogens might otherwise be able to occupy. *Clostridium difficile,* one of the pathogens detailed in the 2013 Centers for Disease Control report on antibiotic resistance,[28] often establishes an infection after a patient has been on an antibiotic regimen that killed a portion of their normal resident bacterial community in the gut. This can lead to a severe disease state, and is a functional example of why intestinal bacteria shouldn't collectively be thought of as a problem.[28]

Science Question 6: Evolution of resistance

"Evolution of bacteria has never been directly observed, and is only a theory."

(True, False)

The correct answer for this question was "False." Examples of the genetic effects of selective pressures placed upon bacteria are well represented in the literature.[11, 21, 32, 33] There is some merit to the claim that genetic changes that have resulted from the intelligent intervention of humans are not true examples of evolution, but are instead artificial selection.

Humans, however, are not the only users of antibiotics. In fact, many of the antibiotic compounds that we now employ have been in use by other organisms (such as the *Penicillium* molds) for tens of thousands of years; 30,000 year old Beringian permafrost was discovered to contain bacterial genes encoding resistance to β-lactam, tetracycline, and glycopeptide antibiotics.[22]

Science Question 7: Bacterial resilience

"Bacteria are capable of becoming immune to our most powerful antibiotics."

(True, False)

The correct answer for this question was "True." Bacteria that are resistant to every known antibiotic compound pose a frightening threat. Extensively drug-resistant tuberculosis, for example, has been observed to become resistant even to the most effective second-line antibiotics.[1]

Science Question 8: Bacteria vs. viruses

"'Bacteria' and 'Virus' are two words that mean the same thing."

(True, False)

The correct answer for this question was "False." Bacteria are single celled, living organisms that contain organelles such as mitochondria and ribosomes that are used in maintaining cellular processes.[60] Viruses are comprised of genetic material encased in a capsid, and are only capable of replicating after taking control of a host cell's internal machinery.[60]

Science Question 9: Do professionals agree

"There is a consensus among scientists and doctors that antibiotic-resistant bacteria are becoming a problem"

(True, False)

The correct answer for this question was "True." It has been thoroughly established that bacteria i) have already developed resistances to some drugs, ii) have the potential to become

resistant to an even wider variety of compounds, and iii) will lead to significantly more negative clinical outcomes if they are not able to be successfully treated.[6, 21, 25, 27, 28, 30, 40, 61, 62]

Science Question 10: Are antibiotics more effective than placebos

"Pharmaceutical companies suggest the use of antibiotics because they profit off of them. In reality, antibiotics are not statistically more effective than taking a sugar pill, or another type of placebo."

(True, False)

The correct answer for this question was "False." Although pharmaceutical companies may promote antibiotics because they have a vested interest in their sales, it has been objectively established that antibiotics are more effective than placebos when used for their intended purpose.[7, 8, 15, 63, 64]

Survey Section 3: Demographic and miscellaneous questions

The information gathered from this group of questions was not accumulated to make up a certain score, but was used to evaluate patterns among various groups of subjects. Several of the questions in this category were also intended to identify respondents who were randomly filling in answers to the survey and not reading the questions.

Demographic & Misc. Question 1: Age

"What is your age?"

Subjects were grouped into several age divisions: 18, 19, 20, 21, 22, 23-30, 31-40, 41-50, 51-60, 61-70, 70+.

Demographic & Misc. Question 2: Sex

"What is your sex?"

(Male, Female, Other)

Demographic & Misc. Question 3: Major

"Is your major related to Biology?"

(I am majoring in Biology, Biomedical Science, Biotechnology, or a related track; I am majoring in another STEM [Science, Technology, Engineering, and Math] track that is not similar to Biology; I am not majoring in STEM or Biology)

This grouped respondents into the categories of (i) biology-related majors; (ii) STEM majors (other than biology-related); (iii) not related to STEM or biology

Demographic & Misc. Question 4: Antibiotic history

"Have you ever been prescribed antibiotics?"

(Yes, No, I am not sure)

Demographic & Misc. Question 5: Opposition to antibiotics

"Are you generally opposed to the use of antibiotics?"

(Yes, No)

Demographic & Misc. Question 6: Awareness of issue

"Have you heard of the problem of antibiotic resistance?"

(Yes, No)

Demographic & Misc. Question 7: Self-rated understanding

"How would you rate your understanding of the topic of antibiotic resistance?"

(Very Poor, Poor, Fair, Good, Excellent)

These responses were translated into scores ranging from 1-5, respectively. In this way, they were able to be considered quantitatively.

Demographic & Misc. Question 8: Remembering to take doses

"If you were to be prescribed antibiotics, would you be responsible for remembering to take your doses?"

(Yes, No)

The two resulting groups determined by this question (autonomous and non-autonomous) were compared by mean adherence scores to determine if there was significant difference.

Demographic & Misc. Questions 9 and 10: Eliminating confounding respondents

Agreement to not guess

"If you are not sure about an answer, please do not guess. Guessing has the potential to throw off the data of the study. If you don't know an answer, just select the 'I do not know option.' Thanks!"

(I will select "I do not know" if I don't know the answer, I will guess when I do not know the answer)

This question was asked before the subjects were presented with the science questions. The correct answer for this question was "I will select 'I do not know' if I don't know the

answer." Since all of the science questions were presented as True/False, there is a potentially misleading effect that would result from respondents guessing on questions they don't know.

With the addition of an "I do not know" answer option to each science question, the survey results allow insight into how many answer the respondents actually knew the material, rather than how many knew the material plus how many managed to correctly guess. Respondents who selected the incorrect option for this query were eliminated from the study.

Ensuring attentive responses

"This question isn't really a part of the quiz. Please select "False" as your answer to this question."

(True, False, I do not know)

This question was placed between the 7th and 8th science questions in the survey. Respondents who chose "True" or "I don't know" were eliminated from the study, with the understanding that they were most likely selecting random answers (or entirely "I do not know") through the science section.

Statistical Analysis

The analysis of the various components of subject responses was conducted using MS Excel. For the nominal variables, absolute numbers and frequencies were used for comparison. For quantitative variables (such as science score), means (M) and standard deviations (SD) were calculated. The relationships between elements of the study were analyzed using: (1) Student's two-tailed unpaired t-test for comparison of mean measurement variables between groups; (2) one-way ANOVA to determine if the means of the measurement variable were the same between

multiple groups; (3) Fisher's exact test of independence to determine if differences in one nominal variable vary significantly with the value of another nominal variable. All Fisher's calculations were done two-tailed, using the method of summing small P values. Normalcy was visualized using a Quantile-Quantile (QQ) plot.

CHAPTER 3: RESULTS

A total of 961 responses were evaluated. Out of these, 117 responses were removed from the study after having met at least one of the exclusion criteria, leaving 844 responses to be considered. Error bars on figures displaying averages represent standard error of the mean. Error bars on figures displaying proportions represent the 95% confidence interval (α=0.05).

