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Curriculum Units by Fellows of the National Initiative
2012 Volume V: How Drugs Work

Antibacterial Gone Viral — Understanding Immune Response in Bacterial and Viral Infectious Diseases

Curriculum Unit 12.05.10, published September 2012
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Introduction

Antibacterial products like soap, lotion, sanitizer, deodorant, and even socks are everywhere. Today's war on germs seems more terrifying than the war on terrorism. With thousands of products designed to combat the ever-invading bacterial or viral hoard who's to say whether we really are gaining a stronghold against infectious disease with our multitude of products. Most consumers today are uninformed — buying needless antibacterial products simply because they assume antibacterial soap must be better than regular old soap. Informed consumers would argue that the overuse of antibacterial products will give rise to drug-resistant bacteria. According to the Center for Disease Control, there is no need to purchase such items to protect yourself or your home from the microscopic army of bacteria and viruses. In fact, good old fashioned hot water and soap will do just fine to impede the spread of bacteria and viruses. [1] In fact, there might be risks with over-protection: a Time Magazine article discusses a possible link between childhood allergies and the overexposure to triclosan, a chemical found in most antibacterial products. [2]

Rationale

My students attend Mt. Pleasant High School in San Jose California. MPHS is one of 12 large high schools in the East Side Union High School District. Our current school population ranges between 1700-1800 students where 41% are low income and 17% are English-learners. The majority of our population is comprised of Hispanic/Latino, Asian, East Indian, and Filipino students. Our minority populations are African America, Caucasian, and Pacific Islander students. Mt. Pleasant High School did not meet its target Academic Performance Index in 2011, scoring 708 instead of 713. Because our largest population is our Hispanic/Latino group, aiding this group to reach their target growth for 2012 is essential in helping our overall school improve its API. According to our School's Student Accountability report, among our student's parents, 34% of them have attended or have graduated from college, which continues to be significantly below the county and state averages. [3] The majority of my students who will be taught this unit will be the first to pursue a college degree.

Objective

My curriculum unit is designed to demystify my students' notion about the need for antibacterial/antimicrobial everything. Over the course of two weeks, I hope to inform my students of the basics of the lymphatic/immune system, and introduce basic concepts of bacteriology and virology, so that they will understand how something as simple as using antibacterial hand sanitizers at each meal could have much larger consequences. In addition, students will be introduced to drugs that are designed to combat bacterial infections and those that can treat viral infections. As a result of this unit, I hope to raise awareness in my students by increasing their understanding that there are such things as good germs (the natural plethora of bacteria that live helpfully on our bodies) versus the bad germs (those causing infectious diseases like tuberculosis, influenza, and HIV).

My intended audience for this curriculum unit is students enrolled in 11th/ 12th grade Human Anatomy and Physiology and 9/10 th grade Biology. Students opting to take Physiology as a third or fourth year of science have intentions of pursuing science or math in college or will be applying for vocational courses in physical therapy, nursing, dental hygiene, or medical assisting. Students of Biology are required to complete the course for high school graduation or to fulfill CA State University (a-g) requirements. Typically, the study of the lymphatic system and immunity is taught during the 5 th quarter of Physiology and introduced in the 6 th quarter of Biology. Introduction to bacteria and viruses is taught during the 2 nd quarter of Biology in which prokaryotic and eukaryotic cells are introduced. It is my intention to teach aspects of this unit to Biology in the 2 nd quarter and the complete unit to Physiology in the 5 th quarter.

Since literacy and raising academic language skills are two of the goals for our school, students will be exposed to a variety of reading material that will foster growth in their writing and reading. The unit will incorporate reading and writing strategies, oral and kinesthetic activities, and collaborative projects. It is also intentional that multi-disciplinary reading materials and activities are a part of the unit in order to foster the idea that learning and knowledge is interconnected among all subject areas.

Background

Pathogens I - Bacteria

Microbes can be one of four types: bacteria, viruses, protozoa, and fungi. Two of the four will be discussed as they relate to disease, drug treatment, and drug resistance. The hierarchal domain Bacteria (prokaryotes) includes Proteobacteria, Chlamydia, Spirochetes, Gram-positive, and Cyanobacteria. All bacteria are singled celled organisms with no nucleus and are 1/100 th the size of an average human cell. [4]

Microbes like bacteria that naturally exist in humans are collectively known as normal flora or indigenous microbiota. In general, bacteria that reside as part of the normal flora are mutualistic, meaning that both organisms benefit from contact with one another; however some bacteria have the potential to become parasitic and even pathogenic. Although a Mayo Clinic article on microbes states that only 1% of bacteria actually cause disease. [5] Through contact with our environment, bacterial populations find residence on

almost every surface of our body.

In researching microbes that exist on the surface of the skin, Grice, from the National Institutes of Health, found the varying preferences of skin-dwelling bacteria. According to her research, some bacteria seek warm, moist places like armpits and toes. Some bacteria prefer dry areas like backs. [6] As we encounter each other, bacterial strains are passing from one person to the next, adding to the diversity of bacteria thriving on the surface of any individual's skin. Interestingly, the Belly Button Biodiversity project found 4,000 different bacterial strains just inside human belly buttons, showing the wide variety of bacterial fauna in small space. [7]

The two most common microbes that exist as part of the normal flora belong to genus *Staphylococcus*. Of this group are the species *S*. *epidermidis* and *S. aureus*. [8] Staphylococcus bacteria are named accordingly to their clustered grape-like appearance. "Cocci" in Greek means round. Both species of *Staphylococcus* are found throughout the skin, in the conjunctiva of the eyes, and on the mucous membranes of the nose, pharynx, mouth, lower gastrointestinal tract, urethra, and vagina. Other abundant bacteria include *Streptococcus pneumoniae* found in the upper respiratory tract and the problematic Bacteriodes, which are found in the greatest number in the lower intestinal tract and which may cause colon cancer.

