Curriculum Units by Fellows of the Yale-New Haven Teachers Institute
2019 Volume III: Human Centered Design of Biotechnology

Vaccines, How They Work: From Individual to Population

Curriculum Unit 19.03.02
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I teach Biology at an urban magnet high school. The high school draws from the city as well as from surrounding towns. The central theme of the high school is the performing arts, though this unit is relevant to any high school biology curriculum. While positioned for an advanced biology class, this unit is certainly adaptable to any level biology class. The importance of vaccinations as part of the biology and health curriculum cannot be understated.

Teaching about vaccines is a critical part of any biology curriculum, be it an entry level class or advanced placement (AP Biology) class. It is fundamentally necessary that students are exposed to vaccine centric content. Vaccines are of a paramount importance to human health, comparable to clean drinking water. Furthermore, it is fantastic fodder to deliver other biology content, for example the immune system, cell to cell recognition, viruses, bacteria, funguses, and drug delivery. One can easily intertwine lessons on any of the aforementioned topics with teachings about vaccines to create a robust and rigorous lesson.

This unit focuses on the blending of vaccine focused content with basic biology content. The blending of content primarily concerns the human immune system. Allowing students to explore human vaccine technology through fundamental immune system knowledge and providing a tangible and relatable way to engage with these two complex topics to aid student understanding of how a vaccine works on the individual level. Prior to addressing the science behind how a vaccine leverages the immune system some vaccine focused content will provide a brief history of vaccines and explanation of vaccine types. Herd immunity will also be discussed within the unit. Herd immunity refers to the percentage of immune population threshold that is necessary to avoid an epidemic. Herd immunity is about understanding how vaccines work on a population level. It is relevant that students understand that vaccines are not just an individual health issue and are perhaps more importantly a community health issue. These topic areas will also allow the unit to explore the pressing and relevant vaccine related issue of barriers to vaccine adoption and public adoption of vaccine protocols. Finally, the likely future of vaccine technology, DNA vaccines, will be discussed. DNA vaccines offer much promise in eliminating some inherent vaccination issues such as transport, storage, ease of production, and safety.

Vaccines protect us from diseases caused by viruses, bacteria, and funguses. Future applications of vaccines will be discussed at the end of this unit, including the development of vaccines to fight cancer. Cancers, such as melanoma, are caused by mutations and not pathogens thus vaccines as preventative therapeutic is a new

realm of vaccine utilization. Typically students will attribute vaccines as protection against viral infections. This is simply not the case and should be addressed within any comprehensive lesson. Though not imperative to understanding how a vaccine works, it is necessary to mention non-viral applications to dispel the common myth. Vaccines help us to protect against bacterial infections such as
tuberculosis, diphtheria, tetanus, pertussis, Haemophilus influenzae type B, cholera, typhoid, and Streptococcus pneumoniae. Bacterial diseases may be remedied with antibiotics but it is more effective to be proactive in some cases and use vaccines. Vaccines are also used to combat aggressive and life-threatening fungal infections such as candida infections.

Vaccines: A Brief History

Many attribute the initial practice of inoculation as being the work of Edward Jenner, but, in actuality the practice of infecting a person in order to protect them from a disease dates much further back. The particulars of the true history of inoculations is beyond the scope of this unit, but there is documentation of inoculations that pre-dates Jenner's work by some 300 years or more. Those activities did also include activity with smallpox. A lesson on vaccines should include some history though, as the discovery of the process is important to the understanding of the result. Exposing the body to the infecting agent allows the body to learn of the pathogen and develop defenses against it. It was not known to those pioneers that they were dabbling with a precarious situation, but they were acutely aware of the fact that a forced exposure of some sort was better than contracting the disease unknowingly.