Distribution of responses

Adherence scores

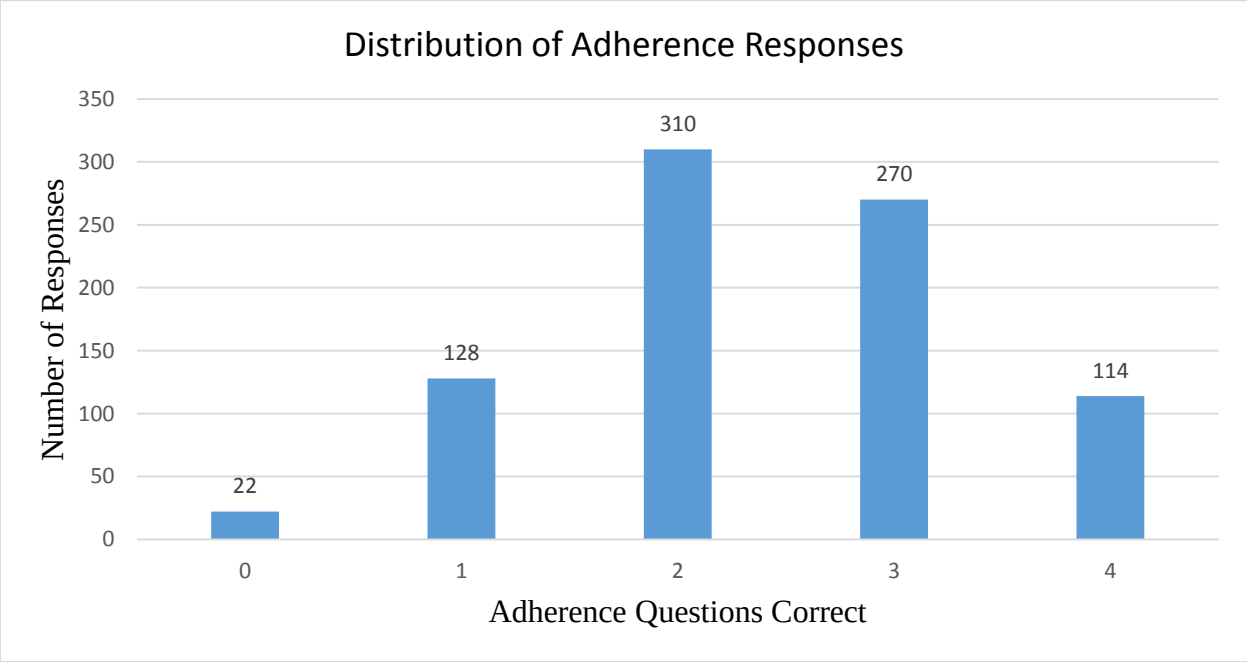


Figure 1: Distribution of adherence responses

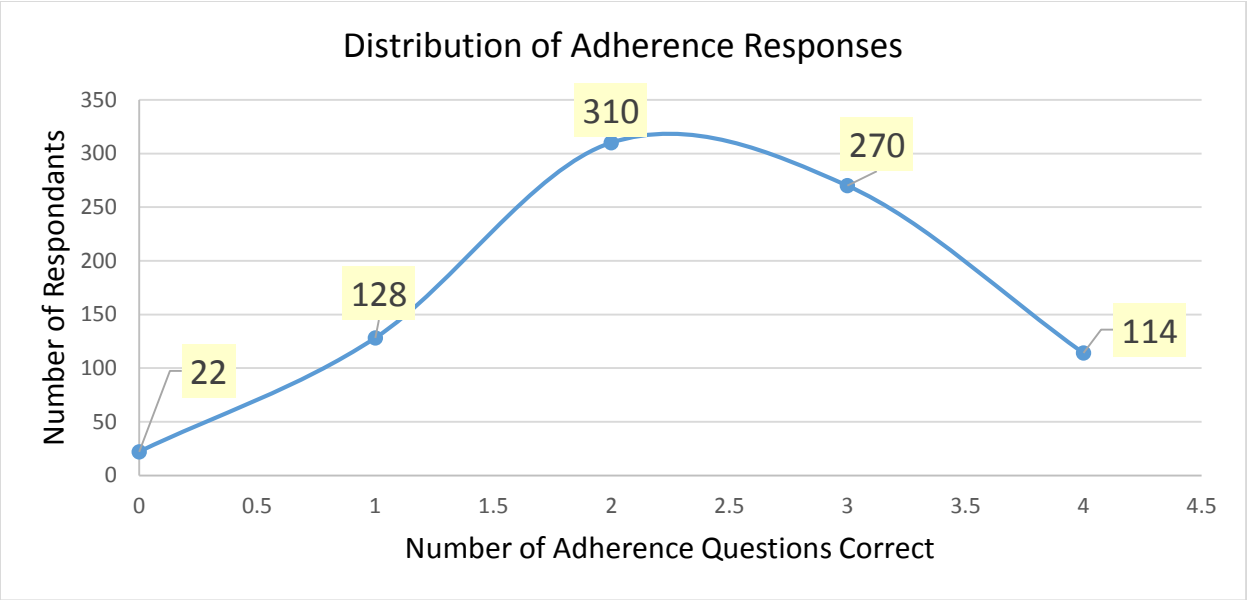


Figure 2: Distribution of adherence responses

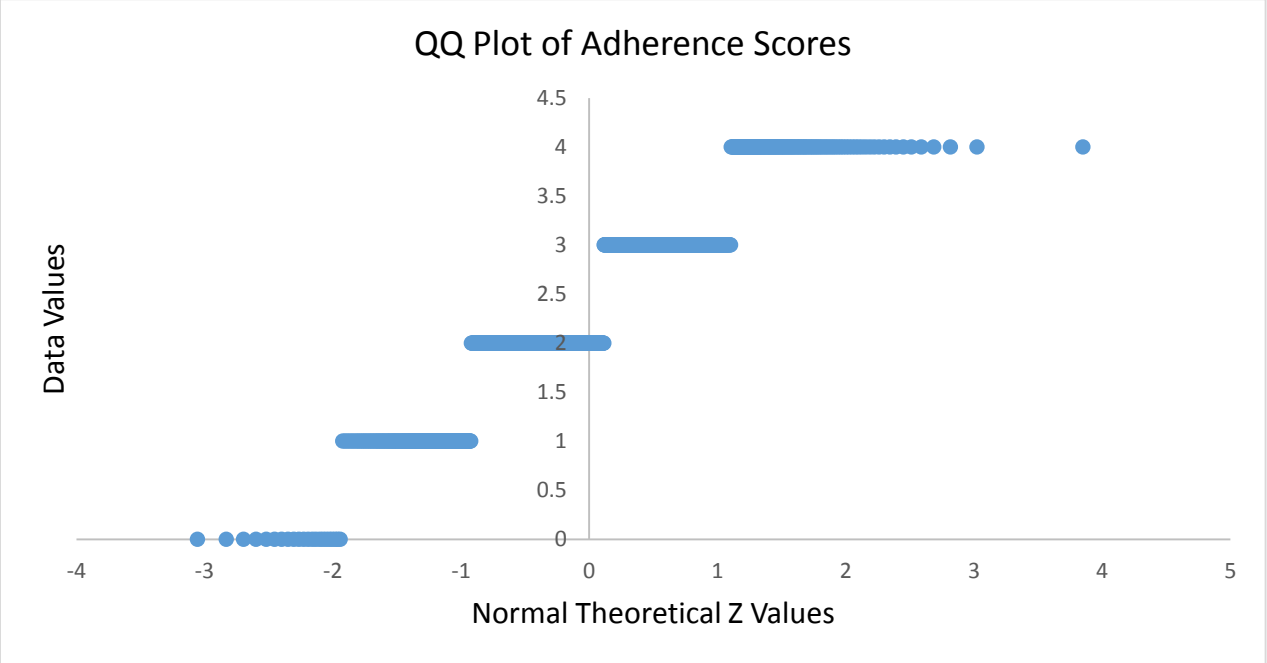


Figure 3: QQ plot of adherence scores

For this QQ plot, Data values (adherence scores) are represented by the Y axis, and the theoretical quantiles are shown by the X axis. QQ plots are used to visualize how the data

collected compare to a theoretically perfectly normally distributed data set. If the actual data collected are completely normal, the plot gives a straight diagonal line. In this case, a slight curve under the diagonal on the right hand side suggests a somewhat heavy right tail. This indicates that the normal distribution of responses is translated slightly to the right, spilling off the bounds of the 0-4 scale used for measurement. If a fifth adherence question had been added, it is likely that the right tail would have lightened.