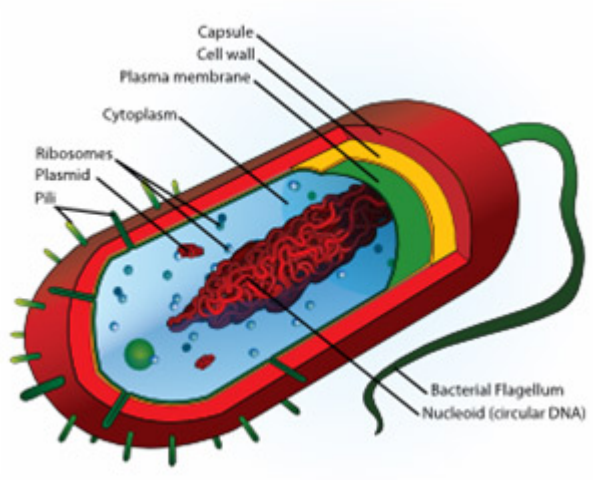
Students may wonder why some bacteria affect humans in specific tissues others do not. The reason for this is because of tissue specificity. Bacterial colonies prefer certain tissues because of the nutrients found on the tissue while others adhere and have special receptors that are complementary to ligands found on the tissue (i.e. some bacterial cells have affinity for certain tissues). Though it may be difficult to change people's minds on the merits of tiny microbes living and thriving on the surface of body, perhaps an awareness of their normal flora's helpfulness will change people's minds. First, bacteria help us to synthesize vitamins (K & B12) and antibiotic medications. Second, some bacterial colonies prevent the invasion of harmful pathogens. Third, intestinal bacterial colonies maintain the balance of our normal flora and prevent gastrointestinal problems and aid in digestion. Beyond the flora found on our bodies, bacteria are used in food preparation, agriculture, decomposition of plant and animal waste, and drug delivery. [9]

Because of the diversity of bacterial life and their ability to reproduce quickly, many bacterial types do cause infectious diseases. Staphylococcus infections and tuberculosis will be discussed as examples of diseases caused by pathogenic bacteria.

Bacterial Life Cycle

Bacteria are prokaryotic, singled-celled, asexually-reproducing organisms. A bacterium has the basic structure of a capsule, cell wall, plasma membrane, cytoplasm with ribosome, plasmid, pilli, plasmids, and nucleiod region (Figure 1). Bacterial motility is dependent upon a whip-like flagella. Unlike eukaryotic cells, the cell wall of a bacterial cell mechanically strong, like a plant cell wall, giving the bacterium its rigidity. All the nutrients, enzymes, water, and electrolytes a bacterium needs in order to survive and reproduce can be found in the contents of its cytoplasm. Ribosomes, like those found in eukaryotes, function in the synthesis of proteins and are an important structure in the formation of new bacteria. Plasmids are short sections of self-replicating DNA molecules that are not part of the remaining bacterial DNA. The nucleiod region, contains bacterial DNA, and serves a template for replication. [10]

Fig. 1. Bacterium Structure showing outer layers and inner nucleoid region. Figure obtained from free public domain site Clker.com [11]



Because bacterial do not require a host, or second bacterium to reproduce, reproduction is done through asexual binary fission. In binary fission, which for some species under the right conditions can occur every 30 minutes, bacterial DNA is first replicated in a loop. Two sets of circular DNA are made for the daughter cells. Once the loops of DNA are completed, they move towards opposite ends of the bacterial cell to prepare for cytokinesis. Cytokinesis finishes binary fission with the pinching-off and separation of the two newly formed daughter cells. The resultant daughter cells of binary fission are genetically identical to its parent; however, mutations due to the rapid reproduction rate and short generation spans can cause mutations. [12]

Genetic diversity among bacterial populations are achieved not only through mutations, but through genetic recombination. One way to achieve genetic recombination is through transformation. This occurs when a healthy bacterial cell takes up DNA from dead or pathogenic bacteria. The nonpathogenic bacteria break the circular DNA of the compromised bacteria and replace the broken fragments with its own DNA, thus achieving recombination. A second method to achieve recombination is conjugation. Conjugation requires two bacterial cells and their plasmids. As mentioned before, plasmids are short circular strands of self-replication DNA. During conjugation one bacterium is a donor and a second is the recipient. The donor bacterium transmits a copy of its plasmid across a sex pilus (a physical structure connecting the two bacteria) and replicates in the recipient bacterium, thus completing conjugation. A third recombinant method is transduction. Transduction involves a bacteriophage (viruses with bacterial DNA). Initially in transduction, bacteriophage injects their phage DNA into a bacterial cell where new phage proteins are made. When new bacteriophage are assembled from proteins, newly assembled bacteriophage containing recombinant DNA, lyse and infect a second bacterium. With the injection of new phage DNA into a second bacterium, transduction is complete. [13]

Types of Bacteria

Staphylococcus aureus

Staphylococcus aureus is a spherical bacterium commonly found in the normal plethora of humans. Clusters of *S. aureus* appear grape-like and accumulate in areas like the nose, skin, gastrointestinal tract, and mouth. Though some species of the genus Staphylococcus are nonpathogenic, *S. aureus* does have the potential to cause disease. A staph infection is an infection from the various strains of *Staphylococcus* bacteria. Typical S. *aureus* infections include pimples, boils, abscesses, pneumonia, endocarditis, and toxic shock syndrome. *S. aureus* is particularly important to health care workers who need to take great care to prevent nosocomial infections (hospital-acquired). *S. aureus* is an effective bacterial pathogen because its surface proteins promote the invasion of its host tissues. It suppresses phagocytosis and disguises itself from immune cells

that would seek to destroy it. Also, *S. aureus* produces toxins on its cell surface that promote the lysis of eukaryotic cell membranes. Finally, *S. aureus* has developed both inherent and acquired resistance to antimicrobial agents.