Edward Jenner is credited for first discovering the concept of vaccination because his work was well documented. Based on the premise that one that contracts the cowpox virus is then immune to the smallpox virus, Jenner inoculated a child with material from a cowpox pustule. He subsequently inoculated the boy with material from a smallpox pustule and when the boy did not contract the smallpox virus Jenner's hypothesis was validated. His initial hypothesis was rooted in the occurrence of seemingly immune individuals. These individuals were milk maids who worked closely with cows and had contracted the milder virus of cowpox and were later unable to contract smallpox. What Jenner was not aware of was how this phenomenon worked which is the intent of this unit. Students should understand the potential of vaccines which requires an understanding of how we leverage the immune system through vaccination. Jenner was not aware that it was on a cellular-level that the body was "learning" about and preparing for the infectious agent and that it was an antigen (the identifying pathogenic factor) that was the key. The antigen is luckily the same for the cowpox virus as it is for the smallpox virus, thus Jenner's inoculation worked. The body learned to defend against anything presenting the antigen and thus was able to mount an appropriately timely defense against a smallpox infection. The antigen is a specific molecule that is presented by the virus, in this case the molecule is identical between the smallpox and cowpox viruses.

Vaccines have immense potential, potential that is being realized with the near eradication of many debilitating and deadly diseases. Using the immune system to protect against pathogens has much more promise than using a drug. The ingestion of a drug will invariably have some collateral damage on the body, wherein the utilization of a targeted attack by the immune system does not have that potential threat. The pathogen is targeted at the molecular level. The immune system targets the specific molecule that it is hunting. Drug therapy, in contrast, is targeting a trait of a cell, traits that may be common to other non-target, non-pathogenic, cells. The premise of the action of vaccinations is now being applied to using vaccines to treat

diseases, not only those that are of foreign origin such as HIV, but also cancers. This is essentially using the immune system as a weapon against a disease that the body has developed on its own. This is different than vaccinating against a disease that you have not yet contracted, wherein you are preparing the immune system for possible invasion by exposing to it something that is not actually able to cause a disease state. This new application is about mobilizing the immune system at times when it is not sufficiently mobilizing itself.

Vaccines: Types

Today the word vaccine encompasses many types of vaccines, for Jenner it was specifically linked to creating immunity to smallpox, the variola virus. The word vaccine today refers to several types of vaccines. The health care industry utilizes live attenuated organisms, killed or inactivated organisms, purified subunits, and even recombinant subunits. Each of these works on the same general premise, delivery of an antigen to the immune system in order to teach it about the antigen of a pathogen.

A live attenuated vaccine is the pathogen with a weakened virulence. This reduced version of the pathogen still has the same identifiable characteristics, namely the antigens that a non-attenuated form would have. Thus, the immune system is given the opportunity to interact and develop defense against the pathogen without the threat of a disease state. We protect against smallpox, tuberculosis, yellow fever, polio, chickenpox, rotavirus, and influenza with live attenuated vaccines. This process relies on eliminating the virulence of the pathogen while maintaining characteristics that will induce an immune response. This can be achieved by causing mutations in the pathogen and then selecting for mutants with reduced or eliminated virulence. Considering the nature of mutations, being random, there is the chance that a non-virulent strain mutates and becomes virulent again. This risk is minimal though. Live attenuated vaccines are effective because they maintain their antigens, have adjuvant effects, and are packaged in an efficient delivery system (the pathogen), all of which help to elicit an effective and lasting immune response.

In some instances, the best strategy for a vaccine is to use killed or inactivated organisms. These pathogens have been chemically killed or inactivated without detriment to the antigens. Because they have been killed or inactivated an adjuvant is required to help induce the immune response. Some examples are the polio, Hepatitis A, and whooping cough vaccinations. These vaccines, as well as attenuated vaccines are cultivated in tissue cultures, eggs, media, or, in the case of the smallpox, directly in the skin of an infected calf. After culture, they are rendered inactive or killed and not just attenuated.

In the case of tetanus, vaccines are developed to target the toxin of bacterial origin as opposed to the bacteria itself. This type of vaccine is called a toxoid vaccine. The body develops an immune response to the inactivated version of the toxin, rendering the human insusceptible to the active version of the toxin.