Science scores

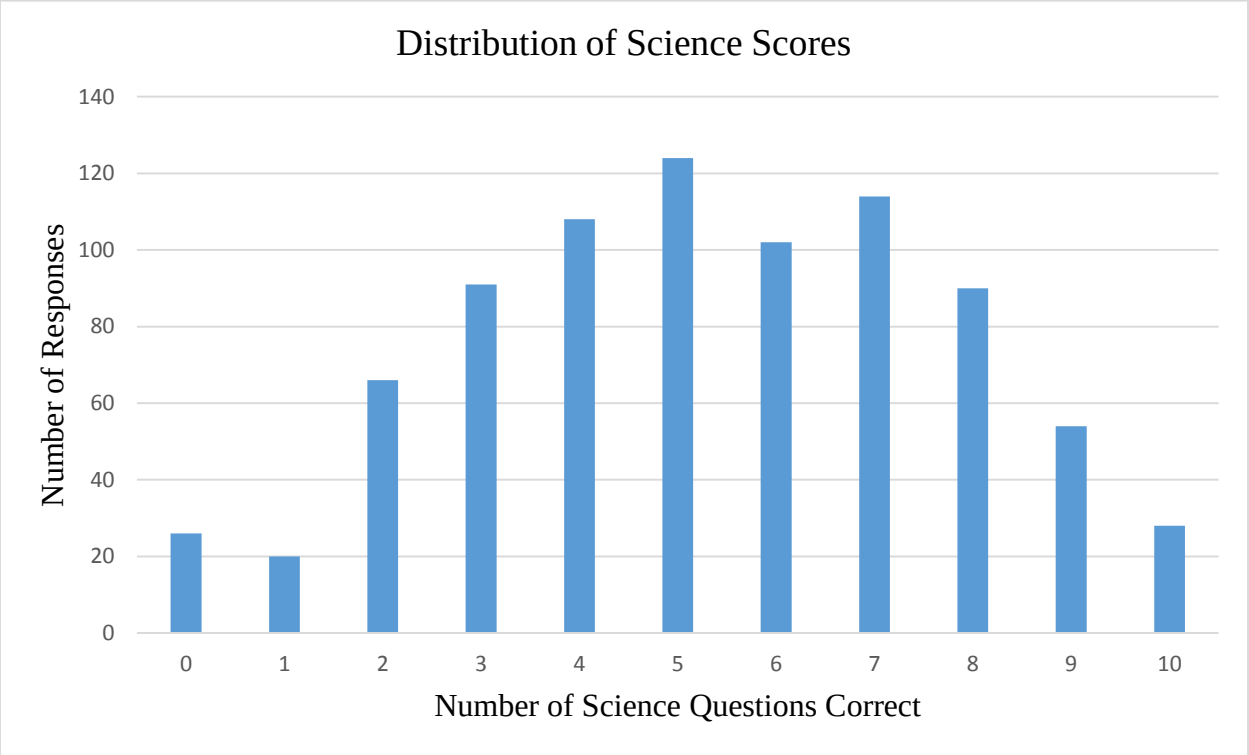


Figure 4: Distribution of science scores

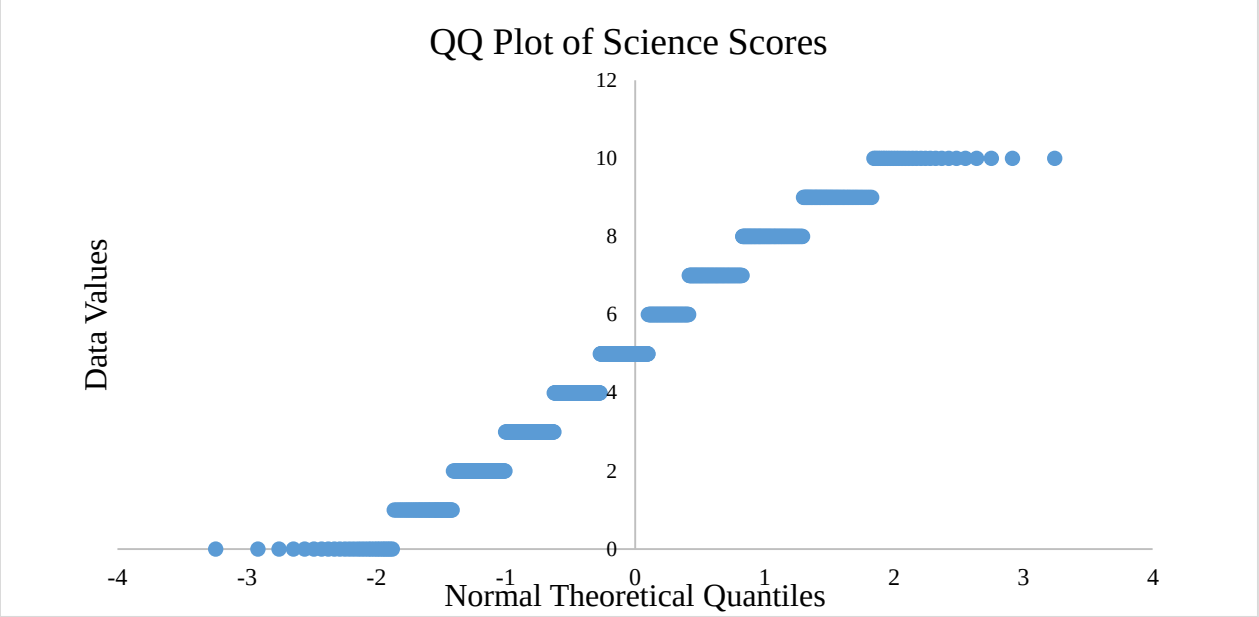


Figure 5: QQ plot of science scores

Data values (science scores) are represented by the Y axis and the corresponding theoretical quantiles are shown by the X axis. There is no systematic deviance from the QQ plot. Slight S shape indicates light tails in both directions, with no apparent outliers.

Significant difference in science scores between adherent and non-adherent groups