S. aureus destroys tissues by first adhering to the surface proteins on their host cell. Their adhesion to the host cell is followed by invasion into the cell. This invasion occurs by a complex process involving membrane-damaging toxins, which can cause the perforation of the host cell membrane. Once inside, the bacterial DNA replicates like other bacteria. [14]

Tuberculosis

One of the earliest known infectious diseases is tuberculosis, which is caused by the *Mycobacteriumtuberculosis*, a bacterium belonging to the phylum Actinobacteria and the order Actinomycetales. Skeletal remains of prehistoric humans has shown evidence of M. tuberculosis, Hippocrates knew its deadly potential in ancient Greece, and before 1900 tuberculosis killed 1 in 7 persons in Europe. [15] During the last 200 years the cause for tuberculosis was wildly speculated, studied, and finally identified in 1882 by Robert Koch.

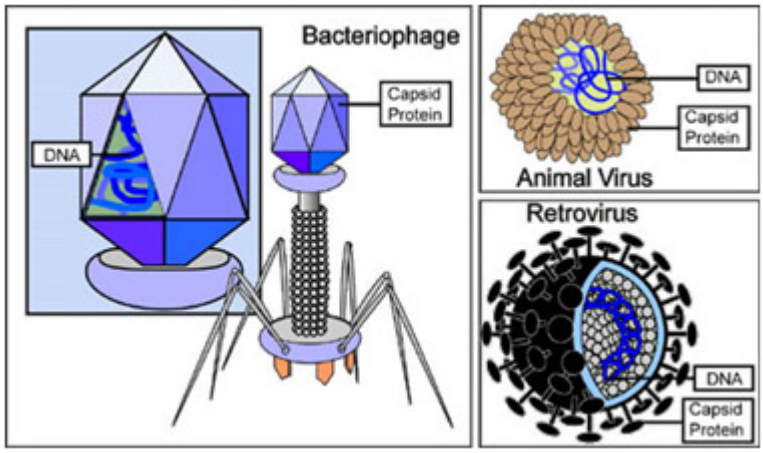
In Aldridge's *How Drugs Work* she mentions that though the number of tuberculosis cases has decreased since 1900 to 1980, the bacterial disease has experienced a recent resurgence. According to WHO (World Health Organization), there has been a steady rise of cases worldwide. [16] A 2011 article from "The Lancet" stated that there are approximately 9 million tuberculosis cases worldwide, primarily affecting sub-Saharan, Eastern Europe, and Asia. India by far has the highest number of cases with 26% of the world total of TB cases. [17]

So what exactly is tuberculosis? Tuberculosis is an airborne infectious disease caused by bacterial growth and accumulation in the lungs. The disease can spread simply through the sneezing, coughing, and speaking of an infected TB patient. Though many people may have been exposed to TB, the bacteria may lay dormant inside an infected person. Those with latent TB can live normally and may not show signs or symptoms of the disease. It is only when the bacterial cells become active that people become sick. If a person has full blown TB, then they are infectious and their immune system is incapable of suppressing the bacterial growth. Signs of TB disease include persistent cough, fatigue, weight loss, fever, and coughing up blood.

Pathogens II - Viruses

Unlike bacteria, viruses, are not prokaryotes since they do not have the internal machinery bacteria possess beyond genetic material, thus viruses depend on its hosts to reproduce. There are four different viral structures: helical, polyhedral, enveloped, bacteriophage (Figure 2). The difference between these structures lies in their protein capsule, known as a capsid. The smallest virus is only 20 nm in diameter. Inside the capsid, the genetic material can either be single-stranded or double stranded DNA or RNA. Though different in size, shape, and genetic content, all viruses are dependent upon their host cell's resources and mechanisms to reproduce. Viruses have a range of hosts that they can infect depending on surface proteins on the virus and receptors on its host cell. In most cases, when the host cell dies and the virus cannot find surrounding cells to infect, the virus does not spread.

Figure 2. Virus types showing the differences in structure between bacteriophage, animal virus, and retrovirus. Figure obtained from free public domain site - Science Kids. [18]



Viral Life Cycle

A virus is an obligate parasite, meaning that it is dependent on its host for reproduction. Some viruses have a broad range of hosts and some may have a narrow range thus making virus specific for its host. Eukaryotic organisms are affected by more tissue-specific viruses, infecting specific cells within organs like the liver or lungs. [19] The process of infecting a host starts when a virus's capsid proteins are recognized by a host's receptors. If there is a receptor-protein match on the cell membrane endocytosis or injection of the viral genome occurs.

The reproductive cycle of a virus begins when the genome of a virus enters its host. DNA viruses and RNA viruses replicate differently from each other but both require the host cell's replication machinery (i.e. DNA polymerase, RNA polymerase, reverse transcriptase). For example, a virus with phage DNA as the genetic material, phage DNA is replicated using the host cell's DNA polymerase, making hundreds of new copies. On the other hand, if the virus contains RNA, then viral RNA would be transcribed into mRNA and then translated into chains of new viral proteins during protein synthesis. The end result of the process is the same — reproduction of new viruses to be released out of the host cell to infect neighboring cells. Viral microbes, influenza, tuberculosis, and HIV are explored as examples of second type or pathogenic microbe.

