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Donovan Lucibello

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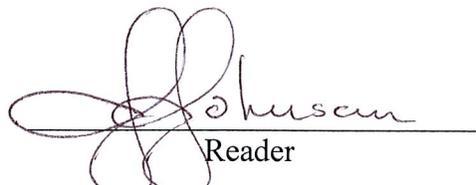
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Department of Nursing


Director
Jennifer Glowienka
Print Name

5-13-19
Date


Reader
Stefanie Otto-Hitt
Print Name

5.13.2019
Date


Reader
Janet Johnson
Print Name

5-14-2019
Date

Space Race, Siri and the Central Dogma:

A Contemporary Nursing Analysis of Antibiotics Resistance

Donovan R. Lucibello

Carroll College, Helena, MT

Author Note

This paper was prepared for NU-499, a senior thesis project for the following Carroll College faculty, Dr. J. Glowienka (professor of genetics), Dr. S. Otto-Hitt (professor of molecular biology), and J. Johnson (nursing instructor). After having each of you for some very challenging coursework, I am most grateful for your willingness to be on a senior thesis committee, working through applications and procedures required for research on humans. Moreover, if it were not for your patience, counsel and forbearance to partner with me, I would have never been able to bring this work from years of scientific curiosity into reality.

This work is written in the hopes that the empirical roots of biology will one day be within the everyday conversations of contemporary nurses everywhere. Since this paper is analyzing antibiotics resistance from a nursing science perspective, the use of the first person throughout is meant to convey a critique from within medicine, not of medicine writ large, as antibiotics are a “shared resource.” While most of my undergraduate training has been in the life sciences, I have benefited immensely from complementary studies into the physical sciences to help me understand the interdisciplinary edification of science informing science. For example, the inspiration for this paper came from a lifelong fascination with space exploration and an informal inquiry into unmanned Mars rover mission payloads. I began with the thought experiment of current rover missions seeking to indirectly detect life through looking for water or biological signatures (metabolic substrates or waste products), but could such a vehicle detect life directly? If we did find a puddle of mud on Mars, then what? In

corresponding over email with Dr. K. Cline (professor of mathematics and astronomy), I was first made aware of nanopore technology from a paper by Goordial et al. (PMID: 29326684, DOI: 10.3389/fmicb.2017.02594) seeking to develop just such a low size, weight and power payload for a Mars rover mission. If science had a way to detect life in a Martian pool of mud, why then are we in a blind spot here on earth at the primary care level to routinely diagnose infectious diseases?

I am also very grateful to the following Carroll College support from A. Dhanens (engineering and mathematics major), J. Woodrow (mathematics major), and Dr. E. Sullivan (professor of mathematics) for their support in compiling, analyzing and rendering these data for this research effort. I also wish to thank J. Ihlenfeldt (computer science and data science major) for his gracious assistance in understanding distributive processing, and the potential for multiple avenues of inquiries as biology and data science converge on their collective lygometry of disease.

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Foremost, this paper is dedicated in honor of the tireless efforts of both Dr. N. Heinzinger (public health sanitarian for the State of Montana) and Dr. S. Alvey (professor of microbiology). Through their exceptional work as collegiate professors, they together opened the world of microbes to me in both the classroom and in the laboratory. Through their collective inspiration, the genesis for this work helped me to push past the edges of what I knew today to envision what a state-of-the-art, empirically-based medical system can look like tomorrow.

Abstract

In the age of information, antibiotic resistance is still a black-box problem in clinical practice; pathogens are often defined in terms of which pharmaceuticals are no longer effective, and treatment protocols are prescribed prophylactically; often at strengths that are in excess of what is known about the pathogen's susceptibilities or even its identity. All antibiotic resistance mechanisms involve the expression of proteins that provide resistance capabilities. These modified proteins should be detectable by analyzing DNA (or RNA intermediates) that code for them in order to determine a pathogen's threat profile. Next-Generation and nanopore DNA sequencing technologies are capable of delivering prompt identity and virulence capabilities for bacterial pathogens, thereby delivering precise information for prescribing appropriate antibiotic solutions. Nursing is well positioned to deliver evidence-based care to patients by advocating for rapid empirical diagnoses where possible.

Space Race, Siri and the Central Dogma:

A Contemporary Nursing Analysis of Antibiotics Resistance

Contemporary Status of Antibiotics

In the microbial world, resources are limited, so fitness-to-survive means intense competition between and among species. Bacteria have been developing chemical means to outcompete and even kill other bacteria while defending themselves, thereby obtaining survival advantage within certain environments. These lethal chemical measures are exactly what humans have patterned and developed into antibiotics. The discovery of clinical antibiotics started in earnest around WWII, giving a near synchronous development of two technologies that forever changed human history: antibiotics and atomic weapons (Blaser, 2014, p. 62). The nuclear age brought about an inevitable arms race, and likewise, the antibiotics age has also rendered a different and even more complex arms race between pathogenic bacteria and our ability to prevent and treat infections – we are presently losing that contest. This paper deals with the problem of antibiotics losing their efficacy, the change over time of resistance in pathogenic bacteria, some contemporary technology solutions, and what a nurse can do about it daily in the twin arms of prevention: education and advocacy.

In the ensuing arms race of antibiotics, the stakes for humanity are very high. Life without effective antibiotics leads to certain peril, and is described as a threat to one of modern medicine's greatest achievements (World Health Organization, 2014, p.

ix). The threat to our precious antibiotic inheritance is so great that the G20 has listed it as a “serious threat to public health, growth and global economic stability” (G20, 2016). Under the current rate of decline in antibiotic effectiveness, a study by RAND Europe and KPMG estimates the economic cost of incurable bacterial infections to be \$100 trillion USD or a drop of 2 – 3.5% in GDP by 2050 (Review on Antimicrobial Resistance, 2014, p. 6). Add to that financial figure the projected death toll of ten million people per year from untreatable bacterial infections (Review on Antimicrobial Resistance, 2014, p. 6), and the magnitude of the antibiotic crisis comes into sharp focus.

Overview of Antibiotic Resistance

There is much discussion and media attention given to the issues of antibiotics losing their efficacy and pathogenic bacteria gaining resistance. This message can be heard from the highest levels, with the World Health Organization stating less than a century ago that people were still dying of infectious diseases that are completely treatable today, and that if humanity loses its quantitative pharmaceutical advantage, it will lead to prolonged illness burdens and death within our lifetime (WHO, 2018, p. 3). This same message is also candidly conveyed from the former Director of the CDC, Dr. Thomas Frieden regarding drug resistant health threats. Dr. Frieden stated, “If we're not careful, the medicine chest will be empty when we go there, to look for a life-saving antibiotic for someone with a deadly infection” (Frieden, 2013). Speaking frankly from the lectern at the CDC, Dr. Frieden's words were not hyperbole. If the future seems discouraging to the contemporary medical professional based on the present status of

antibiotic resistance, an explanation is helpful for understanding how we got here.

Better questions for public health discussions may be, “Why are antibiotics so ineffective against these ‘new’ resistant and more virulent bacteria?”; and, “Why are antibiotic resistant bacteria so abundant in the first place?” These may be the questions that elucidate just what Dr. Frieden meant by, “If we are not careful . . .” To understand this warning in a more meaningful way, contemporary healthcare professionals must understand such an implacable enemy as pathogenic antibiotic resistant bacteria, and in that context realize what options we still have left to best orient medicine for this reality. This contrast between looking passively at antibiotic resistance and actively at how this situation came to be an epidemic is now the question of necessity in order to drive both new research and health care policy before we run out of antibiotics that are still clinically successful at treating patients.

The power of pathogens has certainly shaped the fortunes of individuals and empires to ultimately determine some unimaginable outcomes throughout history. Most recently, antibiotics enjoyed years of uncontested success in what Kim Lewis (2013, p. 371) calls the “golden era of antibiotic discovery” between 1940 – 1960, where scientists could screen soil samples for bacterial and fungal species that endogenously produced novel antibiotic compounds that were immensely effective. Medical scientists were able to observe this chemical warfare between microbes, pattern it, bring it into the lab for research and later commercial synthesis into pharmaceuticals. Humanity

was making huge leaps in medical technology, yet microbes were changing too. What changed to bring about so much resistance?

Bacterial pathogens have changed, and in some cases, expanded their capabilities. These changes took place in the bacterial genetics, which we observe as resistance to antibiotics. Both genomes (bacterial DNA chromosomes) and plasmids (mobile DNA genetic elements) available to bacterial pathogens have increased their functional defense mechanisms. Furthermore, the resistant bacterial pathogens were revealed through over-exposure (Baker, Thomson, Weill, & Holt, 2018, p. 6) to what are now regarded as indispensable antibiotic drugs. Our present abundance of resistant pathogens can be best explained by times when antibiotics are administered indiscriminately, at a sub-therapeutic level, or for an insufficient duration; under those conditions, we only managed to select for the stronger, more resistant species. “Antibiotics save lives, and when a patient needs antibiotics, the benefits outweigh the risks of side effects and antibiotic resistance” (Center for Disease Control, 2017). We simply were not always careful with dispensing the precious antibiotics that we had available in an appropriate manner, and in this short-sightedness implemented prime conditions to develop resistance through a dose-response situation.

Today, the critical connection to make here is that we came very late to the ancient contest of microbes creating lethal chemical weapons to kill each other. First we were observers, then imitators, but now we simply cannot imagine life without these medicines. Our antibiotics are our best attempt to mimic the chemical warfare that we

see in the natural order. The chemical weapons used between species of bacteria are becoming more competitive and fit to survive on the microbial level. For every offense, bacteria have developed countermeasures. This microbial arms race predates all known recorded interactions with medicine. Restated another way, perhaps resistance was always there and the early perceived dominance of humans wielding antibiotics against susceptible pathogens in the 1950's seemed like a victorious asymmetric war at first but is now much more balanced with pathogens acquiring resistance. From where does all of this resistance come? Could the environment itself be a repository of resistance?

Consider the reports from a microbiologist exploring a sealed cave in New Mexico who discovered bacteria samples assumed to be four million years old and devoid of any human contact. These bacteria, scraped from biofilm residue samples, were found to be well-equipped to defend themselves against modern antibiotics using their own pre-historic genes (Mosher, 2012). Further evidence from a 30,000 year old ice core collected in the Canadian Yukon showed meticulously-sequenced DNA from bacteria, which revealed their resistance to several modern antibiotics including vancomycin (D'Costa et al., 2011, pp. 458–460). Both of these isolates demonstrate convincing evidence that ancient microbes already had the genes for antibiotic resistance which were well distributed millions of years before humans discovered antibiotics: "One implication of the ancient arms race is that we didn't cause resistance" (Blaser, 2014, p. 80). The environmental resistome (a genetic reference library providing the means to express antibiotic resistance in bacteria) has a much more rich

natural history, making antibiotic resistance an ancient, rather than a modern phenomenon (D'Costa et al., 2011, p. 457). The means by which bacteria become or are resistant is indeed genetic, which will be discussed in greater detail below in a later section Changes in Gene Expression: Antibiotic Resistance.