Purified or recombinant subunits may be used as vaccines in cases where the antigen is known. Recall that antigens do not have any virulence, equate them to a group of robbers that all where red hats. The red hat may be used to identify them as robbers, but the red hat poses no threat on its own. The antigen can be thought of as the red hat. This is a very safe way to vaccinate as the pathogen, whether live, dead, inactivated, or attenuated is not introduced to the recipient thus there is no threat whatsoever.

Vaccines are also packaged together for a more effective delivery. Vaccines are now polyvalent or multivalent when possible and necessary. The valence of the vaccine refers to how many immunizations are packaged within it. Some vaccines remain monovalent, meaning that they provide immunity to one specific pathogen. Multivalent vaccines may be immunizing against multiple different pathogens or may contain immunizations for multiple strains of the same pathogen. Parents are confronted with this when immunizing their newborns. Multivalent vaccines are used because they are safe and more effective at achieve the desired outcome, herd immunity. There is a simple explanation for why they are more effective and that is less needles. It is as simple as that, less injections are required thus it is more likely that people are immunized against more diseases. It is less likely that a person will follow through with 5 separate immunizations than it is that they follow through with just one. Thus this increases the likelihood that the population is immunized against communicable diseases, decreasing the likelihood of an outbreak. DTaP is the acronym for an infant multivalent vaccine used in the US. The “D” is for diphtheria, the “T” for tetanus, and the “P” for pertussis.

There is much to be taught and explored concerning the production of vaccines but it is beyond the scope of this unit and likely beyond the scope of a high school curriculum. The real lesson in vaccines centers around how they work, the utilization of the immune system to combat a pathogen.

Vaccines: How They Work on the Individual Level

Vaccines are stimulants used to generate the production of antibodies by our immune system. Antibodies are produced by our B-cells, the major player of our humoral immune system. Antibodies are our body’s specific and targeted defense against pathogens and are fundamentally important to our health. The stimulant is a pathogen specific antigen. Pathogens may have several antigens. The antigen itself, recall, is just something that identifies a pathogen and by itself does not pose the threat of disease.

The human immune system has components that are innate and adaptive. Adaptive immunity has specificity wherein innate does not. This specificity, wherein the immune system has the ability to respond with a specific response (antibodies) to a specific invasion, will be discussed further below. Firstly though, innate immunity is comprised of attributes such as skin, mucous membranes, and secretions. Skin, the integumentary system, is considered a first line of defense for the body, hence part of the immune system. Skin is non-specific, the purpose to simply be a physical barrier separating the inside of the body from the outside world. Every bit of your body that is exposed to outside is lined with skin. Consider that when you consume food that that food travels through what is essentially a tube that passes from one end of the body to the other, seemingly through the body, yet the food does not come into direct contact with the body interior. The tube is lined with skin the entire way. The nutrients and water that the food contains must be broken down to the molecular level in order to pass through the lining of lining. Only then is something actually entering the body. Consider also how important it is to clean and sanitize a wound as it is a breach in the skin barrier. Skin, like mucous membranes and secretions, is non-specific because it treats all foreign material the same, no passage is allowed unless at the molecular level.

Internally we have phagocytic cells, antimicrobial proteins, the inflammatory response, and natural killer cells all of which are part of the innate immune system. Again, this system lacks specificity and is simply a response to an invasion or compromise of the body. There is a bridge between the innate and the adaptive carried out by the phagocytic such as dendritic cells.

Adaptive immunity is broken into two factions, cell-mediated and humoral. Adaptive immunity is called as such because it has the capacity to adapt, developing responses to pathogens based on an antigen recognition system. The dendritic cell, a player of the innate immune response communicates with the adaptive immune response via cell-mediated immunity. Dendritic cells patrol the body, within the bloodstream and even sometimes in interstitial spaces, looking for any material that is foreign to the body. Dendritic cells are non-specific and are seeking material that presents molecules common to bacteria and material presented by cells infected by a virus. These are taken by phagocytic action. Dendritic cells work with T-cells which are part of the cell-mediated immune system. Dendritic cells work with T-cells by presenting antigens to them. They are referred to as antigen presenting cells (APC's). These antigens are obtained by sequestering and digesting foreign material. This is where the magic of the vaccine can first be understood. We have immune system players that not only destroy that which threatens the body but also have the functionality to display how to recognize it, its antigen, in order to communicate with the adaptive immune system, thus resulting in a teaching/learning process. The premise behind how a vaccine works is that we have an immune system that can learn, hence adapt.