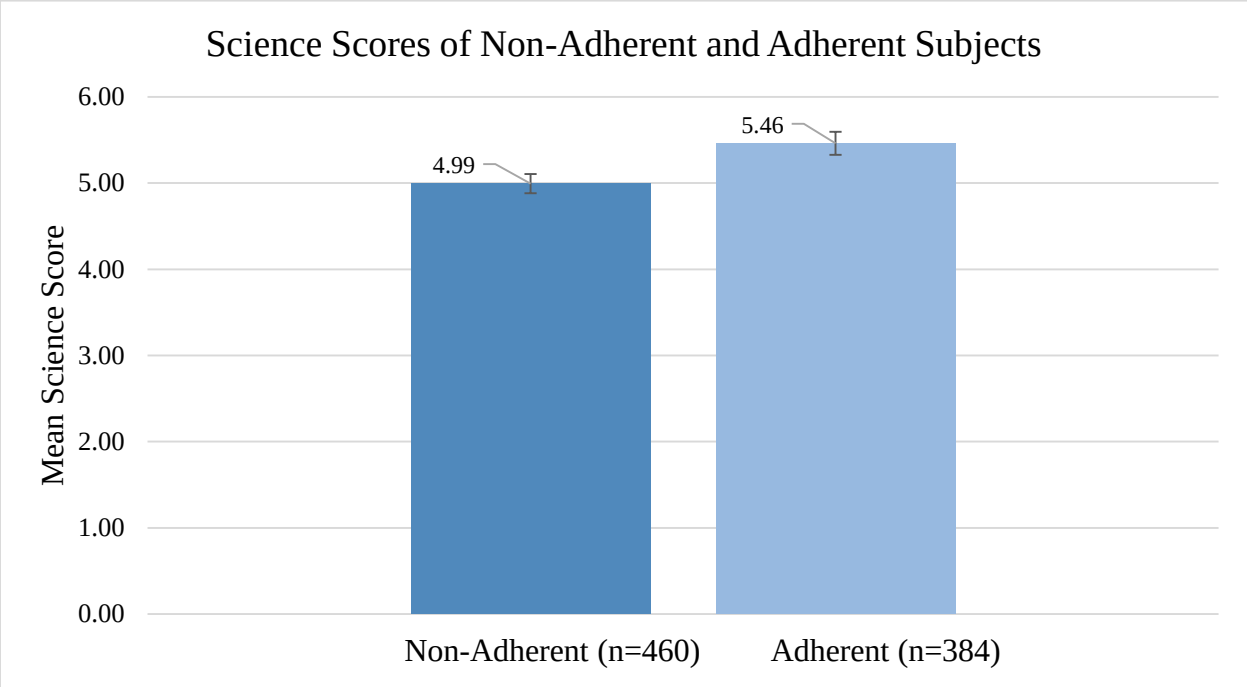


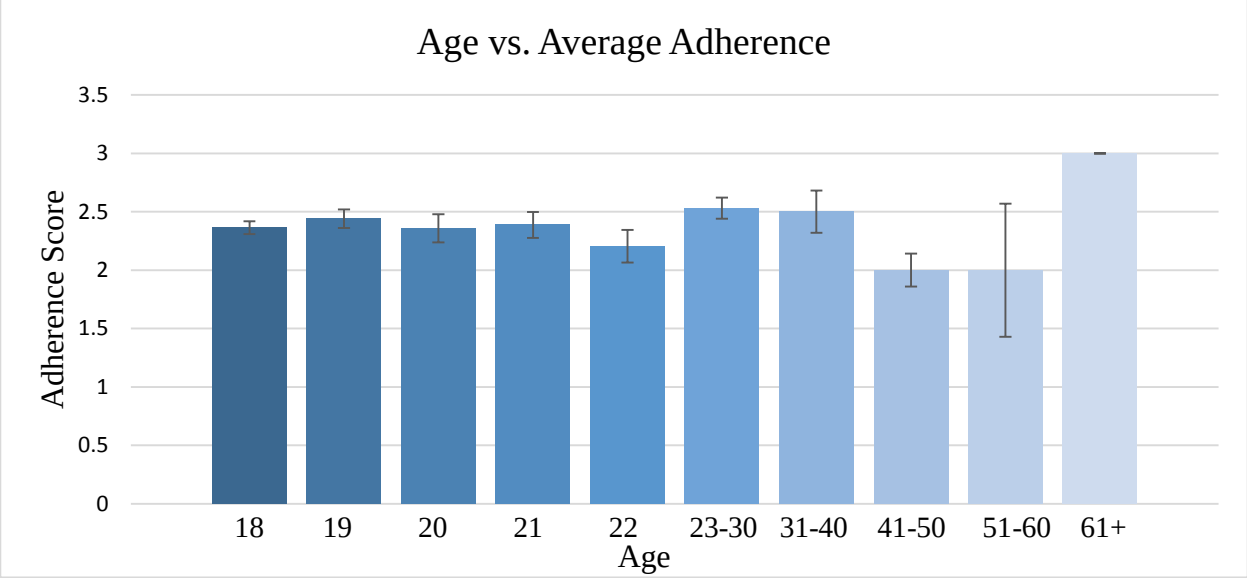
Figure 6: Science scores of adherent and non-adherent subjects

An independent samples t-test was conducted in order to compare scores (out of 10) on the science section in non-adherent and adherent respondents. Error bars represent standard error of the mean. There was a significant difference in the science scores for non-adherent (M=4.99, SD=2.46), and adherent (M=5.46, SD = 2.52) subjects; t(842)= -2.73, p = 0.0064. This suggests that there is a meaningful difference in the science knowledge between patients who are likely to be non-adherent/adherent.

Differences by age

Adherence scores

A one-way ANOVA was conducted to compare the effect of age on adherence responses. There was not a significant effect of age on average adherence score [F(9,827) = 0.954, p = 0.48]. Seven respondents did not wish to report their age.



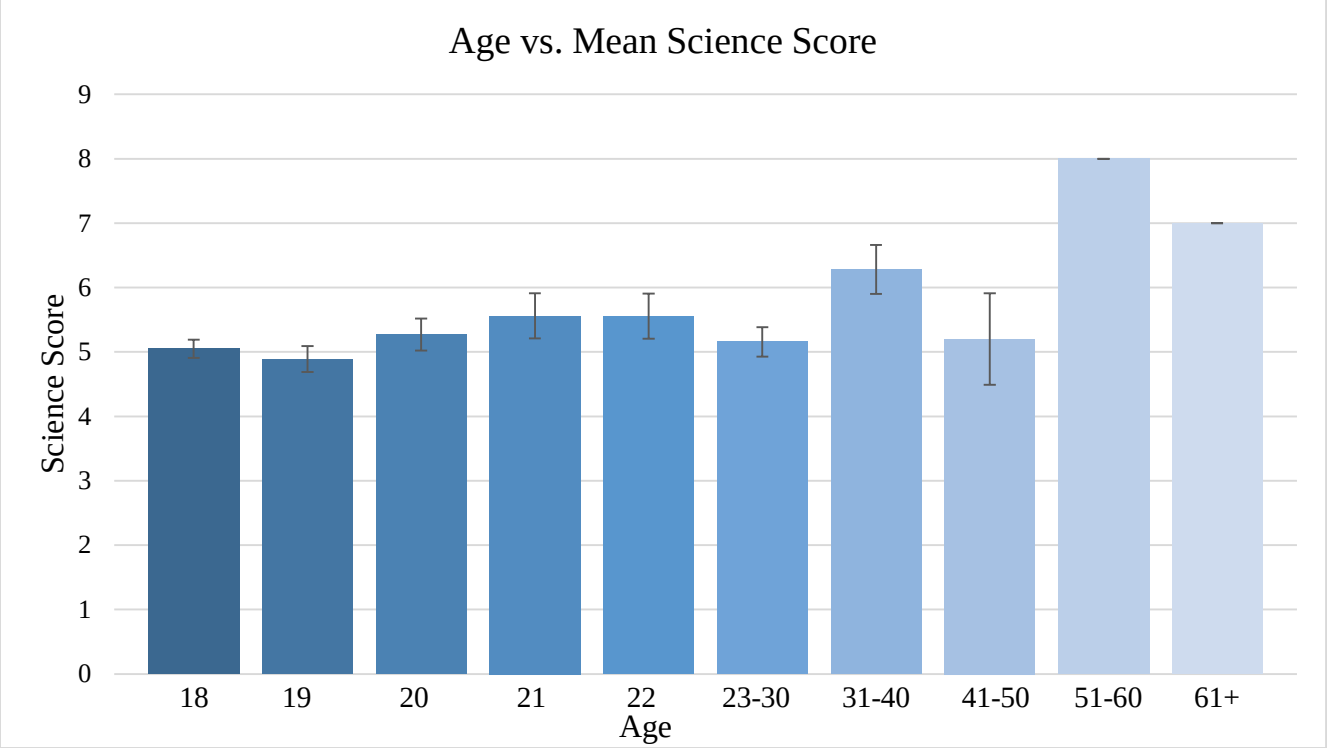
Age	18	19	20	21	22	23-30	31-40	41-50	51-60	61+
Number	313	148	81	75	54	115	32	15	3	1
Mean	2.36	2.44	2.36	2.39	2.20	2.53	2.5	2	2	3
StDev	0.98	0.99	1.09	0.99	1.02	0.92	1.05	0.54	1.0	0.0

Figure 7: Age vs. average adherence

Science scores

Another one-way ANOVA was conducted in order to compare the effect of age on science score. There was not a significant effect of age on sciences scores [F(9,827) = 1.86, p =

0.055]. This p value is significantly closer to the statistical cutoff of 0.05 than it was in the adherence ANOVA (p=0.48), suggesting that age is closer to being associated with scores on the science section than it is with scores on the adherence section.



Age	18	19	20	21	22	23-30	31-40	41-50	51-60	61+
Number	313	148	81	75	54	115	32	15	3	1
Mean	5.05	4.89	5.27	5.56	5.56	5.16	6.28	5.2	8	7
StDev	2.43	2.40	2.23	3.01	2.56	2.52	2.17	2.76	0	0

Figure 8: Age vs. mean science score

No difference in adherence scores in autonomous and non-autonomous Subjects

An independent samples t-test was conducted in order to compare mean adherence scores (out of 4) autonomous and non-autonomous subjects. Subjects were grouped into the autonomous category if they said that they were responsible for remembering to take their doses. Subjects were grouped into the non-autonomous category if they indicated that someone else helped them remember to take their doses. There was no significant difference found in the adherence scores for autonomous (M=2.38, SD=0.98, n=37), and non-autonomous (M=2.54, SD = 1.04, n=807) subjects; $t(842)= 0.98$, $p = 0.33$.