Sources of Antibiotic Resistance

Antibiotic resistance is an arms race and we are losing. No discussion of resistance is meaningful without the knowledge of how resistance works and what causes it. In the modern age of medicine, understanding some basic molecular biology brings a useful framework to comprehend how the problem can be addressed from scientific, policy, medical, and nursing perspectives. In short, antibiotic resistance comes down to the upstream effect of DNA coding for proteins in accordance with a biological principle called the Central Dogma of molecular biology.

All changes in virulence, resistance, and toxin production originate in the information encoded in a bacterium cell's DNA. For example, any features in any organism, such as the color of fur in a cat, fruit production in an apple tree, or beak shape of a finch are influenced by gene expressions flowing from the information contained in DNA or the regulation of it. DNA is the blueprint for life itself and is often packaged into chromosomes, which in total comprise the genome of an organism. Genes are sections of DNA on a chromosome that encode a useful product which, for the purposes of this paper, will be a protein. DNA is made up of four chemical bases named A, T, G, and C. Each of these functions something like a genetic letter, which are

covalently bonded together in a long polymer chain. Two single-strand DNA chains cross link to form the beautiful double helix first captured in the seminal research of Rosalind Franklin (Berg, Tymoczko, Gatto, & Stryer, 2015, p. 109).

Genes are sections of DNA on a chromosome that produce a useful product, such as a protein. The process of DNA transcribed to RNA which is then translated to proteins is called the Central Dogma. When talking about resistance, the DNA that is accessible to a pathogen must be understood as the root cause. Anything useful that is accomplished in a cell is accomplished by a multitude of proteins and a minority of functional RNA molecules. Enzymes are an especially useful type of protein as they catalyze chemical reactions that make the processing of cellular materials more efficient. In terms of antibiotic resistance, we are most concerned about protein products.

Bacteria are unique in that they are not limited to the DNA information encoded within their own genomes; they are also able to take up small circular pieces of DNA called plasmids. If a genome is endogenous, DNA are already present inside of the bacterium cell, controlling every process. Plasmids are exogenous DNA molecules that can carry genes whose encoded proteins carry out additional functions within a cell. Plasmids are not critical for the bacteria to survive, so they may be gained or lost without harm (Tortora, Funke, & Case, 2013, p. 94). The most interesting plasmids to medical science are those that convey antibiotic resistance or toxin production. Plasmids are potentially dangerous because they reside outside of the bacterium's

intact genome, and can be taken up or excreted like genetic trading cards (Wade, 2011).

Plasmids replicate independently of the bacteria host genome and protein synthesis from these plasmids may also be regulated independently of the host genome (Navon-Venezia, Kondratyeva, & Carattoli, 2017, p. 260).

Further blurring the distinction between endogenous genomes and a exogenous plasmids are transposons, or “jumping genes.” Transposons are DNA sequences within an organism’s genome that have the ability to move to different regions of the genome using special enzymes. In bacteria cells, these transposon DNAs can also be transferred plasmid DNA which have been embedded into the genome (Navon-Venezia et al., 2017, p. 269). When microbes interact, these jumping genes can be transferred on a plasmid to another bacterium and “uploaded” to its chromosome (Pierce, 2013, p. 515). The trademark of a transposon is that it alters the sequence of the genome of the host bacteria, differing from a plasmid which only resides in the cytosol, independent of the genome. Transposons may also bear a genetic payload such as antibiotic resistance genes, or R factors (Lodish et al., 2013, pp. 244–245). Transposons are especially potent because they are incorporated into and expand the genome itself. This enhanced primary DNA record is then replicated and passed down to every daughter cell through vertical transmission during the binary fission (asexual reproduction) process. One transposon change can potentially yield millions of cloned organism copies (Tortora et al., 2013, p. 580) in a single day.

Changes in Gene Expression Leading to Antibiotic Resistance

DNA is the primary blueprint for antibiotic resistance, whether it resides within a bacterium cell's genome or within plasmid DNA. A good understanding is necessary to understand how bacteria's DNA relates to survival in order to properly understand pathogenic bacteria resistance to antibiotics. In addition to being an information storage molecule, DNA is also a physical molecule that has a definite cost within the cell to maintain as an information record (Tortora et al., 2013, p. 213). Bacteria with the leanest genomes are the fastest to reproduce, have the lowest metabolic operating costs and are also the most likely to survive and leave offspring. In the bacterial world where competition to survive is very high, the ability to outcompete neighboring bacteria for resources is a constant struggle. With respect to antibiotic resistance, bacteria that have more stream-lined genomes may lack resistance genes and be initially susceptible to antibiotics initially, while bacteria with larger genomes may have the genetic information needed to provide antibiotic resistance in order to defend themselves. It is important to underscore here that antibiotic resistance by any means comes from DNA or changes to DNA. Changes come at a cost, so what best helps explain the required pressure to *change this information* leading to antibiotic resistance?

Accepting that resistance comes from DNA, there are three sources for that information. Bacteria may possess or obtain antibiotic resistance when: (a) the DNA is already present within the genome – bacterium has it; (b) plasmid and/or transposon DNA are acquired – bacterium gets it; or (c) random chance mutations occur - bacterium

incidentally develops it (Sommer, Munck, Toft-Kehler, & Andersson, 2017, p. 689). In all three instances, the DNA providing the information to synthesize the useful protein products are consistent with the Central Dogma.

Bacteria certainly can be resistant if they had the DNA conferring that resistance already. However, the concept of a bacteria species gaining a function is more difficult to conceptualize. Mutations are much more difficult to predict as they are typically accomplished by random chance. In the context where the leanest genome helps bacteria to be the most competitive, mutations have a cost. This helps to clarify why a mutation, even a beneficial one, would not endure if it did not have a purpose. More pointedly, by understanding the pressure to survive under the omnipresent use of antibiotics, we can also understand the drive to maintain these costly contingency genes in pathogens. In our use of antibiotics, we created the perfect conditions for selecting for antibiotic resistance (Crofts, Gasparrini, & Dantas, 2017, p. 430) within medicine and agriculture.

Mutations describe a change, and these changes takes place within the DNA altering the information recorded there. These changes may be by errors in replication, repair, or induced by mutagens that are not subsequently repaired. Regardless of the origin, a mutation is an alteration in the primary record of DNA, which means a different protein (or perhaps no protein) product will be expressed. Most mutations prove harmful overall (Adams, Holland, & Urban, 2017, p. 538), but there is a *small* probability that a mutation will be beneficial giving a bacterium a survival advantage so that it can

leave more offspring and outcompete its neighbors. There are bacteria that are known to be inherently nefarious like *Staphylococcus aureus*, of the MRSA (Methicillin Resistant *Staphylococcus aureus*) notoriety, which routinely have antibiotic resistance genes in their genome (Bryant, Chewapreecha, & Bentley, 2012, p. 3). Noteworthy here is that MRSA is identified by which antibiotics are no longer effective to treat it on account of the antibiotic resistance genes it now is known to carry. Other pathogens like *Klebsiella pneumoniae* (*K. pneumoniae*) are just assumed to have resistance plasmids and are infamous for being a world-wide shuttle for these antibiotic resistance plasmids (Navon-Venezia et al., 2017, p. 252). *Staphylococcus aureus* (*S. aureus* - also known as MRSA) and *Pseudomonas aeruginosa*, a more recent opportunistic pathogen, are both resistant to a primary family of antibiotics called β lactams (Sykes, 2010, p. 1844).

Rampant in some media messages is a skewed theory that pathogens somehow develop resistance through exposure, and that they have even “learned” to adapt to certain antibiotics. It is important to clarify that mutations are not a directed process at the cellular level; that is to say, bacteria do not react to antibiotic environmental threats by going back to the drawing board to engineer a solution according to some unicellular intelligent design scheme. There is not a research and development section within bacteria, and any mutation that yields any type of useful product is evolutionary pragmatism. Mutations happen at all times in all directions, as a coincidence some of these mutations happen to be beneficial and bestow a survival advantage. The possibility that some bacteria incidentally have a beneficial mutation is a very

improbable, yet certainly possible, event. When bacteria reproduce, they can do so very quickly through binary fission to yield an enormous quantity of single-celled organisms in a colony.

To illustrate this, consider the following thought experiment. Imagine that an average person, who is not skilled at breaking into vaults, was given an undisturbed and limitless amount of time to attempt to open a single bank vault door. It is plausible that given time, and enough trials, the vault could be opened by such a person. If that was just one person doing serial trials, then it would indeed take a long time to open the vault, and so the contents of the vault would remain safe until there was a successful breach. How would it be then if there were billions of the exact same doors into the same vault and billions of average people attempting to simultaneously open any one of them; might the time to get a solution be much shorter? The contents of the safe are indeed made vulnerable through limitless attempts to crack it, and so it is with pathogens responding to billions of attempts to mutate under pressure from chemicals designed to kill them. Antibiotics are made vulnerable with the near-infinite opportunities afforded to bacteria cells world-wide in order to develop mutations that may culminate in a gain of function like resistance (Berg et al., 2015, p. 1053).

In computer science, such a division of labor as the bank vault analogy is called “distributive processing,” where discrete entities are tasked with working on a separate piece of a problem (J. Ihlenfeldt, personal communication, January 31, 2019), thereby solving the problem much sooner. This describes the present situation with developing

antibiotic resistance in bacterial pathogens, whether in industrial farm manure lagoons, or in local hospitals, the clear statistical advantage overwhelmingly favors the bacteria on numbers alone but clearly does not favor the immunosuppressed patient in the ICU (Blaser, 2014, p. 83).

Published in their landmark study, Baym et al. (2016) devised an experiment using antibiotics to create increasing pressure on bacteria in a large dish, to observe if antibiotic resistance mutations occurred and if so, to quantify them. Summarily what was investigated in this experiment is if an omnipresent pressure from antibiotics is applied, would the bacteria produce beneficial mutations that increase their fitness in these increasingly more hostile conditions, and if so, could they be measured? This experiment had different stages that resembled a football field with yardage lines painted on it. Between each line was a log increase of antibiotic concentration (0, 1, 10, 100, 1000 minimum inhibitory concentration [MIC] of a certain drug). *Escherichia coli* (*E. coli*) were inoculated in a zone with zero concentration, followed by a zone with one time the amount of antibiotic that bacteria should be able to survive (1 x MIC). In other words, a reasonable person may predict at the beginning of the experiment that the bacteria would completely fill up the antibiotic-free zone and then stop at the first antibiotic front. Yet, this is not what happened. Instead, the bacteria paused at the 1 x MIC line and, after some time, started to fill the next zone of agar medium infused with the lethal dose of antibiotic through a defined breach point. At the next increase to 10 x MIC, again the bacteria halted, and the bacteria that was able to mutate first crossed

over to leave progeny and fill the next zone. This followed past the 100 x MIC and finally into the 1000 x MIC zone.

What can account for this change in just eleven days to see the same species of bacteria initially halted at the 1 x MIC and then eventually able to cross over into 1000 times the amount of antibiotic that should be lethal to them? The researchers directly cite whole genome sequencing data that showed a > 60 genetic nucleotide base (a letter of DNA, *e.g.* A, T, G or C) change called a single nucleotide polymorphism (SNP) (Baym et al., 2016, p. 1149). These individual base changes can be accounted for by comparing one genome to another under high-resolution sequencing where a single nucleotide base has been added, changed, or deleted (SNP's). Baym et al. (2016, p. 1149) were specific where the changes took place in the genome: the mutations were on the DNA Polymerase III enzyme coding region.