Type of Viruses

Influenza

The story of the flu virus parallels human history. Early accounts can be found in ancient Egypt in pictographs depicting Egyptian royalties with polio, clubfoot, and smallpox. [20] Viral diseases were known in Greece in 412 B.C as told by Hippocrates. The British in 1485 called it the "sweating sickness" and probably the most well documented of the epidemic was the 1918 outbreak where 50 million people died of Spanish flu. [21] Today, the different variations and permeations of the flu are consistently in the news: avian flu, H1N1, swine flu. With so many variations, the difficulty of keeping the virus in check is easy to understand.

So why has the influenza virus been so successful? One reason is its ability to adapt to its host (antigenic shift), and to take over its hosts' replication machinery. This reason alone, according to Aldridge in *Magic Molecules*, makes the virus difficult for the immune system to handle. [22] Second, because most humans have some form of the virus from previous exposure, there's almost an endless supply of existing genes to create new re-assorted genes. Finally, influenza virus has been successful because of its mode of transmission. The virus can be spread through the air in a simple sneeze or cough. Symptoms of an influenza virus infection

include fever, sore throat, aches, and pains. These symptoms usually create an opportunity for other infectious diseases like pneumonia to infect a person: even if the influenza infection is not fatal, it might weaken a person sufficiently that they die from other infections.

Influenza virus is an RNA virus about 130 nm in size and spherical or filamentous in shape. Its human variants, A and B, differ from each other by the number of proteins on its surface. The proteins on its surface are hemagglutinin and neuraminidase. Hemagglutinin's various mutations can cause antibodies, already produced in a person from a prior years experience with influenza, to not be able to recognize its new form. This antigenic shift is the reason for seasonal flu. Neuraminidase is also a protein but in the form of an enzyme that allows the virus to penetrate through mucosal layer protecting the respiratory tract. Neuraminidase functions to penetrate the cell membrane of its host cells in order to allow entry of the viral RNA. The virus replicates by first attaching to the host cell surface using its proteins. It then enters the host cell by receptor-mediated endocytosis. When the structure surrounding the virus is disintegrated the viral RNA is released and transmitted to the nucleus. In the nucleus polymerase reactions take place to eventually synthesize new viral proteins. When the cell reaches a high concentration of virions, it is released into the environment by an enzyme that lyses the cell membrane of its host. Health care professionals are simply incapable of predicting the virulence of the virus, its host target, where it will strike, and who it will strike because of the multiple permeations and reproductive rate of viruses. Health care professional's main action is to inform the public, and manage the outbreaks as best as possible.

Retroviruses and HIV

Retroviruses like HIV have an additional complication in its reproduction within the host cell. The genome of retroviruses is encoded in RNA. Retroviruses, upon entering the host cell, can create DNA from the genomic RNA template, because of the presence of a viral protein, reverse transcriptase. Reverse transcriptase allows for the production of a provirus (viral genes embedded into the hosts' genome) that can eventually become the template for viral proteins to create new HIV. Unlike unaffected cells, the genomic DNA of the host is modified to include a template containing portions of viral DNA that are ultimately transcribed into mRNA and finally into new viral proteins. These new viral proteins repackage themselves into mature viruses ready to infect other cells. [23]

HIV (human immunodeficiency virus) is a type of retrovirus responsible for AIDS (acquired immunodeficiency syndrome). The virus, and subsequently the disease, gained increasing incidence in the early 1980s among young homosexual men, blood transfusion patients, infected mothers passing the disease to their babies, and those having sexual intercourse with infected persons. According to the group AVERT, an organization dedicated to averting the spread of HIV and AIDS, as of 2010, 34 million people are living with HIV/AIDS. In fact, the number of newly infected persons continues to rise by an estimated 2.2 to 2.7 million every single year. [24]

The Lymphatic System

Incredibly, the human circulatory system's average vasculature can span over 60,000 miles, thus being able to circulate the circumference of the earth at least two times. [25] This vast and intricate system not only regulates the flow of blood and nourishes body tissues, but it plays a key role in defense. This is because the

circulatory system comprises not just the cardiovascular system but also includes the lymphatic system. The lymphatic system aides the circulatory system by re-circulating lymph fluid back into the heart. Lymph fluid (recycled blood plasma) accumulates as a result of high blood pressure forcing fluid out of the capillary into surrounding interstitial space and tissue cells. Out of all the fluid leaving the arterioles and returning to the veins, about 15% is lost between the arteriole end of the capillary bed and the venous end. Lymphatic vessels surrounding capillary vessels catch this fluid, now called lymph, diffused from the capillaries.