No difference in adherence scores in those who had and had not heard of antibiotic resistance

To investigate whether there was a meaningful relationship between having heard of antibiotic resistance and adherence scores, an unpaired t-test was conducted. Of the 844 subjects, 626 (74%) had heard of the problem of antibiotic resistance. There was no significant difference found in the adherence scores for those who had heard of antibiotic resistance (M=2.40, SD=0.99, n=626), and those who had not heard of antibiotic resistance (M=2.35, SD = 0.98, n=218) subjects; $t(842)= -0.64$, $p = 0.52$.

Strong relationship between knowledge that bacteria and viruses are different and that antibiotics do not kill viruses

	Incorrect (Bacteria and viruses are the same)	Correct (Bacteria and viruses are different)	Total
Incorrect (Antibiotics kill viruses / don't know)	106	444	549
Correct (Antibiotics don't kill viruses)	10	284	295
Total	116	728	844

Figure 9: bacteria vs. viruses and antibiotics on viruses

Out of the 844 respondents, 116 did not know that bacteria and viruses are not two words for the same thing. A total of 549 subjects did not know that antibiotics have no effect on viruses. A 2x2 Applying Fisher's test of independence, the proportion of knowing that antibiotics do not kill viruses was found to be significantly higher ($p < 0.0001$) in those subjects who did know that bacteria and viruses are different.

Test for relatedness between knowledge that bacteria and viruses are different and that antibiotics are more effective than placebos

	Incorrect (Bacteria and viruses are the same)	Correct (Bacteria and viruses are different)	Total
Incorrect (Antibiotics are placebos / I don't know)	81	329	410
Correct (Antibiotics work better than placebos)	35	399	434
Total	116	728	844

Figure 10: bacteria vs. viruses and placebo comparison

A total of 410 subjects did not know that antibiotics are more effective than placebos. Applying a 2x2 Fisher's exact test of independence, the proportion of respondents who knew that antibiotics are more effective than placebos was found to be significantly higher ($p < 0.0001$) in those subjects who did know that bacteria and viruses are different.

Does opposition to the use of antibiotics affect adherence proportion

	Non-Adherent	Adherent	Total
Opposed to the use of antibiotics	77	50	127
Not opposed to the use of antibiotics	375	330	705
Total	452	380	832

Figure 11: Opposition and adherence

Of the 844 respondents, 12 did not wish to respond to the demographic question regarding whether they were opposed to the use of antibiotics in general. Of the 832 who did respond, 127 were opposed to the use of antibiotics, and 705 were not. Applying a 2x2 Fisher's exact test of independence suggests that there is not a significant relationship ($p = 0.15$) among the proportions of adherent and non-adherent subjects, depending on whether they were opposed to the use of antibiotics.

Does major affect adherence proportion

Of the 844 Respondents, 799 were willing to report their major. Multiple Fisher's exact tests of independence were run to test whether major was predictive of adherence. Subjects were grouped into three categories of major: (1) Biology-related; (2) STEM, but unrelated to biology; (3) Not related to biology or STEM.

Biology-related majors

	Non-Adherent	Adherent	Total
Not Biology-Related	324	279	603
Biology-Related	109	87	196
Total	433	366	799

Figure 12: Biology majors and adherence

Applying a 2x2 Fisher's exact test of independence suggests that there is not a significant relationship ($p = 0.68$) among the proportions of adherent and non-adherent subjects, depending on whether they had a biology-related major.

Not biology or STEM

	Non-Adherent	Adherent	Total
Not Biology or STEM	277	219	496
Biology or STEM	156	147	303
Total	433	366	799

Figure 13: Non biology or STEM majors and adherence

Applying a 2x2 Fisher's exact test of independence suggests that there is not a significant relationship ($p = 0.24$) among the proportions of adherent and non-adherent subjects, depending on whether they had a major unrelated to biology or STEM.

STEM (not including biology-related majors)

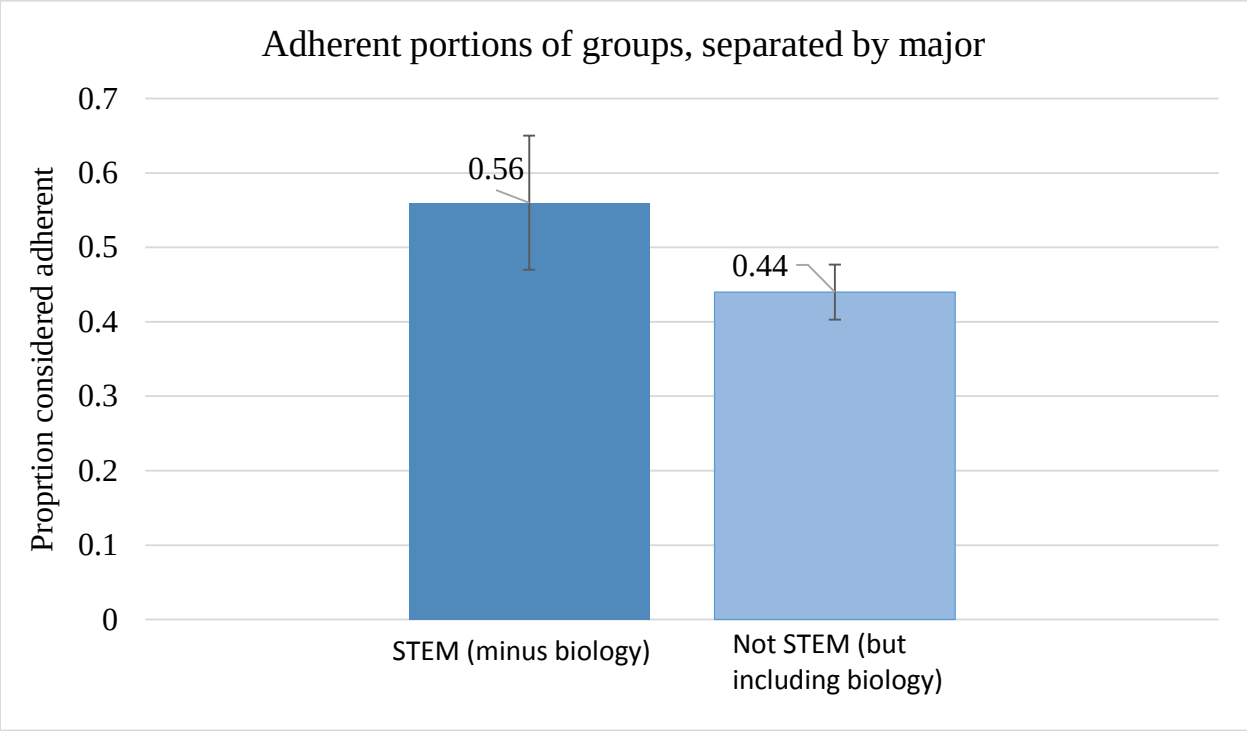


Figure 14: Proportion of adherence, STEM majors vs. others

	Non-Adherent	Adherent	Total
Biology or not STEM	386	306	692
STEM	47	60	107
Total	433	366	799

Figure 15: STEM majors and adherence

Applying a 2x2 Fisher's exact test of independence suggests that there is a significant relationship ($p = 0.028$) among the proportions of adherent and non-adherent subjects, depending

on whether they had a major related to STEM (but not biology). This indicates that STEM majors (not including biology) were more likely to be adherent when compared to other majors.

Accuracy in self-assessment of science knowledge

Figure 16: Self-rated score distribution

The above chart (Figure 16) is a representation of the distribution of self-assessed understanding of the topic of antibiotic resistance.

The accuracy with which subjects rated their own knowledge of antibiotic resistance was calculated by comparing their self-rated score (0-4) with their science score (0-10). To obtain a "self-rated accuracy score," the subjects' self-rated number was multiplied by 2.5. Their science score was then subtracted from that number:

2.5(self-rated score) – (science score) = (accuracy score)

Using this definition, overestimates of knowledge would lead to a positive accuracy score, and underestimates would lead to a negative accuracy score. An example calculation would be as follows:

If one particular subject scored a 6 out of 10 on the science section and they self-rated their understanding of antibiotic resistance as being 3 out of 4 their accuracy score would be:

$$2.5*(3) – 6 = 1.5$$

This particular subject would be said to have overestimated their knowledge of biological topics related to antibiotic resistance.