What does DNA Polymerase III do exactly in the cell? This is known as the “proof reading” enzyme in the mechanisms responsible for DNA replication. If DNA Polymerase III were impaired or altogether missing and a mistake was made during DNA replication at each binary fission event, there would not be a viable proof-reading mechanism to not catch and/or correct the error. This leaves the bacteria progeny with a residual mutation. In a sense, the lack of proof-reading is also the freedom to experiment (Fowler, Schaaper, & Glickman, 1986, p. 130). Like the bank vault cracking analogy illustrated, mutation is a probability event. Roy Kishony explains that given enough time and opportunities spread across billions of bacteria, one of them may be able to

generate a successful mutation allowing them to pursue the food resources in the next zone of ten-fold increasing antibiotic in front of them (60 Minutes Australia, 2013).

This experiment is especially illustrative for the concept that great numbers of bacteria in a system can mutate by chance. This mutation brings with it the possibility to gain a function like antibiotic resistance. This context clarifies why simply discussing antibiotic resistance as an effect is incomplete, where genomic evolution (a change over time) is the cause. Did humans cause antibiotic resistance? Likely not, but we certainly did exacerbate it. Bacteria are free to pick up resistance genes in the environment, and they certainly do so (Crofts et al., 2017, p. 425). However, given enough time and exposure to the pressure from antibiotics, bacteria will find a way to survive; a successful mutation can yield a survival advantage. Clinically, we rarely have the tools with the resolution needed to detect new mutations, which can be stated with certainty because we currently do not use the means to rapidly sequence bacterial pathogens at all. The next section describes what resistance looks like in a clinical situation and what is being done to combat it in both the fields of medicine and nursing.

Current Methods for Combating Resistance

In order to understand how to move forward in the field of antibiotic resistance, it is important to first address how antibiotics are currently used in clinical settings. Any case study that deals with a septicemia infection is a demonstration of a race against the clock to save the life of a patient. As the adverse effects of the pathogenic bacteria in the vasculature quickly cascade, often heroic measures are enacted to thwart a fatal

outcome. Before the rapidly deteriorating circumstances involving systematic inflammatory response syndrome (SIRS), early goal-directed therapy (EGDT), or sequential organ failure assessment (SOFA or qSOFA) can be understood in the context of their complex physiologies, there needs to be a sense of how diagnoses are made. Pathogen identification and appropriate antibiotic prescription is currently rather crude.

Antibiotics Usage in Medicine

Diagnosing bacterial infections is currently slow but reliable. Bacterial disease processes can move very rapidly, deteriorating the health of an effected patient. Death from bacterial infections, however, are difficult to quantify by health statistics. One incidence rate estimates the number of cases each year in the Unites States alone to be between 650,000 and 750,000 (Hoffman & Sullivan, 2017, p. 266). Once an infection is diagnosed and is actively being treated in a hospital, mortality estimates range from 10 – 52% based on comorbidity, presentation, site of infection, identity of the pathogen (if known) and general health at the time of admission (Neviere, 2018). Further obscuring the data of fatalities from systemic bacterial infection (e.g. sepsis, septic shock and septicemia) are complications from end organ failure or a patient's reaction to medications like antibiotics. In either instance, systemic bacterial infections are extremely serious and are often a race against the clock. Moreover, the diagnosis process itself is very hard to quantify among a constellation of different medical data points like clinical presentation and clinician judgment, laboratory values, and radiography, as well as findings returned from the microbiology lab (Neviere, 2018).

Based on this limitation in time to receive empirical data results, treatment protocols are streamlined to a page in the clinical playbook: suspect infection, stabilize respirations, establish venous access, draw blood cultures, give broad spectrum antibiotics, monitor closely, de-escalate antibiotics slowly, and wait for results (Schmidt & Mandel, 2019). All that is known is that there may be a bacterial infection judging by presentation, and it is likely that drawing blood cultures and administering broad-spectrum antibiotics would help if administered without delay (Society of Critical Care Medicine, 2016). In effect, this leaves medicine in a blind spot from a lack in technology to bacterial virulence and resistance factors, or other pathogens that would not respond to antibiotics like fungal or viral infections.

Concerning systemic bacterial infection diagnosis, current protocols dictate drawing blood cultures without delay (Society of Critical Care Medicine, 2016). However, the current methods for getting empirical microbiology test results from those cultures are too slow to be of any clinical value or to empirically inform antibiotic treatment. The online medical resource UpToDate succinctly identifies the current weaknesses in clinical microbiology laboratory techniques performed on cultured media: (a) they rely on speed of bacterial growth (a profoundly rate-limiting step), (b) current means are not necessarily looking for or are able to culture fastidious or uncommon bacteria, (c) results may vary between laboratories performing the assessments (Turbett & Pierce, 2017). The gathering of empirical data using current technology means culturing pathogenic specimens, which goes at the speed of the

organism's ability to grow in a lab and respond to selective and/or differential media with inhibitors (*e.g.* antibiotic laden disks).

Despite the issues stated above, culturing pathogenic specimens is not without its considerable benefits. The laboratory tests performed on these specimens are very reliable due to longstanding protocols (*i.e.* disk diffusion, β -lactamase testing, etc.) with reliable and reproducible results. They are relatively inexpensive and do not require facilities with high-end equipment, but it can potentially take 24 – 72 hours to receive results (Chidester et al., 2016, p. S158). Given a patient with a diagnosis of septicemia or meningitis, they would already be dead in the elapsed time necessary to get empirical data back on how to treat the infection. These situations call for an inexpensive, easy to operate, low-cost solution that can return empirical data in a short period of time, thereby allowing medial professionals to both save lives and preserve the remaining effectiveness of our antibiotics.

As stated, the antibiotic resistance capabilities and virulence factors are owed to DNA encoded on a plasmid or bacterial genome. Here I make the claim that in the molecular age of biology, those DNA virulence signatures can be quickly detected in order to make a rapid and informed diagnosis. In the interest of clinically pathogenic bacteria, the question needs to be asked, "At the time of infection, what are the virulence capabilities of the bacteria?" More specifically, does the bacteria have the ability to, (a) become invasive, (b) generate toxins, or (c) both become invasive and generate toxins (Adams et al., 2017, p. 536)? At present, there is a severe delay in our

ability to answer these questions, and so high-strength antibiotics are all too often given prematurely and reflexively without empirical data.

Antibiotics in Nursing

Nurses do their best work in areas of prevention, education and advocacy. When an antibiotic is clinically warranted, there is simply no substitute. The history of nursing and the history of antibiotics have a far more intimate connection since the first patient to have her life saved in America was a nurse. Anne Sheafe Miller lay in a hospital bed in Yale New Haven Hospital in 1942 spiking fevers of 107°F, coming in and out of consciousness. Blood transfusions, surgery and sulfa drugs were all unsuccessful and her doctors were running out of options (Saxon, 1999). Her doctor knew that Anne's streptococcal infection (septicemia) would precipitate to a lethal situation, so he used a government connection to reach out to a scientist he knew was working to commercially produce penicillin at a pharmaceutical laboratory in New Jersey (Rothman, 2016). The request was a steep one: to please send a tablespoon of penicillin (about one half of the entire supply of penicillin existing in the United States at the time) to Yale New Haven Hospital (Rothman, 2016). The experimental drug had only been dispensed in limited trials with mice and people yielding mixed and largely disheartening results (Saxon, 1999), yet the laboratory honored the request. The penicillin arrived by airplane so that a Connecticut State Trooper could escort it to the bedside where it was administered to Anne (Blaser, 2014, p. 55). Her fever broke and her recovery, regarded

as miraculous, began within hours; she was eventually fully recovered and discharged (Blaser, 2014, p. 55).

Since nurses administrate medications every day, they are very familiar with and conscious of medication side effects. Regarding antibiotics, the higher the potency (*e.g.* the broader the spectrum), the more adverse the side effects. Such mental calculations encompassing risk vs. benefit are called the therapeutic index of a medication (Adams et al., 2017, p. 52). Largely, this becomes an intuitive thought process for a nurse. Nurses understand that all medications have side-effects of some kind, however antibiotics can have some very harsh side effects such as: chronic diarrhea, renal, hepatic and/or cardiac problems, and even hearing loss (Tortora et al., 2013, p. 584).

Regarding education, there is a large opportunity for nurses to contribute *daily* to the fight to save patients and antibiotics. It may be hard for patients to grasp the nuance of how antibiotics even work. Medications are not intuitive; they work on the cellular or even molecular level in the body, a scale poorly understood by most of the population. Critical to preserving the efficacy of antibiotics is the proper patient education for their use. For example, the duration of the prescribed treatment, and the consequences of not finishing a course of antibiotics should be discussed. As discussed previously, bacteria can and do mutate in general. There is no better experiment model to test this than to take antibiotics sub-therapeutically.

To get a sense of the magnitude of this, I will adapt and expand an example given by Dr. Martin Blaser, MD, who is a former CDC research doctor. Imagine a Petri

dish inoculated with a species of bacteria, say *E. coli*. Using some simple laboratory techniques, say that an estimated count of the bacteria in the dish is calculated to be 10^9 or one billion individual cells. Now administer a sub-therapeutic level of antibiotic which reduces the count to 10^3 , or effectively a 99.9999% reduction! However, we are still left with 10^3 or one thousand remaining bacteria to reproduce. Given that the relative handful of residual bacteria may have even mutated under sub-therapeutic treatment, this leaves them with a survival advantage to be more fit to defeat subsequent antibiotics. To put that another way, by not finishing an antibiotic course, we have allowed conditions for the weak ones to survive (Berg et al., 2015, p. 1053). If this proportion in reduction was happening inside of a patient, there would still be that residual 0.0001% left to generate toxins, trigger proinflammatory cytokine surge, shut down organs and admit an immunocompromised patient into the ICU. With these odds, the bacteria have the advantage when antibiotics are not followed to the full extent of the prescribed course. If that newly-emerging resistant strain becomes prolific in a hospital or community, the bad news just keeps getting worse and worse where mutations beget mutations. “This is a simple example of natural selection, but competition is eternal. May the best microbe win” (Blaser, 2014, pp. 19–20).

While working with actual people and not Petri dishes, these exact circumstances are where nurses can have a *daily* contribution to patient education. Encouraging a patient to finish the course of antibiotics to their full extent ensures that the applied chemotherapy will have all of the effect that it could possibly have in the

patient's system. Moreover, if the infection is in a place where the antibiotic concentration is uncertain (*i.e.* inside of a biofilm in a urinary tract infection), this education has all the more effect to pay dividends on the individual patient, health care agencies and the community level. No one benefits from reoccurring infections, except perhaps pathogenic bacteria.