The lymphatic system is network of afferent and efferent lymph vessels that regulates about 3 liters of lymph fluid daily. Like veins, lymphatic vessels have valves that prevent backflow of lymph flow. Unlike veins, lymphatic vessels require skeletal muscle contraction to move lymph fluid into its draining ducts at the heart. Afferent vessels carry lymph fluid into the lymph nodules while efferent vessels carry lymph fluid away. [26]

One of the major functions of the lymphatic system is to defend the body against foreign microorganisms and disease. Circulating lymph fluid can carry microorganisms into filtering lymph nodes before the lymph fluid is returned to the circulatory system. Lymph nodes are masses of B and T-lymphocytes (lymphatic cells) and macrophages (big eaters of foreign objects) clustered together and encapsulated into a kidney bean shape structure. These lymph nodes are found in chains of nodules that are concentrated in number around the neck, armpits, groin, and abdomen. Faced with an infection, the lymph nodes swell due its increased numbers of T-cell, B-cells, and plasma cells accumulating within the structure. Thus, when a person is sick with a sore-throat, or a cold sore, a person may feel small hard, nodules under their chin or around their neck, since the lymph nodes in that region swell as the body mounts an attack against the invading microbe. The primary function of the lymph nodes is to cleanse and filter lymph fluid of foreign microorganisms and cellular debris before it is returned to the blood. Larger organs like the spleen, tonsils, and thymus also accumulate lymphocytes in response to foreign microorganisms. [27]

Defense and Resistance

The body's ability to fight pathogens, or disease-producing organisms, is called resistance. The human body has different mechanisms to defend itself against microbial agents that may or may not have the potential to cause disease. The first line of defense is external. The skin, mucous membranes, and secretions of the skin provide a non-specific defense line. Since the skin is the largest organ of the human body, it is effective physical barrier and chemical barrier against microbes. Secretions of the skin increase the acidity of the surface making it uninhabitable for certain microbes. Other secretions like tears, saliva, mucosal secretions have antimicrobial enzymes like lysozymes that break down bacterial cell walls. [28] (See the cell wall in Figure 1.)

A second line of defense is achieved through non-specific phagocytosis, antimicrobial proteins, and inflammatory responses. If microbes like bacteria are able to pass the skin's defense lines then phagocytic cells (neutrophils and monocytes) ingest the microorganism. Phagocytosis means cell-eating. Phagocytic cells make up 60-70% of white blood cells and are responsible for identifying, engulfing, and destroying infected or damaged cells. [29] Other cells helpful against viral attacks are Natural Killer Cells (NK), which can kill viral infected cells by causing them to burst or lyse. Beside phagocytic cells, an inflammatory response occurs at a site of injury and is responsible for calling phagocytic cells to the site. The response begins with edema

(swelling) and an increase in blood flow. An increase in blood flow not only raises the number of blood clotting elements but also promotes the migration of phagocytic cells to the area.

The third line is specific immune defense, which is selective for specific foreign organisms: they function by selective action on invaders and exhibit memory of invading organisms for quicker defense during a second assault or infection. Specific defense mechanisms that possess memory are often called "immunity," which is dependent upon the action of lymphocytes and macrophages. Immunity works through the differentiation of self vs. non-self. A key part of immunity is the ability of cells of the immune system to recognize molecules that do not belong in the body: those "not-belonging" protein or carbohydrate molecules are called foreign antigens. [30] Macrophages, and other antigen-presenting cells, have mechanisms for alerting other immune cells to the presence of foreign antigens, by displaying them on the macrophage surface in ways that stimulate the rest of the immune system.

More specifically, macrophages recognize the difference between infected cells and healthy cells because infected cells present a piece of the infecting microbial protein (antigen) on its surface glycoproteins. These surface glycoproteins are known as major histocompatibility complex (MHC), which are found on almost every nucleated cell of the human body and make us uniquely different from one another. An antigen presentation on the MHC signals lymphocytes to an infection.

Types of Immunity

There are several types of immunity. Cell-mediated immunity is dependent upon T lymphocytes (T-cells) recognizing antigens presented on the MHC. This type of immune response is effective against viruses and bacteria inside infected body cells. When T-cells recognize an antigen, the immune responds by stimulating T-helper cells to create clones or copies with specific tasks. T-helper clones may help to activate other T-cells like cytotoxic T-cells, or B-cells. Other clones may differentiate to become memory T-helper cells which will aide in the recognition of antigens during a second immune response. In cell-mediated immunity, cytotoxic T-cells will lyse infected cells, or produce more memory T-helper cells for an antigen.

Humoral Immunity or Antibody-Mediated Immunity is dependent upon B-cells, which recognize a specific antigen and differentiate into cells that produce antibodies, which are proteins that can neutralize that antigen. Initially T-cells and B-cells function similarly. However, B-cells do not directly attack antigens, instead they proliferate and differentiate into both plasma cells and memory B-cells. Plasma cells secrete antibodies that disrupt the function of the antigen and form complexes with antigen, making them more easily removable by macrophages. Memory B-cells make the recognition of invading pathogens easier during a secondary attack. Finally, acquired immunity includes two subgroups: natural and artificial immunity. Natural immunity depends upon natural exposure to a pathogen and slow building immunity, whereas artificial immunity occurs when someone is deliberately exposed to a pathogen. For example, getting a vaccination for measles or smallpox is a type of artificial acquired immunity. [31]

Antibiotics

Penicillin

Bacterial infections like tuberculosis, syphilis, and salmonella are treated with antibiotics. The term antibiotic originates from the Greek term anti meaning against, and bio meaning life. The history of modern antibiotics began with the discovery penicillin from the Penicillium mold by Sir Alexander Fleming in 1928. [32] During his work with Staphylococcus, Fleming found that his culture plate had patches that were bacteria-free: he discovered that these patches were produced by a mold, which fell on the plates and produced a substance that killed bacteria. [33] The reason why penicillin was an effective antibiotic is because penicillin disrupts the synthesis of the peptidoglycan cell wall of bacteria. It does this by preventing cross-linkages from binding to the long chains of peptidoglycan, causing the molecules to be unlinked and unable to synthesis a rigid cell wall. Unfortunately, today there are certain bacteria that are resistant to penicillin thus scientist have had to create other drugs that similar but different enough from penicillin to combat bacteria that have become resistant. Methicillin is an example of this.