Data from the accuracy scores of the entire sample (n = 844) showed a mean of -0.36 and a standard deviation of 2.43, suggesting a slight underestimation of knowledge, on average.

No difference in adherent and non-adherent subjects' accuracies in self-assessment of science knowledge

A two-tailed independent samples t-test was conducted in order to compare mean accuracy scores of adherent and non-adherent subjects. There was no significant difference found in the self-rated accuracy scores for non-adherent (M= -0.40, SD=2.43, n=460), and adherent (M= -0.32, SD = 2.44, n=384) subjects; $t(842) = 0.186$, $p = 0.85$.

No significant difference in self-rated knowledge scores between those who had and had not heard of antibiotic resistance

A two-tailed t-test revealed no significant difference in the self-reported "understanding of the topic of antibiotic resistance" scores between those who had heard of the topic of antibiotic resistance (M=1.91, SD = 0.95, n=626) and those who had not (M=2.02, SD = 0.91, n=218) subjects; t(842)= 1.49, p = 0.14.

Does sex matter

Significant relationship between sex and science score

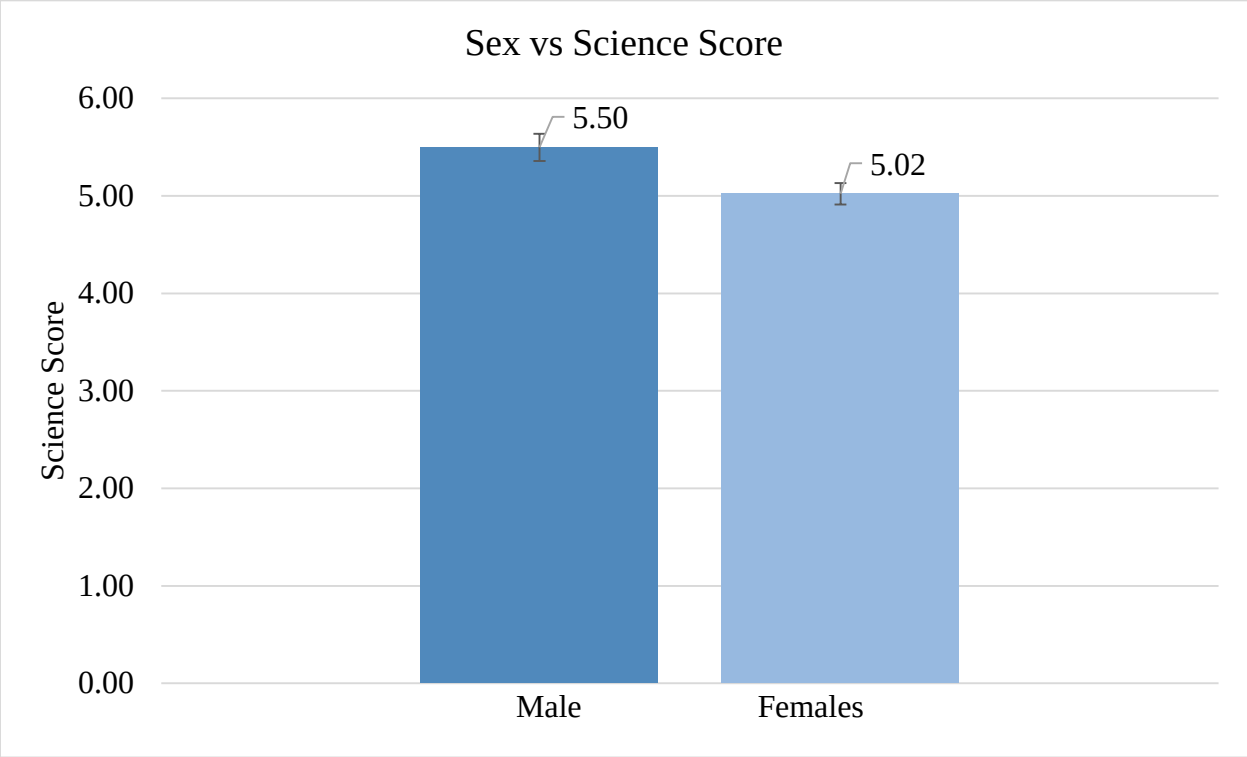


Figure 17: Sex vs. science score

A two-tailed independent samples t-test was conducted in order to compare mean science scores of male and female respondents. There was a significant difference found in the science

scores of males (M=5.50, SD=2.44, n=311) and females (M=5.02, SD=2.44, n=524); t(833) = 2.70, p = .007.

Significant relationship between sex and adherence

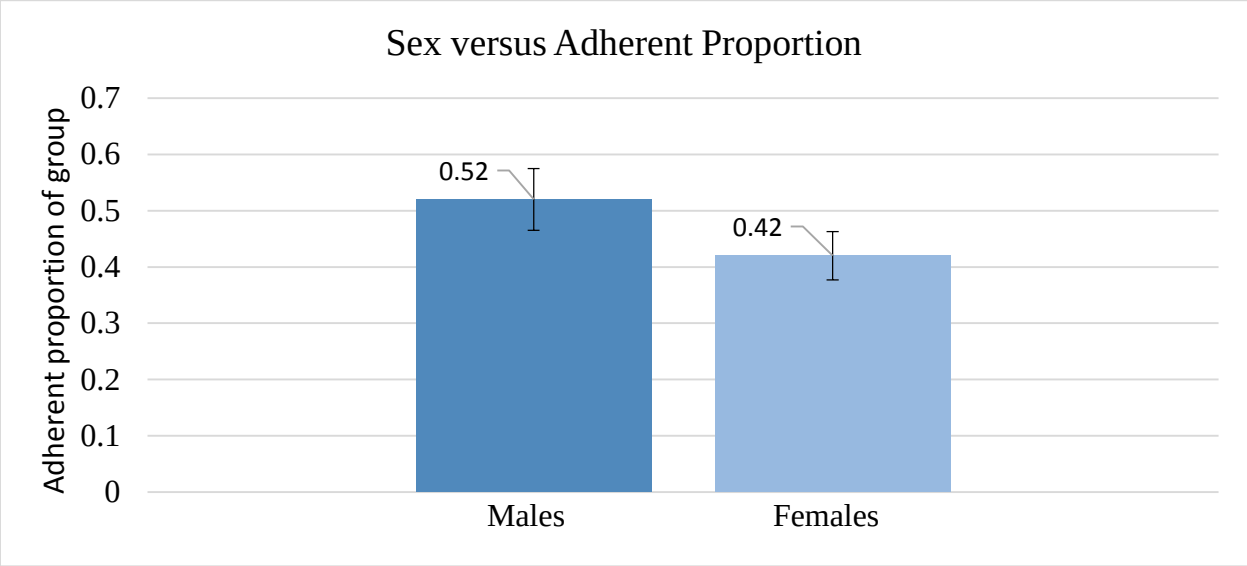


Figure 18: Sex and adherence

Of the 311 males who responded, 161 of them were determined to be adherent (52%). Of the 524 females who responded, 218 were determined to be adherent (42%). Applying a 2x2 Fisher's exact test of independence yields p = 0.005; there is a significant difference in the adherent/non-adherent ratio between males and females.

Adherent and non-adherent subjects took the same amount of time

A two-tailed independent samples t-test was conducted in order to compare mean times spent taking the questionnaire.

There was no significant difference found in the times to completion of non-adherent (M=5.94 minutes, SD=6.32 minutes, n=460), and adherent (M=5.47 minutes, SD = 5.20 minutes,

n=383) subjects; t(841) = 1.16, p = 0.25. Adherent and non-adherent respondents took the same amount of time to complete the questionnaire.