Infection control positions nursing to have an even greater opportunity. Imagine if infection control could inexpensively survey, identify and isolate obstinate pathogens that lurk in some of the highest acuity care locations in a hospital. As discussed, the patients who are treated for the most serious infections are given the highest strength antibiotics, and this typically occurs in the ICU. As mentioned previously, the pressure applied to bacterial pathogens can foster conditions favorable to mutant survival. The higher the potency of the antibiotic, the higher the pressure for mutants to survive, leaving the most dangerous of the superbugs in the same places where we would treat our highest acuity patients (*e.g.* the ICU, and the oncology or medical floor). Little seems to be done presently about prospectively intercepting outbreaks in any type of quantitative manner, at either a local or national level. Infection control is a wide-open area for nursing to develop quantitative surveillance measures. In order to do this, nurses in infection control positions would need a method to be able to sample, isolate and identify ambient bacteria and viruses in the environment quickly by their DNA or even RNA signatures without the need for patient identifiers. Ideally, all of this would be able to run in a disposable flow-cell cartridge set up, with results cataloged via

automated post-processing. Such logged events could even be converted to a queried function of private and publicly-available national or international databases. If there were a distributed net of low-cost sensors like this in health care agencies, they could even upload results automatically to regional, state, national or international agencies as early warning threat monitoring systems. This type of analysis simply could not be carried out using manual processing on cultured media as it would be far too slow and does not lend itself to automation.

Survey of Nurses to Measure Their Beliefs about Antibiotic Resistance

Clearly DNA holds the information to produce antibiotic resistance and virulence for pathogens. But would a nurse be able to identify DNA as the etiology of antibiotic resistance? In order to measure this and to create new knowledge, I designed a survey for nurses to investigate this question. Those rationales are included in Table 1 to provide greater familiarity with the current research.

Materials and Methods. The intent was to give a survey questionnaire to determine in a quantitative sense what a nurse believes to be the cause(s) of antibiotic resistance. In order to do this, a survey was created with an identical “select all that apply” question containing ten options of potential causes. Two separate surveys were conducted for both student nurses and professional nurses. The investigation hoped to investigate if student nurses and professional nurses could identify the cause(s) of antibiotic resistance from a list of options that implicated DNA or a change/mutation in DNA.

In the select-all-that-apply-style question given in the survey, there were six valid causes of antibiotic resistance, three effects, and one red herring statement for a total of ten possible options from which to choose (see Table 1 for the scoring scheme and rationales). Both a null and an alternative hypothesis were devised to evaluate the data from the survey:

H₀: There is not any difference between the options selected in the given question by a nurse or by any person randomly choosing options;

H₀ = 3/6 correct answers.

H_A: Options selected by a nurse in the given question are more likely to be correct;

H_A: = > 3/6 correct answers.

The survey was conducted in two iterations: one on-campus survey using the student nurses in the Carroll College Nursing Program in Helena, MT; and then a broader email survey to professional nurses through Survey Monkey. For each survey, the principle research question was identical, but the demographic questions differed as were appropriate to the sample. This serial approach was advised by Dr. A. Street (Professor of Political Science at Carroll College). This allowed for a test with a smaller population of student nurses on campus to first validate the survey instrument before incurring the costs associated with going live with a larger sample. All research on human subjects was done under the oversight of the Carroll College Institutional Review Board.

The survey of student nurses was conducted across three cohorts of students (*i.e.* sophomore, junior and senior) enrolled in the Carroll College Nursing Program in Helena, MT. The on-campus survey was conducted on paper forms in a classroom setting familiar to the students. The population of Carroll student nurses was 127, and the number of voluntary participants was 122 ($n = 122$ or 96% response). The professional nurse sample consisted of 20,006 individual email recipients from a purchased list of email addresses advertised as contact information for professional nurses. This survey was conducted through a Survey Monkey (www.surveymonkey.com) interface accessed by a link sent to the prospective participants' email addresses. Of the 20,006 nurses contacted, 625 participants elected to reply ($n = 625$ or ~3% response).

Analysis. Original data files (spreadsheets, R code files, etc.) can be found here: <https://github.com/dlucibello/NU499-Thesis-Antibiotics-Resistance>. Numerical totaling of these data was done in Microsoft Excel spreadsheets (.CSV format using Microsoft Office Professional Plus 2019), while statistical analysis of the results was conducted using R (Version 1.1.463 – © 2009-2018 RStudio, Inc.) with both the tidyverse and ggplot2 packages installed.

Tallying the data was done in Microsoft Excel, where each participant was entered on a separate row that captures all of their endorsed responses. For student nurses ($n = 122$), their endorsements were entered manually from the paper survey forms and triple-checked for accuracy. For professional nurses, their endorsements

were downloaded from the Survey Monkey dashboard interface into a readily imported flat file. For student nurses, a “=SUM” command was used within Microsoft Excel to score each row for the number of correct options (*e.g.* 2, 4, 6, 8, 9 and 10) endorsed by the participant out of the six possible correct options (without penalizing for guessing). To calculate correct answers for professional nurses, a “=COUNTA” command was used within Microsoft Excel to score each row under the same scheme. Of the “select all that apply” question options, options 2, 4, 6, 8, 9 and 10 are correct (that is to say support can be found in the literature for these options) and were counted, options 1, 3, 5, and 7 were not counted. Options 11, 12, and 13 are technically exclusive (see Table 1), but were also not counted as an extension of the no-penalty-for-guessing motif of scoring this survey. Of the ten options, the six correct options are ones that can be supported in the literature (see Table 1).

A simple 50/50 “coin toss” analysis was used in order to establish how likely it would be to have a random person take this same survey and select correct options without penalizing for guessing. Using an R script to import the scored .CSV spreadsheets, participants endorsed options which were tested against the mean of 3 using a T test (“t.test”) function in order to test the hypotheses. The results were evaluated in R using the default $\alpha = 0.05$ to assess significance, as well as the mean of the sample and a 95% confidence interval.

Discussion and Results. Admittedly, it is a difficult thing to draft a check-the-box survey to ask about someone’s professional beliefs on a potentially delicate topic.

Compounding this difficulty was the need to have an instrument that could be delivered en masse and then scored quickly and objectively. There is a case to be made that a free-response format would have been a better format. However, the select all that apply style question in the end proved to have the widest utility for the following reasons: (a) a free-response-style questionnaire would require an extensive rubric to compile and rate keywords or concepts that would be very time intensive to score; (b) a select-all-that-apply-style question is quite common and familiar in nursing education; (c) the select-all-that-apply-style question lent itself quite well to the automated scoring and data extraction from a web-based medium like Survey Monkey.

After collecting and analyzing the data, the results were mixed. The sample of professional nurses selected a mean of 3.054 out of six correct responses ($p\text{-value}_{\text{Professional}} = 0.342$, which is not significant). Response data for professional nurses are summarized in Figure 1. Evaluating the calculated $p\text{-value}_{\text{Professional}}$ of 0.342, there is room for improvement with professional nurses in practice, the majority of which (88%) report > 15 years of experience as a nurse. Regarding whether the participants in the professional nurse sample can identify the causes of antibiotics in the survey, I fail to reject the null hypothesis (H_0) in light of the evidence.

The sample of student nurses selected a mean of 3.795 out of six correct responses ($p\text{-value}_{\text{Student}} = 7.3 \times 10^{-12}$, which is highly significant). Response data for student nurses are summarized in Figure 2. Evaluating the calculated $p\text{-value}_{\text{Student}} = 7.3 \times 10^{-12}$, shows good evidence to reject the null hypothesis (H_0) in favor of the alternate

hypothesis (H_A), that student nurses can identify DNA and changes to DNA as the cause of antibiotic resistance as supported by the literature. These results are encouraging as they suggest that upcoming nursing professionals entering into their prospective healthcare specialties can correctly identify causes for antibiotic resistance at a time when medicine will be embracing these new technology and treatments. Regarding whether the participants in the student nurse sample can identify the causes of antibiotics in the survey, I reject the null hypothesis (H_0) in light of the evidence.

Demographic data for professional nurses (as given voluntarily by participants on the Survey Monkey entry form) can be seen in Figure 3. All data files can be found here: <https://github.com/dlucibello/NU499-Thesis-Antibiotics-Resistance>.

Table 1

Selections, Scoring, and Rationales

Survey question reads: <i>"Please select all that apply from the options below as to what you believe the cause(s) is/are for bacterial antibiotic resistance."</i>			
Number	Selection to be Evaluated by Survey Participant	Scoring	Rationale
Selection 1	Chemical countermeasure compounds that the bacteria generate are able to defeat the antibiotic medications (making them ineffective).	Not Counted, Incorrect	A chemical countermeasure is the product of a protein, which is a downstream gene expression of DNA. Proteins are an effect, not a cause of antibiotic resistance.
Selection 2	The creation of biofilms can prevent antibiotic medication from reaching the bacteria inside.	Counted, Correct	Biofilms can actually be a cooperative effort of unicellular organisms functioning in a "multicellular" scheme (Kalia, Wood, & Kumar, 2014, p. 2) with collective resources and a slime layer protecting the bacteria from harm of all kinds to include antibiotics (Willey, Sherwood, & Woolverton, 2017, p. 779). Part of this functionality is to share resources, even something called "external DNA (eDNA)," (Okshevsky & Meyer, 2015, pp. 341, 347) which serves a dual role for both structural scaffolding and information sharing. The NIH accounts for 80% of human infections involving biofilms, making their resistance to treatment very "medically important" (National Institutes of Health, 2002). In a biofilm, the inter and intra-species business becomes very Darwinian (Sykes, 2010, p. 1842) with eDNA within its more important role as the information-bearing molecule of life. Equally complex is the chemical signaling between bacteria within a biofilm called "quorum sensing," which is so important that bacteria carry up to 10% of their genome to support this communication capability (Kalia et al., 2014, p. 9). Within the collective of the biofilm, cells will often be targeted to be lysed in order to harvest the DNA (Allocati, Masulli, Di Ilio, & De Laurenzi, 2015, p. 4) looking for survival advantage genes (<i>e.g.</i> resistance) within the biofilm to take up that DNA, and proliferate this survival advantage to progeny as part of the "biofilm lifestyle" (Okshevsky & Meyer, 2015, p. 345). When comparing the causes of resistance, the means to acquire coding DNA in order to gain a function with gene expression (resistance), horizontal transfer is indeed the "low hanging fruit" for bacteria to gain capabilities when compared to the much more improbable mutation (Sykes, 2010, p. 1844).