Methicillin

By 1953, the wide use of penicillin led to development of *S. aureus* organisms that were resistant to penicillin. Staph infections steadily rose in hospitals despite efforts to create modified penicillin antibiotics to combat the new strains. One example of this new antibiotic was methicillin. Methicillin was initially effective because it was able to prevent *S. aureus* from producing beta-lactamase, the enzyme responsible for penicillin resistance. The problem stems from genetic alterations and auxiliary gene expression that ultimately disrupts the drug's main function. [34] However, just like penicillin within the first decade of its use, resistance against methicillin began to sprout. By 2005, 55% of ICU and 59.2% of non-ICU patients showed signs of MRSA. [35] Today, 95% of patients with *S. aureus* infections show signs of multi-drug resistance. Thus, health care professionals are forced to prescribe numerous antibiotics, increase dosages in order to treat infections that once were cleared away by one drug.

Natural antibiotics like penicillin, actinomycetes, and bacillus are found in soil and are designed to destroy surrounding organisms that may make survival more difficult, i.e. competition for space or food sources. Modern antibiotics are highly specific for the bacteria they are to affect. The antibiotic may be designed to inhibit the bacteria's ability to enter a host cell, disrupt the bacteria's energy source, create a cell wall, modify transcription, and change ribosome function and the synthesis of proteins, thereby preventing bacterial reproduction. [36] [37] In the end, all antibiotics function to either kill or inhibit its target bacterium.

Antibiotic Resistance

How exactly do bacteria become resistant? One way is for the bacteria to use enzymes like beta-lactamase to destroy the antibiotic's chemical make-up. B-lactamase is an enzyme that is produced by bacteria. Antibiotics, like penicillin become ineffective if the bacteria are producing beta-lactamase to protect its cell wall because the enzyme attacks the B-lactam ring on the antibiotic. [38] Second, bacteria can develop methods to prevent the insertion of antibiotic into itself. Third, the receptor-protein targets can change causing the antibiotic to no longer recognize its molecular target. Because of the wide-use, misuse, and abuse of antibiotics and antiviral

drugs by clinicians and their patients, targeted bacteria and viruses have adapted and evolved to too many drugs that were once affective in their eradication. As a result, scientists struggle to keep up with the rate of antimicrobial resistance to produce drugs that are affective against new or more evolved strains of the microbes.

Antiviral Drugs

Antiviral drugs like antibiotics are designed to inhibit a virus from replicating and infecting other cells. Scientists seeking to cure people of their infection look for weaknesses in the virus to create antiviral drugs. Drugs like Tamiflu and AZT (zidovudine) disrupts a virus's ability to replicate. [39]

Tamiflu

The pharmaceutical giant Roche successfully marketed a neuraminidase inhibitor to combat multiple strains of the influenza virus. Tamiflu (osteltamivir) is an effective oral antiviral drug if taken within the first 48 hours of infection. It works by binding to the neuraminidase active site and thereby competing for the enzyme's substrate. Later, during protein synthesis inside the host cell, Tamiflu binds to neuramidase proteins, preventing them from reassembling to create a new virion. [40] Because Tamiflu can affect both A and B strains of the influenza virus and disrupt the virus's replication mechanism later in its life cycle, the drug is more than likely to not develop drug resistance strains. Currently, 33 million patients have been treated with Tamiflu worldwide. Studies show that the drug is effective in reducing influenza's symptoms. Furthermore, Japanese studies on the development of resistance to the drug shows that there is a low frequency of resistance among the 1180 influenza patients used in the study. [41]

AZT & AZT resistance

AZT (zidovudine) was the first approved treatment for HIV infected persons. AZT is an antiretroviral drug which has promising affects on HIV disease. Patients using AZT have prolonged lives due to its ability to reduce opportunistic infections, prevent deterioration of the body, increase T-lymphocyte counts, and decrease mortality. Among asymptomatic HIV infected persons, AZT seems to delay the virus's progression. It is given to HIV infected mothers to prevent transmitting the virus to their baby. As an antiviral drug, AZT falls under the category of reverse-transcriptase inhibitor: AZT selectively inhibits the viral protein reverse transcriptase, preventing the virus from making a DNA copy of its genome and, therefore, preventing the virus from inserting its genes into the host genome. In higher doses it may also inhibit the function of DNA polymerase, a key enzyme in DNA replication. Despite AZT's effectiveness against the HIV virus, resistance to the anti-retroviral drug has developed. With use and time, HIV's reverse transcriptase becomes less and less susceptible to the inhibitor, thus decreasing AZT's efficacy.

Vaccines

Unlike antibiotics and antiviral medications, vaccines make use of the immune system's natural processes to fight disease. Once a person has been exposed to a microbe, a normal immune system will produce antibodies to recognize future exposure to the microbial pathogen. When the microbe is seen for the second time, antigens are recognized by the immune system rapidly and more aggressively, owing to the previous experience of the immune system and the production of more copies of the antibody.

The term vaccine came from Edward Jenner who serendipitously discovered a milkmaid's immunity against smallpox because of their exposure to cowpox. Jenner coined the term vaccine from the Latin word vac-

meaning cow. Later, Louis Pasteur, developed vaccines against rabies, and by the 1950s and early 60s vaccines for polio, measles, and rubella were readily available. Vaccines require scientists to isolate either a live virus, a dead virus, or a genetically engineered virus: in the application of a vaccine, a healthy human is exposed to its weakened or less virulent form. In doing so, the body's immune system creates antibodies and vaccine-activated T cells, which can prevent disease upon future exposure to the more virulent strain.