A look at the respondents

How many subjects had ever previously been prescribed antibiotics?

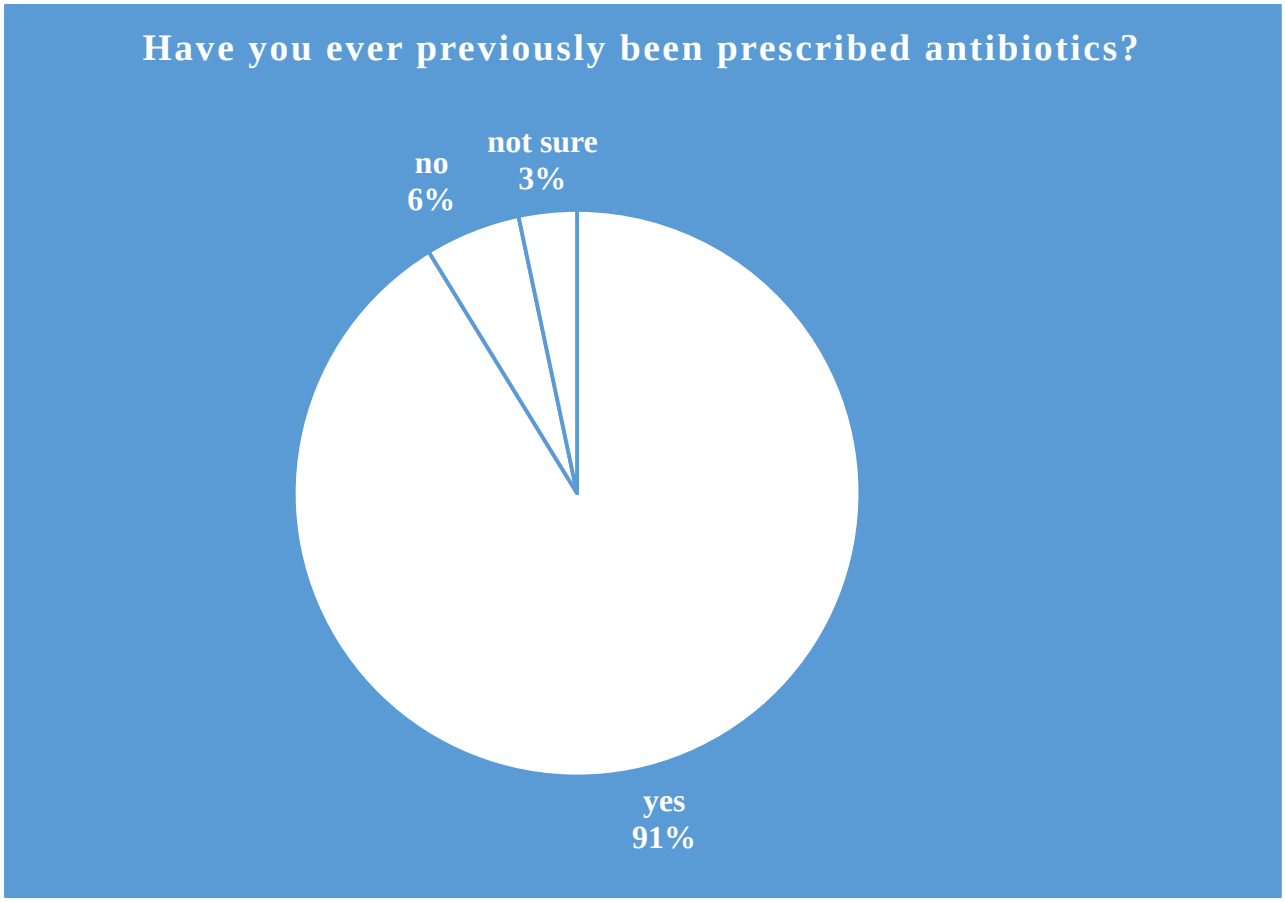


Figure 19: Have you ever been prescribed antibiotics

It was determined that 770 (91%) of the 844 respondents said that they had previously been prescribed antibiotics.

How many subjects said they were "generally opposed" to the use of antibiotics?

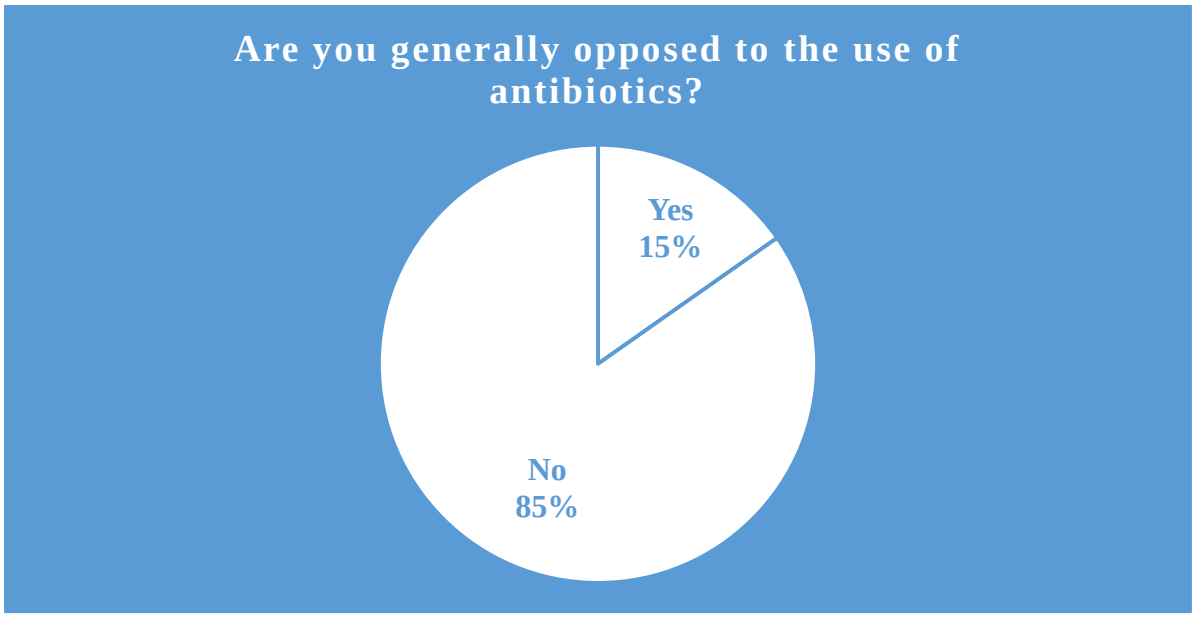


Figure 20: Are you generally opposed to the use of antibiotics

Most respondents (85%; n=706) were not generally opposed to the use of antibiotics.

How many subjects had heard of the problem of antibiotic resistance?

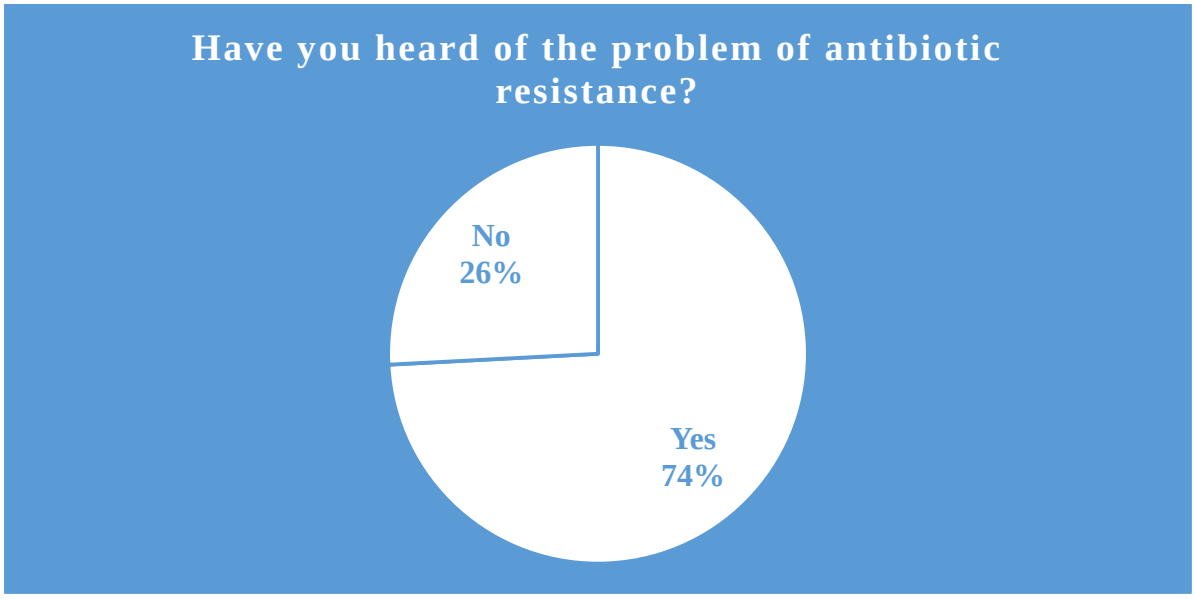


Figure 21: Have you heard of the problem of antibiotic resistance

The majority of respondents (74%; n=626) reported having heard of the problem of antibiotic resistance, but 26% (n=218) said that they were not familiar with the issue.