Selections, Scoring, and Rationales

Survey question reads: *“Please select all that apply from the options below as to what you believe the cause(s) is/are for bacterial antibiotic resistance.”*

Number	Selection to be Evaluated by Survey Participant	Scoring	Rationale
Selection 3	Protein pumps in the bacteria that allow it to efflux (pump) out antibiotic medications designed to kill them.	Not Counted, Incorrect	Bacteria are also able to enter a state of dormancy in a biofilm because they are essentially nutrient and resource starved. Here in this state, they can metabolically slow down or even nearly shut down (Lewis, 2013, p. 372) due to the lack of nutrients and oxygen in a biofilm (Santajit & Indrawattana, 2016, p. 5). By being metabolically inactive, the antibiotics are able to “pass by” the bacteria and eventually be excreted by the host over the course of the treatment, while the bacteria in the biofilm are just waiting for the times of plenty to come back again to resume metabolic activity (Willey et al., 2017, p. 188). For example, the action of ampicillin affects cell growth, specifically synthesis of a cell wall, but if the bacterium is not growing and dividing because it is in a state of dormancy, it will persist pass the course of antibiotic treatment (Dubnau & Losick, 2006, p. 566). Interestingly, bacteria in a biofilm are 1,000 times more difficult to treat with antibiotics than free-swimming bacteria (Kalia et al., 2014, p. 2). This severely complicates treatment, even exceeding the highest tolerable dose of antibiotics that can be administered to a patient. A protein pump is the product of downstream gene expression of DNA. Proteins are an effect, not a cause of antibiotic resistance.
Selection 4	Random mutation of bacteria genes accelerates the evolution of bacteria to defend themselves.	Counted, Correct	In their landmark study, Baym and Kishony show empirically that as bacteria constantly mutate in all directions. Interestingly, those mutations which lead to antibiotic resistance are observed in the selective conditions of agar infused with increasing amounts of antibiotics (Baym et al., 2016). The mechanism is by random chance, which by definition is undirected; however, the bacteria are able to do this by sheer numbers. See bank vault analogy in this paper on page 17.

Selections, Scoring, and Rationales

Survey question reads: *“Please select all that apply from the options below as to what you believe the cause(s) is/are for bacterial antibiotic resistance.”*

Number	Selection to be Evaluated by Survey Participant	Scoring	Rationale
Selection 5	Bacteria have alternate pathways to utilize for necessary metabolic functions that the antibiotic medications are designed to block.	Not counted, Incorrect	Alternate metabolic pathways are the work of proteins and enzymes, which are the products of downstream gene expression of DNA. Proteins are an effect, not a cause of antibiotic resistance.
Selection 6	Patients not taking a course of antibiotics to its full prescribed duration.	Counted, Correct	An incomplete course of appropriately prescribed antibiotic treatments is only selecting against weak bacteria involved in an infectious process, leaving the stronger variants behind to reproduce (Tortora et al., 2013, p. 582). See section on the 0.0001% residual bacteria left in a Petri dish on page 25.
Selection 7	Higher acuity of patient presentations in contemporary clinical setting.	Not Counted, Incorrect	Patients being sicker in a clinical presentation is an effect of higher virulence in pathogenic bacteria and thus cannot be a cause of the same.
Selection 8	Selective pressure from the overuse of antibiotic medications and antiseptic cleansers make bacteria develop new antibiotic resistance (e.g. “dose-response”).	Counted, Correct	<p>Bacteria must be very competitive to survive, and since DNA – the true cause of antibiotic resistance – is expensive to maintain, bacteria simply will not carry genes that they do not need. Applying this principle, if bacteria are not exposed to antibiotics, they will not maintain those resistance genes since they are not needed (Dar & Sorek, 2017, p. 111). The “dose-response” theory states that a increase in the input of one (independent) variable causes a proportional increase in a resulting (dependent) variable. Here for the purposes of antibiotic resistance, it means that the more antibiotics are used, the more resistance we see over time. There are different modalities where antibiotics are used in excess (see option 10 rationale below); however, one large offender would be the inappropriate use of antibiotics to treat viral symptoms (Doyle, 2015, p. 269; Lodish et al., 2013, p. 244).</p> <p>There is good evidence that the highly-resistant ESKAPE pathogens (<i>Enterococcus faecium</i>, <i>Staphylococcus aureus</i>, <i>Klebsiella pneumoniae</i>, <i>Acinetobacter baumannii</i>, <i>Pseudomonas aeruginosa</i>, and <i>Enterobacter</i> species) have become resistant from such routine exposure</p>

Selections, Scoring, and Rationales

Survey question reads: *“Please select all that apply from the options below as to what you believe the cause(s) is/are for bacterial antibiotic resistance.”*

Number	Selection to be Evaluated by Survey Participant	Scoring	Rationale
Selection 9	Something to do with the genetics of the bacteria itself that it has or picked up.	Counted, Correct	<p>antibiotics (Navon-Venezia et al., 2017, p. 253). The pathogens’ response is resistance and their location is typically in a hospital where the most powerful antibiotics are routinely used (Willey et al., 2017, p. 205). See also: (Berg et al., 2015, p. 1053; Dar & Sorek, 2017, p. 113; Kalia et al., 2014, p. 1).</p> <p>According to the Central Dogma, if a cell has the required DNA, either in its genome or in a plasmid, it can make the proteins necessary to mount countermeasures to block entry of, chemically neutralize, or pump out antibiotics via efflux pumps. All of these actions are the work of proteins which are downstream gene products of DNA. DNA is the foundational molecule for all of genetics, so it is listed as a cause of antibiotic resistance.</p>
Selection 10	Overuse of antibiotics in agriculture.	Counted, Correct	<p>Most animals raised for meat, milk, or eggs are raised in high-density living situations which are prone to bacteria. However, antibiotics in agriculture are surprisingly not used because animals are primarily sick; rather antibiotics are dispensed to keep livestock growing to market weight and can even be purchased over the counter for this purpose (Doyle, 2015, p. 269). The use of antibiotics for non-medical treatment has been banned in the EU since 2005 (European Commission, 2005). Since the 1980’s, antibiotic resistance can be traced to the “perfect storm” conditions (Crofts et al., 2017, p. 423) of mass sub-therapeutic doses in agriculture (Baker et al., 2018, p. 5). Just how many antibiotics are used in agriculture? Using the unit of measurement of a Boeing 747-8 with a maximum takeoff weight of 447,696 kg (987,000 lbs) (Boeing Commercial Airplanes, 2012, p. 7), the US Food and Drug Administration (FDA) reports that the amount of “medically important” antibiotics used in agriculture during 2017 were equivalent to 12.4 Boeing 747-8’s (Food and Drug Administration, 2018, p. 26). This is down from the high water mark in 2015 of 34.7 Boeing 747-8 aircraft – and that figure does not count “non-medically important” antibiotics; adding these to the count would indeed double that number (FDA, 2016, p.</p>

Selections, Scoring, and Rationales

Survey question reads: *“Please select all that apply from the options below as to what you believe the cause(s) is/are for bacterial antibiotic resistance.”*

Number	Selection to be Evaluated by Survey Participant	Scoring	Rationale
			12). See also: (Crofts et al., 2017, p. 431; Doyle, 2015, p. 269; Forsberg et al., 2014; Navon-Venezia et al., 2017, p. 259).
Selection 11	None of these.	Not Counted	This option was included as a provision for a participant who could not endorse any of the above. Since six of the above ten are correct, this logically cannot be scored as correct. Any endorsements of this option were not also not counted as an extension of the no-penalty-for-guessing motif of scoring this survey.
Selection 12	I do not have enough information to answer the question.	Not Counted	This option was included as a provision for a participant who could not endorse any of the above. Since six of the above ten are correct, this logically cannot be scored as correct. Any endorsements of this option were not also not counted as an extension of the no-penalty-for-guessing motif of scoring this survey.
Selection 13	I did not understand the question being asked.	Not Counted	This option was included as a provision for a participant who could not endorse any of the above. Since six of the above ten are correct, this logically cannot be scored as correct. Any endorsements of this option were not also not counted as an extension of the no-penalty-for-guessing motif of scoring this survey.

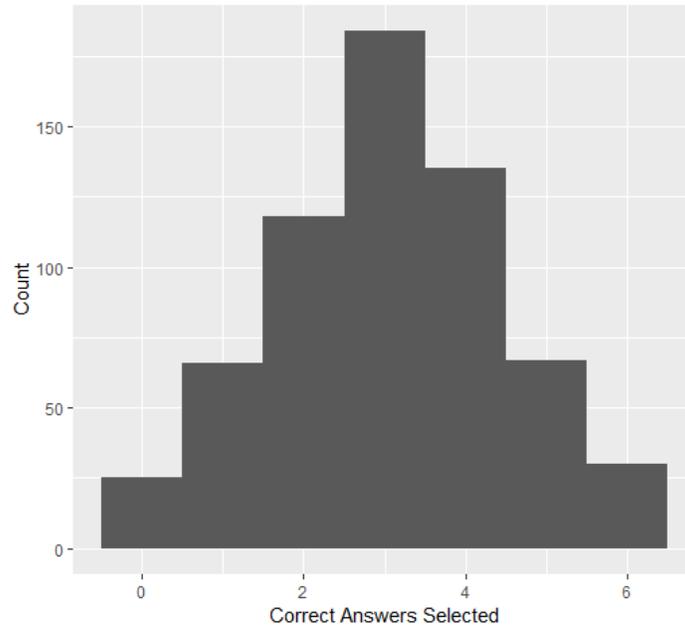


Figure 1a. Scored responses from professional nurses (n = 625 participants). Out of six possible correct options in a list of 10 inclusive options appearing in a “select all that apply” question, professional nurses scored a mean of 3.054, df = 624, p-value 0.342, sd = 1.431, 95 percent confidence interval: 2.94, 3.17.

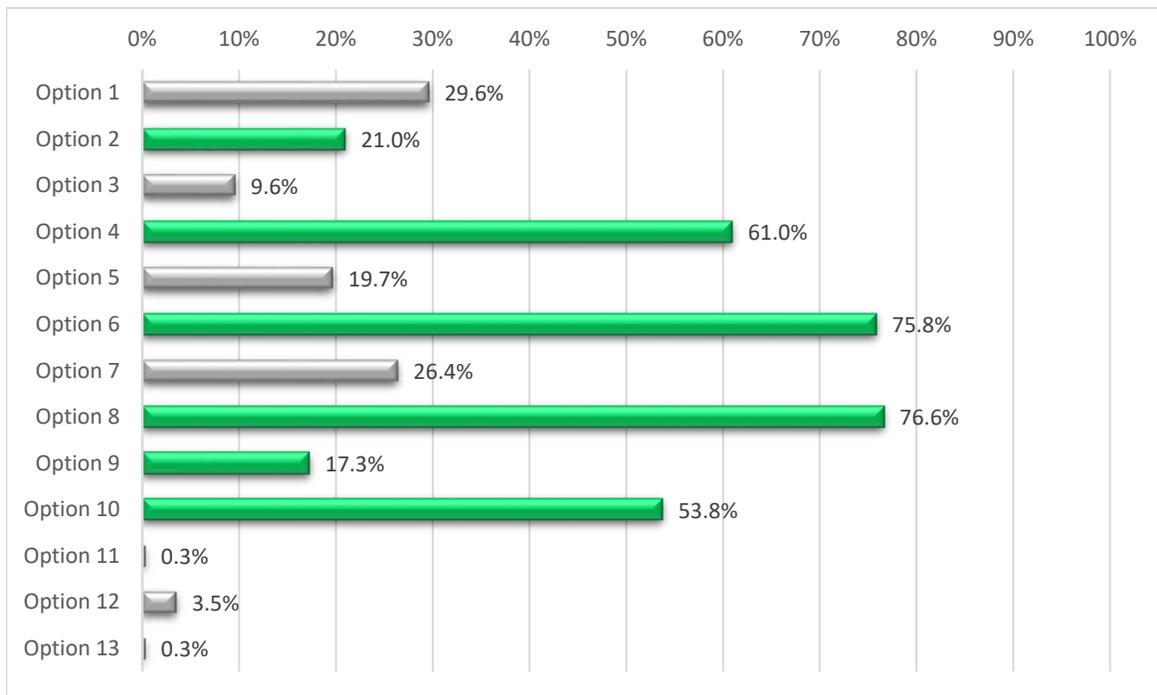


Figure 1b. Scored responses from professional nurses (n = 625 participants). There were six possible correct options in a list of 13 options appearing in a “select all that apply” question. Correct answers that were scored appear in green, answers that were not counted appear in grey. Under this scoring system, no penalty was given for guessing. Percentage of participants who endorsed that option appear to the right of the bar.