Disinfectants

The practice of disinfecting household and hospital surfaces could potentially lead to bacteria that are both resistant to disinfectants and antibiotics. Doctors and researchers are worried that the increased use and misuse of disinfectants are selectively allowing for the evolution of bacterial strains. Thus, the defense lines that hospitals have in place to reduce infection are threatened. Furthermore, using biocides (chemicals used to kill bacteria), appear to help in the mutation of *Staphylococcus aureus*, such that *S. aureus* developed protein pumps that allowed it to produce an anti-antibiotic chemical. Fortunately, scientists are developing chemicals that may disrupt the protein pumps from producing their anti-antibiotic product. Researchers in Tel Aviv have found the enzyme causing the antibiotic against *S. aureus* to become ineffective. In finding the enzyme, they were able to use it against the bacteria by integrating it into antibiotics, thus improving the efficacy of the antibiotic against S. aureus. [42] The message is clear, misuse or antimicrobial products, not finishing an antibiotic/antiviral regimen, overdosing, and overuse can lead to more resistant strains of bacterial and viral strains. Over time, what are scientist and health care professionals going to do with strains of infectious diseases they do not have the power to treat?

Strategies

The standards or expectations we hold for our students are ever-changing. With the current CA State Science Standards and the upcoming Common Core Standards, one thing is similar. [43] [44] Teach students to think and apply their understanding of the content taught in your class. Maintaining student's interest in the lesson, giving them opportunities to be creative, and expecting a high level of rigor is the best way to keep students in engaged in class. The strategies and activities of this curriculum unit are designed to address these goals and to provide students with a variety of learning experiences.

Like many high school students, students at Mt. Pleasant High School are exceedingly gregarious. This is their strength and their weakness, which I hope to direct to better use than talking in the hallways of our school. Beyond the normal lectures (direct instruction), students will engage in multiple learning modalities. These will include a mixture of indirect instruction and interactive instruction.

Indirect Instruction

Each Monday, most science teachers at Mt. Pleasant High School focus on increasing literacy in the subject area. To do so, students will be given guided readings of the textbook and non-fiction text from a variety of science article sources. For example, historical excerpts regarding the influenza virus, chapter readings on the physiology, and science magazine articles regarding immunity and bacterial/viral infectious diseases. In order to help them attain concepts from their reading, they will take part in reflective discussions which will help to first summarize their understanding but also pose questions. The questions generated by students will then be

used in the overall class discussion regarding the particular reading.

Another learning strategy students will take part in will be to create a short story describing the Immune System and its function. In crafting and creating their own stories, students not only have to show their mastery of the content they have learned, but have to apply their learning in order to inform others. The creation of this unit will force students to work collaboratively, to practice their writing in an order logical and organize matter, and to write concisely while retaining all the pertinent facts needed to convey their message. [45] This activity is further discussed in the activities section of this unit.

Interactive Instruction

As mentioned, students at Mt. Pleasant love to interact with one another. The challenge I have is to structure their interactions. Thus, in this unit, I will engage my students in multiple interactive learning experiences. Early in the unit students will be asked to brainstorm on the antimicrobial products. This will lead into a discussion on whether antimicrobial products should be widely used. Students will then formulate their own positions into a clear and concise statement which will be revisited once the unit has concluded.

A second interactive experience students will participate in is a sing-off. I have found that if my students can relate a musical experience to a topic they have to learn, they are more than likely to retain the information they were asked to learn. In the past, students have created rap-songs and rhymes about hypertension. While doing these activities, they were clearly engaged and were willing to share their song with anyone who would listen. For this unit, students will be modifying or writing their own songs about the immune system.

Experiential learning

In order to foster self-learning and students ability to analyze and apply their learning, students will be asked to create public service announcements highlighting an issue important to them. This issue will be generated from students own analysis of the overuse of antimicrobial products. It is my hope that my students will inform each other of the dangers of overuse but I would like for them to formulate their own reasons why. The culminating public service announcement project mentioned in the classroom activities section describes the details of this project.

Beyond the direct instruction, interactive, and experiential learning students will be exposed, practiced, and become comfortable users of technology. Since incorporating technology use is a major goal for me as a teacher, I embed tech use throughout this unit. This is an important task because it makes word processing programs, presentation programs, media creation programs far more significant to my students.

Classroom Activities

Biology and Physiology Activity

Class activities beyond lecture will include readings, historical and scientific, that will focus on the impact of pathogenic diseases on human beings. This activity is designed to specifically meet the demands of the upcoming Common Core Standards, in which students must be able to read and extract information from a variety of texts. Thus, students reading and writing skills will be reinforced within this course in order to utilize

and practice the same skill set. Students, for example, will read historical excerpts related to the Influenza Epidemic of 1918. As a way to reinforce writing, students will practice Cornell Note-taking skills that to recall and reflect upon their readings. This activity will be reoccurring in both Physiology and Biology classes.

Physiology Activity

Students in Physiology will be focused more on the physiology of the lymphatic system and immune system. Their activities will lead to the writing of a storybook in which the major characters and scenarios involve immunity, bacterium or virus, and an antibiotic or antiviral drug. In an early activity within the unit, students will have to describe their understanding of the immune system in words and shorts phrases. This will be accomplished by having students think and record what their thoughts on the function of immune system. After students have had a chance to share with the whole class their words relating to the immunity, students will then be asked to formulate ten sentences that include the terms and phrases that were shared. After jotting down their sentences, students will share their ideas with at least four other people in class. In this way students are forced to practice their collaborative skills, correct each other's information, clarify their own understanding and add to their own knowledge by including other students' sentences into their list of ten. This activity should be well monitored since students often get distracted and off-task. Thus, time limits will be set in place, opportunities to share out what they learned was new, and ask questions to the rest of the class to further their learning, or get clarification.