CHAPTER 4: DISCUSSION

Contributions to our understanding of the differences between adherent and non-adherent patients will allow physicians and health care staff to tailor drug regimen guidelines and explanations to individual patients. This is important because patient adherence is directly linked to discouraging the development of antibiotic resistant strains of bacteria. This study sought to examine the response profiles of adherent and non-adherent patients, with the translational goal of building upon our understanding of what features might distinguish those two groups.

The distribution of subjects' responses to several components of the questionnaire suggests relatively normal proportions. Responses to the four adherence questions were used to classify each respondent as being non-adherent (less than 3 adherence questions correct) or adherent (3 or 4 adherence questions correct). The distribution of adherence scores had a slightly heavy right tail, indicative of a potential translation to the right that was cut off by the upper score boundary set at 4. The direct regression between adherence scores and science scores was not relevant because adherence scores were being used to group respondents. The distribution of science scores had somewhat light tails on either side, suggesting that science knowledge among the respondents carried tendencies toward the center.

The relationship between adherence and science was determined to be statistically significant. The null hypothesis that adherent and non-adherent subjects would have equal means was rejected with a p value of 0.0064. This showed that adherent subjects demonstrated a higher level of education on the science topics presented, relative to their non-adherent counterparts. This result alludes to the findings of previous studies on the impacts of patient education on

adherence to various other types of regimens, including endocrine therapies for cancer patients and lifestyle changes for cardiac patients.[51, 52]

This finding opens the door to potential avenues by which the issue of patient non-adherence may be addressed. Increasing efforts at patient education could lead to a decreased rate of patient non-adherence. In turn, a reduction in patient non-adherence will lead to less opportunities for bacteria to become resistant to antibiotics. Although this will reduce the rate at which antibiotic resistant bacteria will develop, it is by no means a mechanism by which to completely halt the evolution of resistant mechanisms. Improving adherence is suggested only as a method to slow down the development of that resistance.

There are many possible avenues by which increased patient education can be obtained. The source of information could begin in the entertainment sector. News outlets could present the topic of antibiotic resistance from an educational standpoint, rather than speaking about the frightening possibility of superbugs. Patient education could continue in the doctor's office, where educational handouts could be distributed with each prescription for antibiotics. Pharmacies who fill orders for antibiotics could then reinforce the previous messages by including reminder messages to complete the entire drug regimen, even if the patients start feeling better.

Organizations such as the Centers for Disease Control already create and publish informational pamphlets on the topic of antibiotic resistance.[65] Although these pamphlets are in production, it seems that they are not fully addressing the needs of the population assessed in this study. This could be due to a lack of availability; it is possible that many of the subjects in this

study have not previously visited the CDC website or come across a printed version of those materials. In this social-media dominated age of information, efforts at public awareness could be made through a variety of channels.

It was determined that the only group of students that was significantly more likely to be adherent was STEM majors (not including majors related to biology). The null hypothesis that subjects with majors related to biology would be equally likely to be adherent (when compared with non-biology-related majors) was not able to be rejected; subjects with majors related to biology were not shown to be more adherent than subjects whose majors were not related to biology. Similarly, subjects whose majors were related to neither biology nor STEM were not shown to be more adherent than biology and STEM majors.

Men were shown to be significantly more likely to be adherent and also more knowledgeable in the biological competencies assessed in this study. This is a logical grouping of correlations, given the association found between knowledge and adherence (Figure 6).

Adherent and non-adherent respondents took the same amount of time to complete the questionnaire. It was estimated that subjects would take less than 15 minutes to complete the survey. This ended up being true for 96% (n=814) of the respondents.

Overall, respondents seemed to be fairly good at estimating their knowledge on the subject of antibiotic resistance. Subjects displayed an average accuracy score of roughly -0.36. This means that subjects slightly underestimated their knowledge, on average.

Future studies could examine the impact of educational interventions on the adherence rate of patients. Such studies would benefit from using a clinical model of adherence, rather than

relying upon a survey, as did this study. Counting pills and interacting with actual patients would provide a more reliable grouping of adherent and non-adherent subjects than this study was able to achieve.

The results in Figure 19 demonstrate that 91% of subjects included in this study have been prescribed antibiotics in the past (i.e. they have real world experience with antibiotics). The remaining 9% included those who were not sure if they had been prescribed antibiotics in the past (3%), so the real number of subjects with past experience with antibiotics is likely to be higher than 91%.

Several unexpected results were observed over the course of data analysis. About 65% of subjects were not aware that antibiotics are ineffective against viruses. Furthermore, it was discovered that 13.7% of respondents did not know that viruses and bacteria are different.

This finding brings to light the potential source of a fundamental disconnect between physicians, researchers, and patients. Public service announcements that spread information on the fact that antibiotics are only effective against bacteria do not seem to have been effective for most of the subjects in this study. Importantly, such announcements will be of little use to patients who do not recognize that there is a difference between bacteria and viruses.

It was found that 48.6% of respondents did not know that antibiotics are more effective than placebos. If patients believe that the medication that they have been prescribed is not truly effective, they have less reason to continue taking their doses as prescribed. To individual patients, the negative consequences that might result from stopping a regimen partway through

are not nearly as recognizable as the potential positive consequences (such as an immediate tangible reduction in unpleasant side effects).[48]

Doctors and nurses who are made aware of the types of misunderstanding that could be taking place during their exchanges with patients will have the opportunity to allocate more attention to ensuring that the patient is up to speed with the basic biological principles underlying their disease. This assumes that doctors and nurses themselves have a good understanding of the topic at hand. While this intuitively seems like it would be the case, past research has indicated that up to 43.5% of pediatricians overestimate the risks of not prescribing antibiotics in conditions such as ear infections and tonsillitis.[66]

From a systemic approach, increased education on basic biological facts related to the development of antibiotic resistance could help to lessen the gap between patients and health care professionals, bringing their understandings closer together before patients even step foot in the examination room. Physicians could be made more aware of the realities of antibiotic outcomes, and patients could be made more aware of the potential consequences of their decision to be non-adherent.

The results visualized in Figure 21 show that about 24% of respondents had not heard of the problem of antibiotic resistance. The most basic step in increasing the level of education of the public will be ensuring that everyone is at least aware that antibiotic resistant bacteria are a problem. Another step will be ensuring that doctors are aware of actual trends in the development of resistance. The White House's 2016 budget allocations for combatting antibiotic

resistant bacteria will arm doctors with a variety of tools, such as the ability to monitor resistance geographically in real time, which should help refine prescription tendencies.[67]

The development of antibiotic resistant strains of bacteria is a threat that must be tamed from a variety of angles. Even as drug discovery teams race to develop new classes of drugs and farmers are pressured to use less medically important antibiotics in their livestock, clinicians and patients must each do their part to increase their understanding of the issues at hand and seek to maximize positive outcomes brought about by proper adherence to antibiotic regimens.

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