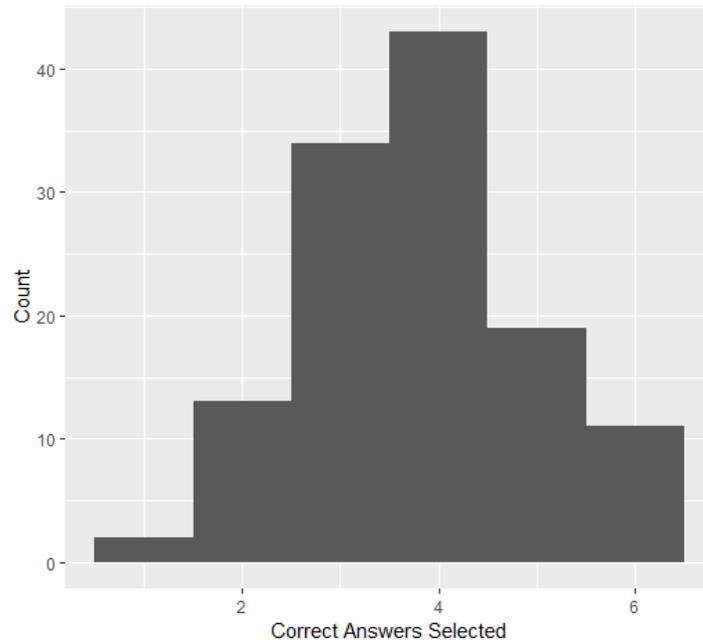


Figure 2a. Scored responses from student nurses (n = 122 participants). Out of six possible correct options in a list of 10 appearing in a “select all that apply” question, student nurses scored a mean of 3.795, df = 121, p-value 7.3×10^{-12} ***, sd = 1.157, 95 percent confidence interval: 3.59, 4.00.

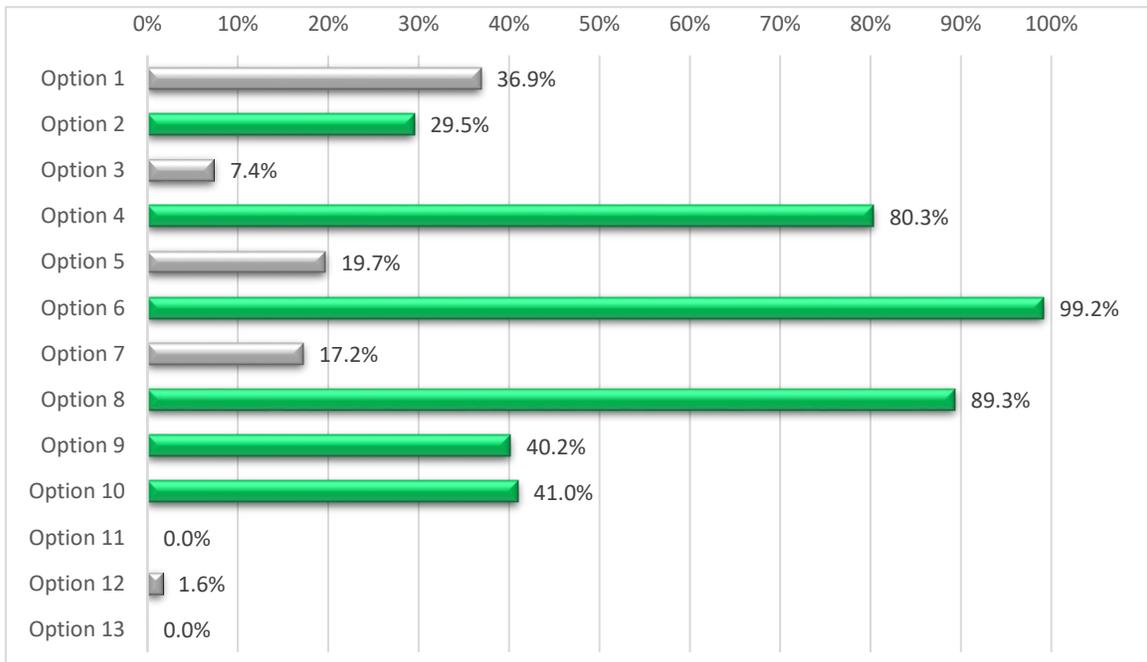


Figure 2b. Scored responses from student nurses (n = 122 participants). There were six possible correct options in a list of 13 options appearing in a “select all that apply” question. Correct answers that were scored appear in green, answers that were not counted appear in grey. Under this scoring system, no penalty was given for guessing. Percentage of participants who endorsed that option appear to the right of the bar.

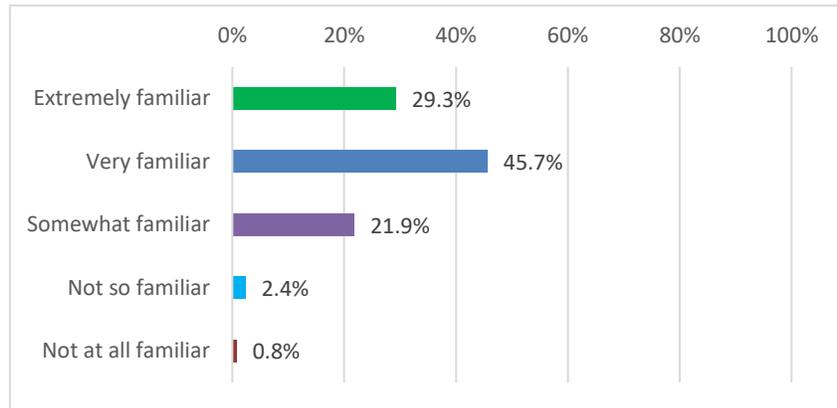


Figure 3a. Optional response question at the beginning of the survey asking the participants (n = 622) to rate their level of familiarity with antibiotics and their use.

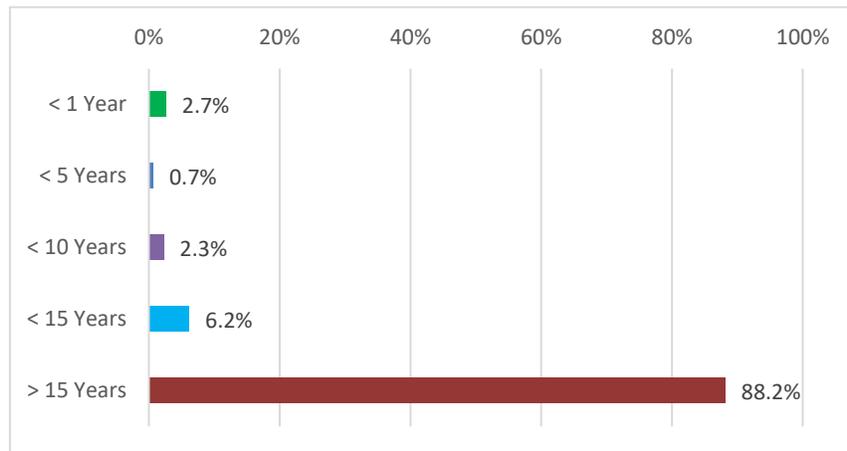


Figure 3b. Optional response question at the end of the survey asking the participants (n = 566) to quantify their years of experience working as a nurse.

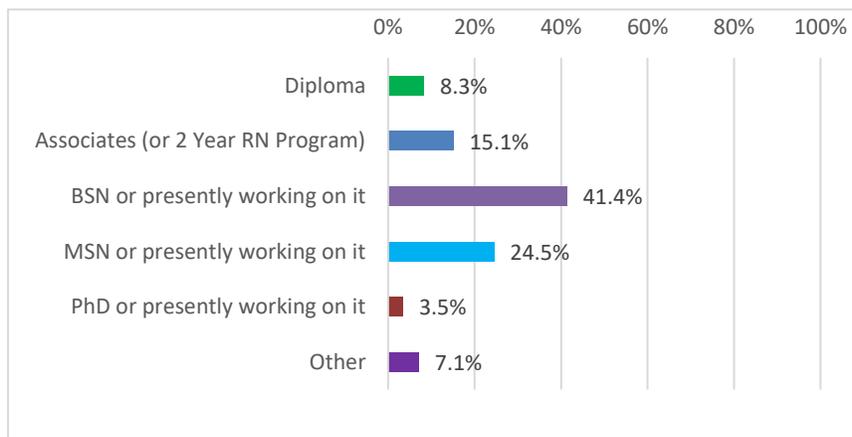


Figure 3c. Optional response question at the end of the survey asking the participants (n = 576) to describe their level of education.

Applications in Nursing Practice. Based on these survey results, it is encouraging to know that many student nurses can identify the causes of antibiotic resistance as they enter their profession. While nurses administer antibiotics daily, it is still within the domain of medicine to prescribe antibiotics for treatment. What then can a nurse do about antibiotic resistance? Medicine should not be left to shoulder this alone; what is needed is more information delivered promptly and inexpensively at the patient interface level. Under the broad mandate of prevention is the nurse's role to be both an educator and an advocate. A 2016 meta-analysis study out of Australia characterized the public as having "an incomplete understanding of antibiotic resistance and misperceptions about it and its causes and do not believe they contribute to its development" (McCullough, Parekh, Rathbone, Del Mar, & Hoffmann, 2016, p. 27). The report from this meta-analysis canvassing Europe, Asia and North America went on to specify that a median of 88% of patients surveyed named some change in their body as the cause of antibiotic resistance (McCullough et al., 2016, p. 28). These data present a ready state for patient education, and as such nurses can contribute daily to the fight against antibiotic resistance.

The list of action items that a nurse can do to lessen antibiotic resistance starts with patient education about their proper use. It is not plausible for most patients to differentiate between the signs and symptoms for viral and bacterial infections. Patients should feel empowered to seek care from their primary physicians when they are not feeling well. However, once in the examining room, it requires a fine sifting of details by the physician to determine a diagnosis. If the diagnosis is an upper respiratory or sinus infection, it is not likely

that bacteria are the cause, and so no antibiotics are appropriate. When an antibiotic is needed, nothing else will do since no other chemotherapy has the ability to do what antibiotics can.