Once all students have had a chance to discuss and share with multiple students, they will then be asked to evaluate their sentences choosing ten lines that they feel are the most important aspects of the immune system. As their instructor, I will review their list and give feedback on their choices. This process will be repeated and slightly modified for a brainstorming activity on bacteria and viruses. The essential question students will be asked when brainstorming and researching bacteria and viruses will be, "How do certain bacteria/viruses become pathogenic?" Thus, students will need to delve into the physiology occurring inside a human body cell or tissue.

Once their immune system and bacteria and viruses sentences are approved, students will be given instructions as to how to proceed with creating a story that will highlight their 20 sentences. We will review the elements of story, including plot, setting, protagonist, antagonist, etc. Like many teenagers I am expecting my students to balk at the thought of writing a story for a science class. But, it is my intention of introducing to them the Common Core Standards which specifically includes a writing and critical thinking aspect (Appendix I). In their stories, students will have to incorporate one villain. This villain will be a bacteria or virus or a drug resistant bacteria/virus. Students with the most creative stories and those who can incorporate a third component, antibiotics & antiviral drugs, will be given added points to their overall stories.

These stories will then be shared with other students or read to a local elementary school, since our students are volunteers with reading partners in K-6th grade. In allowing students to share their learning, students become owners of their work and are held accountable by their peers and their teachers as well.

Biology Activity

Biology students who have strengths in art will also be given the opportunity to use materials found from everyday household items or non-conventional items to create a model of a bacterium, or a virus. Day one of the lesson will be an introduction to bacteria vs. viruses using a Venn diagram. Within the same hour, instruction will be given regarding the details of four day project and groupings. With a given list of pathogenic viruses and bacteria, students groups will have to choose one pathogen from the list. On Day two students will

work in groups of three to four. In their cooperative groups, students will divide into engineers and researchers. Researchers will use web-based resources to gather the following information: Genus and Species, general description, type of microbe, host-parasite relationship, and pathogenic capability (what diseases can it cause). Over the course of three days engineers will have to complete their model, provide a materials list, and a list describing the structural components of their microbe. On the fourth day students will be asked to participate in presentations. Presentations will be divided into two groups A and B. Group A students will present to B students and vice versa. At the end of the class period, students from opposite groups must state one item learned from presentations in order to leave class for the day. Assessments will include group evaluations, individual evaluations, and formative assessment throughout the four days of the lesson.

A second, and larger, culminating project will involve their own research into antimicrobial products at their local drug stores and homes. Throughout the course of the unit students will be asked to gather data regarding the variety of antimicrobial products. This data will be reported into a logbook for a period of two weeks. This will be followed up with small group discussions relating to the necessity of these products. As a part of this assignment students will include individual reports to their group on drug resistant bacteria and viruses in order to open their eyes to the number of microbes that are increasingly more and more difficult to treat. Finally, as a way of communicating their learning beyond my class, students will take part in a poster contest designed to address the need to prevent the spread of germs but at the same time inform their student body of the harmful potential of resistant bacteria.

Another optional Biology activity which incorporates Common Core Standards regarding writing is to have students create a metaphor book. Students' metaphor book will have to explain the different aspects of bacterial/viral life cycle. Since I am a firm believer that students should have options to showcase their learning or understanding, students will be given the option of using multiple media to complete their book (i.e. movie, posters, songs). As long as students are given multiple venues to express their learning, students will rise to the challenges we set forth for them.

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Chicago formatting by BibMe.org.

Appendix I

CA State Standards:

1. The fundamental life processes of plants and animals depend on a variety of chemical reactions that occur in specialized areas of the organism's cells. As a basis for understanding this concept:

c.Students know how prokaryotic cells, eukaryotic cells (including those from plants and animals), and viruses differ in complexity and general structure.

2. Mutation and sexual reproduction lead to genetic variation in a population.

7. Scientific progress is made by asking meaningful questions and conducting careful investigations. As a basis for understanding this concept and addressing the content in the other three strands, students should develop their own questions and perform investigations.

10. Organisms have a variety of mechanisms to combat disease. As a basis for understanding the human immune response:

a. Students know the role of the skin in providing nonspecific defenses against infection.
b. Students know the role of antibodies in the body's response to infection.
c. Students know how vaccination protects an individual from infectious diseases.
d. Students know there are important differences between bacteria and viruses with respect to their requirements for growth and replication, the body's primary defenses against bacterial and viral infections, and effective treatments of these infections.
e. Students know why an individual with a compromised immune system (for example, a person with AIDS) may be unable to fight off and survive infections by microorganisms that are usually benign.
f. Students know the roles of phagocytes, B-lymphocytes, and T-lymphocytes in the immune system.

Common Core Standards: Reading

-Cite specific textual evidence to support analysis of primary and secondary sources, connecting insights gained from specific details to an understanding of the text as a whole

-Integrate and evaluate multiple sources of information presented in diverse formats and media (e.g., visually, quantitatively, as well as in words) in order to address a question or solve a problem.

-Determine the central ideas or conclusions of a text; summarize complex concepts, processes, or information presented in a text by paraphrasing them in simpler but still accurate terms.

Common Core Standards: Writing

-Develop and strengthen writing as needed by planning, revising, editing, rewriting, or trying a new approach, focusing on addressing what is most significant for a specific purpose and audience.

Use technology, including the Internet, to produce, publish, and update individual or shared writing products in response to ongoing feedback, including new arguments or information.

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