Understandably, with the increase in both regulatory and financial burdens on health insurance, medical care is more difficult and expensive to obtain. Some people seeking care at their doctor's office may understandably ask for something tangible to take home, even thinking that an antibiotic would help. Here, nursing is well suited to discourage the practice that a physician's office can be sought out like an antibiotic vending machine during the current lack of empirical evidence. Signs and symptoms alone may be the sole premise for antibiotic prescriptions and are also the same reasons why someone comes to see their primary care doctor in the first place. When this is true, further work is needed on a systemic level to help patients understand rudimentary microbiology to differentiate a bacterial pathogen (operating outside of the cell) and a viral pathogen (operating exclusively inside the cell where the ribosomes are located) when the diagnosis does not support a bacterial etiology. Nursing is well represented in healthcare with a disproportionately high ratio in staffing. This makes nursing well-positioned to use its presence as a means to close the knowledge gap with more patient education. More information from the CDC on antibiotic guidelines can be found at www.cdc.gov/getsmart.

Other impactful, nurse-led opportunities include forming study groups on narrowly-focused topics, and then reporting those evidence-based process changes to decision makers. Such "unit counsel" models are a highly-effective means of changing operating procedures from

within a health care agency. These nurse-initiated actions are a great example of advocating for patient well-being in a very effective manner that does not require outside regulatory authorities to implement for the whole nation. For example, the following is a compiled list of recommendations to help with antibiotic stewardship:

- Prevention, prevention, prevention. Nurses can follow up with patients on their vaccination schedules, as it is easier to prevent an infection than to treat one (Adams et al., 2017, p. 539). While most, vaccinations are for viral pathogens, preventing these viral diseases removes the conditions for opportunistic secondary infections from bacterial pathogens, which can be very difficult to treat and can have deadly consequences.
- While not likely to make headline news, there is still more to be done with routine prevention. American grocery stores are set up to sell inexpensive food, not to prevent Type II Diabetes Mellitus or obesity. A nation of nurses working hard and in unison to help patients manage healthy weights through portion control of better food choices which are higher in nutrient density and unprocessed can prevent diabetes and its inevitable sequelae – vasculature disease (Hoffman & Sullivan, 2017, pp. 928, 930). Diabetes Mellitus is not an infectious/communicable disease, so what does this have to do with antibiotics? I have personally hung piperacillin/tazobactam, a very strong and potent broad-spectrum antibiotic, for a post-op patient admitted for a surgical repair to a foot that had become infected secondary to diabetes related impaired vasculature. If the vasculature is not there to deliver the antibiotic to the distal site, then very little

clinical benefit can be expected. An ounce of prevention is worth 3.375g/50mL over 30 minutes of cure.

- For instances where antibiotic resistance is known or strongly suspected, there are significant benefits for the patient and the healthcare system in getting the infection resolved the first time. Studies support implementing combination therapies to simultaneously hit multiple mechanisms of action, thus killing the pathogen, and decreasing the opportunity for it to persist and resist (Baker et al., 2018, p. 6; Lewis, 2013, p. 375). Two specific, narrow-spectrum drugs are better than prophylactic broad-spectrum antibiotics (Tortora et al., 2013, p. 562).
- For organisms that are slow to demonstrate clinical symptoms and assumed to be resistant (e.g. *Mycobacterium tuberculosis*), ensured delivery of antibiotics is the best policy. Such initiatives as directly-observed therapy (Willey et al., 2017, p. 205) are a heavy-handed, albeit situationally-necessary measures, delegated to nursing to implement. Directly-observed therapy is a means to ensure compliance when the larger world-wide risk of pan-resistant M. tuberculosis is a real and growing concern (Anderson, Salm, Allen, & Nester, 2016, p. 555).
- Encourage patient compliance to finish the full course of an appropriately-prescribed antibiotic treatment (Tortora et al., 2013, p. 582). Nurses can recommend that patients set reminders on their smart phones or perhaps help those who are not familiar with those features on their devices to do so in order to ensure that adequate reminders are in place. Additionally, strongly discourage the use of available antibiotics that may be

left over from a different prescription associated with a past diagnosis, or given for another person. The practice of reaching for antibiotics as an expedient without supporting evidence only exacerbates the current problem.

- Advocate for the implementation of agency protocols for prescribing authorities informed by board-certificated professional organizations to avoid prescribing antibiotics when unnecessary (especially for pediatrics) in accordance with CDC and AAP guidelines (American Academy of Pediatrics & Committee on Infectious Diseases, 2012, pp. 803–805). Adams et al. (2014, p. 540) advise to give antibiotics when there is a clear need to do so and when the pathogen has been properly cultured and its susceptibilities have been identified. While sound advice, this is currently not practical or even possible at primary care or pediatrician's office, nor is it especially expedient at a larger hospital; see the section Culture and Sensitivity Empirical Data for more information on the current limitations.
- When nurses draw up antibiotics from a vial into a syringe, the syringe is typically held vertically (needle upwards) to clear the delivery path of air bubbles; this practice should be modified. Instead, the syringe should be cleared into a sterile cotton ball or gauze to avoid aerosolizing the antibiotic, which can be taken into the sinus cavity and foster antibiotic resistance through exposure to the potentially pathogenic colonies of bacteria living there (Tortora et al., 2013, p. 582). By doing so, patients and healthcare workers are not incubating resistant bacteria within their own nasal cavities that may inadvertently spread to the most vulnerable patients within the hospital.

Promising Technologies for Combating Resistance

Gone is the “Golden Era of Antibiotics,” where novel drugs were readily developed by applying Koch’s postulates to a random handful of soil. This era was then followed by the unpleasant discovery that there was such a thing as the resistome, which has led us to the present time where antibiotic development has all but halted due to complexity and cost (Crofts et al., 2017, p. 426). There are more than 2,000 known discrete variants of β lactamase resistance mechanisms (Navon-Venezia et al., 2017, p. 235). Indeed, the days of imagining that there was a “fabled silver bullet” to vanquish pathogens inside of the body – to which no resistance would form – is presently very unlikely; we must now assume resistance against any and all available antibiotics (Crofts et al., 2017, p. 430).

No serious discussion about new research for developing antibiotics can be had without bringing up the topic of pharmaceutical company financial interests as well as regulatory and market realities. Of course, everyone would like to see the development of new and more effective antibiotic drugs, but how can these feasibly be brought to market? New drugs make it to the clinical level after receiving approval by the FDA for their use, which is a very long and expensive process. In a time when all of our present antibiotics have known resistance, and there is pressure to use less of them, why would a pharmaceutical company want to invest \$2.5 billion (with a “B”) over a decade (Adams et al., 2017, p. 15) to develop and receive FDA approval for a new antibiotic drug that would be used for two weeks or less? The money that brings sure return on invested research capital is in long-term treatments like hypertension drugs, hypercholesterolemia medications, or pharmaceuticals to support lifestyle measures like

erectile dysfunction. “There is no money in fixing acute problems” (T. Richardson, Pharmacist, personal communication, March 06, 2019).

The reality is that the promise of such radical cures like the one nurse Anne Miller experienced has made antibiotics indispensable to medicine, but their overuse has diminished their impact to treat bacterial infections. Now we must deal with the worldwide concern for medicine operating in a scenario where our antibiotics simply may not work anymore (WHO, 2014, p. 2). There are likely not any new antibiotics being developed or brought to market anytime soon. The seemingly only effective near-term strategy is to use the antibiotics we already have in the wisest manner possible. This will require information that is clinically useful with a quick turnaround time to bring back results to prescribing clinicians where they interface with patients now.

What is needed is a way to sequence the DNA of bacteria from some type of sample from a patient, find out if there are pathogens present, sequence their DNA and run automated searches against known databases to see what matches can be found to identify the pathogen and predict their virulence and even sensitivities to the antibiotics that we still have left. What would such technology look like, and how much would it cost?

Currently, there are highly reliable laboratory-grade DNA sequencers available that produce rapid and highly accurate results. The two major downsides are that these sequencers require a biologist to operate them and their cost *starts at the six-figure level*, making them well out of reach for any primary care clinic. Fortunately, a recent scientific discovery was made that changed the scale and cost of DNA sequencing from bench-top size to a device that

would fit in the palm of the hand. This technology is called nanopore sequencing, and it has not only changed DNA sequencing in size scale, but in terms of also economies of scale for cost.

Nanopore technology follows in a long and entertaining tradition of great scientific discoveries made completely by accident. In 2010 Nobel Prize in Physics given to Andre Geim and Konstantin Novoselov for the discovery of graphene, a two-dimensional material (exactly one carbon atom thick) that is extremely strong and conducts electricity as well as copper (Huss, 2010). This new material was able to bring about a technological revolution in bioinformatic devices as it allowed researchers to employ discoveries in materials science to the nanometer or 10^{-9} meter resolution, which is perfect for DNA sequencing.

DNA has a predictable quantum of inherent negative charge, and nanopore technology capitalizes on this characteristic of DNA and its four nucleotide bases, each of which have a unique electrical signature. Imagine a silicon chip, much like any other computer chip in consumer electronic devices, with a hole in it (Farimani, Min, & Aluru, 2014, p. 7915) roughly wide enough to allow a single-stranded DNA molecule (ssDNA) to pass through it in an aqueous solution (Chen & Conlisk, 2010, pp. 236, 241). On each side of the silicon chip is a layer of 2-D material (i.e. graphene or MoS_2) which has a charge applied to it (Farimani et al., 2014, p. 7914). The attached electrodes read the change in current as each individual nucleotide or “genetic letter” in the ssDNA (or ssRNA typical of virus applications) generates an electrical signal (Garalde et al., 2018, p. 1) as it passes through the nanopore in the chip (Farimani et al., 2014, p. 7914) at a rate of 250 nucleotides per second. These signals are read in real-time to generate “base calls,” or determinations of which DNA nucleotides passed through the pore

based on the signature of the electrical signal generated. These base calls are cataloged by software which starts to build a sequence whose length is determined by the care taken and the technique used in the lab preparation (Oxford Nanopore Technologies, n.d.).

In an organism, DNA is found in a double-strand configuration (dsDNA) where two matching strands run parallel to each other in a rather aesthetic double helix. However, to get DNA to fit through the hole or nanopore, it has to be denatured or split into ssDNA by a special enzyme reagent called a motor protein (Cummings, Olszewicz, & Obom, 2017, p. 1), which takes about ten minutes of preparation.

The workhorse of the nanopore user community is the MinION, which is about the size of a deck of playing cards split in half lengthwise, and delivers real-time base calls up to 2 Mb (Oxford Nanopore Technologies, n.d.). Two years ago when this research began, this technology cost \$10,000 for one MinION. Complete kits (hardware and reagents) cost \$1,000 USD at the time of this research (Oxford Nanopore Technologies, n.d.). The electrical signals generated by the ssDNA which pass through the nanopore on the chip can be read by any number of bioinformatic software processing packages and rendered into industry-standard formats like FASTQ or FAST5 format, which are readily integrated into BLAST searches (Cummings et al., 2017, p. 1) on the National Center for Biotechnology Information (NCBI) database. This ability to be able to efficiently read/sequence DNA is owed to a relatively novel and inexpensive device. The ease of operating the device is remarkably friendly, allowing it to be implemented anywhere an internet connection can be obtained. The applications for short

turnaround empirical feedback in any doctor's office or even home health visit will rapidly close the information gap and usher in a new era of rapid empirical diagnosis.

The Space Race and Siri Meet Modern Medicine

Technology has forever changed the way humans interact with their world. For example, aviation went from Kittyhawk to the Apollo 11 mission in a mere 66 years. When President John F. Kennedy said, "We choose to go to the moon!" (Malangone, 2017), there was an enormous gap in the available technology that would allow America to actually attempt a lunar landing on a manned mission. Since then, technology has also profoundly changed medicine and nursing. What do infrared ear thermometers, heart rate monitors, automatic insulin pumps, precision dialysis pumps, artificial hip joints, ventricular assist device and light-emitting diodes (LED's) all have to do with nursing and space exploration? These are all indispensable clinical technologies that a nurse is likely to see every day, and they were all developed by the National Aeronautics and Space Administration (NASA, 2008).

Powerful rockets can get a space module off of the earth's surface, but a lunar landing is far more technologically complex. To then guide that module carrying astronauts from earth to the moon on an arc-shaped course, land on the moon, launch from the moon's surface to dock with a separate space craft in the moon's orbit, and then return home (while everything is spinning and orbiting in space itself) demands a computer. While NASA did not invent the computer, they funded much of the research required to perfect what we now recognize as a computer. The original order from NASA was simple but extremely exacting, small, lightweight and mistake-proof (PC Plus, 2010), as tech support would not be available in space flight.

Numerous companies and universities contributed to the computing backbone upon which NASA relied including Texas Instruments, IBM, and MIT, to name a few. It was from these efforts to accomplish the impossible – a manned lunar mission before the age of advanced technology – that revolutionized the computer. When President Kennedy cast the vision to go to the moon, the technology was not even available, but the following Space Race brought the long succession of more powerful, smaller and less expensive devices that make rapid DNA sequencing possible today.

The Apollo Guidance Computer that navigated the Apollo spacecraft to the moon and back had 36kB of memory, ran at 1 MHz and cost NASA \$26.6 million in 1960 (PC Plus, 2010). Compare that to the newest (at the time of this research) Apple iPhone XS which has 3GB of memory, runs at 2.49 GHz on a hexa-core 64-bit processor and had a launch price for \$1,100.00 (iPhone XS, 2019). Just on the metric of memory alone, the iPhone has more than 83,000 times more memory than what enabled one giant leap for mankind, but a present-day Apollo Guidance Computer would cost approximately \$225,656,966.22 (when adjusted for inflation) (Coin News, n.d.); and yet currently the iPhone XS costs over 200,000 times less. How is this possible? Computing technology follows a cost arc downwards in accordance with Moore's Law. After some urban legend embellishment from technology enthusiasts over time, Moore's Law states that every two years the density of chips (amount of processing power) will double, as the cost continuously goes down to the consumer (Shah, 2015). Without this principle, we would not see something as powerful as an iPhone that fits in a hand (Shah, 2015).

Applying this concept to the downward-cost curve to modern nanopore DNA sequencing, a standard culture on media of *Tuberculosis* (TB), a fastidious organism, takes 4 – 6 weeks to receive conclusive results regarding the organism's phenotype (Mahomed, Naidoo, Dookie, & Padayatchi, 2017, p. 137). The MinION can render *Tuberculosis'* virulence profile through sequencing its DNA (genotype) in just twelve hours (Oxford Nanopore Technologies, 2018, p. 4). From the perspective of the WHO, a hybrid between media culture, slow but reliable, and nanopore technology, fast and inexpensive which can identify virulence and resistance factors overnight. This, in turn, can expedite the prescription protocol for the most appropriate combination of TB drugs (Mahomed et al., 2017, p. 141). In impoverished countries around the world where TB is endemic, competent laboratories with high-end benchtop DNA sequencers are simply unaffordable, making state-of-the-art TB therapy unattainable in places where it is desperately needed the most. Given the ever-growing robust cellular data networks, DNA sequencing will be able to be run on a device called a SmidgION (Oxford Nanopore Technologies, 2018, p. 4) that literally plugs into the port on a smartphone. Real-time DNA sequencing in sub-Saharan Africa? There's an app for that now.

A lower stakes example of this thought exercise can help to elucidate the power of this networked technology. Think about when you get a few lyrics of a song, stuck in your head. Say you had the words, "easy as 1 2 3 . . . simple as do re mi," stuck in your head but cannot place the song. If you have an Apple device, you speak the phrase, "easy as 1 2 3 simple as do re mi" to Siri and ask her if she knows the song. It is likely that her search engine will return the Motown classic, "ABC" (Gordy et al., 1970, track 5) as a top search result. The application here

is that modern technology is inexpensive, extremely powerful, and interconnected with deep and robust databases. Connected nanopore devices may one day soon be able to make DNA sequencing and species identification as simple as asking Siri. Given that nanopore technology is so easy to use and so accessible, it can change the way we practice medicine anywhere there is an Internet connection from small regional hospitals in rural limited-access regions to the International Space Station (Singh et al., 2018).

There are limits to this technology. Exact 100% matches may not be possible, but what we can learn and catalog into databases today, will help medicine tomorrow. Bacteria are prone to mutate in a multitude of directions, and with all of the antibiotic pressure, they have ample opportunity to do so daily. In application we simply cannot expect to know everything today. Inevitably, there will be inherent ambiguity in DNA from a genome or plasmid sequenced today. Moreover, we will always need cultured media to puzzle out the exact biochemical and phenotypic features of suspected pathogens (Crofts et al., 2017, p. 430). However, as we know more, we can get more rapid diagnosis techniques from the increasing confidence gained by larger data sets. The more sequencing is done, the more robust databases become, the smarter the search algorithms become, the higher confidence can be returned from future queries. This can take medicine a large efficacy multiplier for knowing what the pathogen is, and what antibiotics will still work against it. Someday in the near future, sequencing bacterial pathogenic DNA may be as trivial as scanning a bar code in a retail self-checkout lane or asking Siri to correlate a song title with a fragment of its lyrics.

In our present age of antibiotic resistance, what can a nurse do about it? The profession of nursing itself has its roots in leveraging empirical data amidst uncertainty. During the Crimean War, it was better to be killed in battle than wounded, for of the wounded, 60% would die of diseases and infections – twice the rate from the Black Plague (Cohen, 1984, p. 133). Florence Nightingale went to this highly volatile and dynamic situation. She did not have perfect information to know that keeping the lamp lit on her nightly rounds with the wounded would have the outcome that it did. What did she do in this lack of empirical evidence? She started keeping statistics to show that within 6 months of the arrival of her and her team of nurses the mortality rate of the wounded dropped from 42.7% to 2.2% (Cohen, 1984, p. 131). If Florence Nightingale was concerned with what the decision makers thought of her work during a time when men made all the decisions (Steele, 2017, p. 57), she did not let it show, rather she was content to let the opposition argue with the numbers. From its roots, nursing has been a pioneering work of prevention and empirical evidence. The most resistant bacteria will be found where antibiotics are used the most – in hospitals. Medicine must internally reform its own methods for using DNA sequencing for diagnosis, but nursing has an opportunity with infection control (within the domain of nursing) to survey, sequence, identify and catalog pathogens preemptively. Nursing has been here before, and has done the hard-empirical work to show great gains. Surveying nosocomial pathogens is low-hanging fruit, and after proper analysis can be presented as convincing evidence to corroborate infection trends in patients as well as inform further infection control measures.

Conclusion

On December 13th, 2015, I sat speaking with Dr. E. Ramirez late at night, in the middle of his 36-hour shift, at the Hospital Regionale in Iquitos, Peru. I was there for an Infectious Diseases course and had a very unique opportunity to speak to Dr. Ramirez at length through a translator. He was recounting the high incidence and burden rates of the top seven infectious diseases that he sees in Iquitos, which is the capital city of the Department of Loreto. By comparison, Loreto is almost as big as the state of Montana. Iquitos is a land island, which cannot be reached by a road – only by boat or by air – making their three hospitals truly frontier facilities. During the discourse, our very proficient translator was unfamiliar with the term in English for the particular pathology Dr. Ramirez mentioned. The translator, who was a devout Catholic, paused to ask a probing question in order to try to locate the word, “Do you know that disease in the Bible?” I thought that she was joking, when I chuckled my way incredulously to respond, “Do you mean leprosy?” She nodded in agreement, over-joyed to have made the successful transfer of ideas. I displayed a look of shocked disbelief on my face, thinking that this was some affliction of the distant past. However, Dr. Ramirez was completely somber as he continued to describe the suffering he saw.

The last leprosarium in America, located in Carville, LA, closed in the last century as leprosy (or Hansen’s disease) can now be treated with antibiotics in an outpatient setting (Anderson et al., 2016, pp. 694, 705). In America today, the leading causes of death are not infectious disease, but rather heart disease and cancer (first and second respectively totaling to almost 45% of mortalities), both of which are non-communicable diseases that one is not able

to “catch” (Heron, 2018, p. 9) in the sense of an infectious disease via a pathogen vector. Neither heart disease nor cancer are infectious, and so they do not concern antibiotics. Likewise, people in America do not think much of Malaria. However, throughout history, infectious diseases were once the scourge of humanity, shortening life expectancies and making childbirth dangerous before the discovery and development of antibiotics. *Yersinia pestis*, the pathogen responsible for the Black Plague, decimated 30% of Europe (Rascovan et al., 2019, p. 295). During the civil war, more soldiers died from Typhoid Fever and Dysentery than from bullets (Blaser, 2014, p. 56). For more than 60 years now, neither *Yersinia pestis*, nor Typhoid Fever have been of concern in America, because through sanitation, public health initiatives and the availability of antibiotics, we hardly hear of them. However, today in the part of the world that benefits most from modern medicine, the words of Dr. Thomas Frieden (CDC, 2013), “If we're not careful . . .,” bear even more weight as we are in danger of losing our pharmaceutical edge. There probably are not any new antibiotics coming anytime soon, so we need to be wise with the ones that we have now.

There is a lot that nurses can do to affect change to preserve antibiotics through the twin functions of prevention: advocate on behalf of their patients and being an educator. To be the very best advocates and educators, we need a contingency of nurses who are familiar with or even proficient in molecular biology, as medicine is certainly heading that way for diagnosis and treatment in near future. Even still, we are currently losing this arms race with pathogenic bacteria, since those implacable enemies have the DNA to render our best drugs ineffective.

What, then, is needed to make the best of an unfavorable situation and to keep our remaining quantitative chemotherapy edge? The answer is simple: *information*. The fields of medicine, nursing, pharmacy, and laboratories in hospitals everywhere need information as a technological edge that can quickly close the gap in our ability to rapidly and empirically diagnose bacterial pathogens in order to save what is left of our precious antibiotic inheritance. Imagine the day where a nurse can draw a sample (e.g. blood, urine, sputum, or even CSF) on the medical floor or in the ICU and place it into a flow cell on a MinION connected to some small wireless Internet device on the hospital's network. As the sample travels through the pneumatic tube to the lab, imagine that the DNA sequencing has begun, an NCBI database search is already underway looking for high confidence matches and the pharmacy computers are simultaneously referencing effective antibiotics. At that point, we can say that we are doing all we can to save antibiotics through rapid, empirically-based diagnosis.

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