Cell-mediated immunity communicates with the humoral response via helper T-cells. Helper T-cells will "share" antigen information with B-cells of the humoral system. B-cells develop antibodies specific to the antigen. The antibodies are the defense, attaching to a specific antigen. The antibody attachment stops the action of the pathogen through one of multiple ways. Some antibodies neutralize the pathogen, while others increase phagocytosis. There are other more complex effects but they are beyond the scope of this unit. Cell-mediated immunity develops memory T-cells to prepare for future infections by anything bearing the same antigen and the humoral system generates memory B-cells for future infections as well. The humoral response is about creating and storing antibodies specific to the antigen. These antibodies will be carried in and released by plasma cells when needed. A vaccine is a method of delivering an antigen in a safe way to the cell-mediated system so that the body can learn about and prepare for the antigen. The vaccine is simply a way to leverage the immunological response that we all have.

When vaccines are delivered they are targeting lymphocytes, those phagocytic cells of the immune system such as dendritic cells. Vaccines are delivered into muscle tissue because it is more likely that the lymphocyte will find the "pathogen" in this area as opposed to in the blood stream. Somatic cells, such as the muscle tissue cells, may also take in the vaccine and present the antigen to a T-cell. This presentation, when effective, is presented on a major histocompatibility complex (MHC). These are extracellular surface level proteins that present antigens to T-cells. There are two classes of MHC molecules. Class 1 MHC's are utilized by most all nucleated cells of the body and are recognized primarily by cytotoxic T-cells. Cytotoxic T-cells have the capability of destroying cells as well as activating more cytotoxic T-cells and memory T-cells. Class 2 MHC's are used by the APC's and are recognized by cytotoxic T-cells and helper T-cells. APC's are the dendritic cells, macrophages, and B-cells.

I have presented a relatively brief overview of the immunes system, how it is organized and how some action and communication occurs. Just this cursory look at the system is still confusing. The goal in the high school classroom is that students understand that the immune system is complex because it involves many layers of defense with many different cell types and that the system is adaptable, allowing for the use of vaccines. High school students need to gain an understanding of the method of presenting a fragment of a pathogen to the immune system so that the immune system can prepare a defense in the case that the actual pathogen infects the body. The defense is primarily antibodies, produced by B-cells based on information provided by other B-cells, helper T-cells, or a phagocytic lymphocyte. Ultimately the understanding is crucial to the student's comprehension of vaccine technology as a way to leverage the immune system to fight off infection

as opposed to introducing chemicals to the body, medicine, in order to kill off an infection. It is also imperative that students understand that a vaccine is not infecting the body, but simply showing the body what the infecting agent will look like.

Furthermore, there is room in this unit to focus on the biology concept of structure equals function. The structure of the antigen is what the entire defense is based upon. Antigens are proteins and thus have a defined structure. Receptors and antibodies that bind to antigens are doing so based upon the structure of the antigen. This concept can be tied back to other units in the curriculum concerning cell to cell recognition and cell transport. Considering that antigens are proteins will help students to understand the difficulties of storage and transport of vaccines which is discussed later in this unit.

Vaccines: How They Work on the Population Level

The true mark of a successful vaccine is a successful vaccination protocol. Though barriers related to the adoption of the protocol by the public will be discussed later, this section discusses the reason that a vaccine is deemed successful based on the community level immunological barrier created by individual immunizations. If a sufficient, that which protects vulnerable members, proportion of a population has immunity this is considered herd immunity. Thus achieving herd immunity indicates that the vaccine is a success because the threat of the disease becoming epidemic has been mitigated. In some cases diseases can be eliminated from a population when the herd immunity threshold is reached.

Surely it is important that individuals do not contract diseases and fall ill, but it is arguable that it is more important that there are not outbreaks. Considering communicable diseases the immunity of one person actually protects other people. If a disease can be passed from person to person, the fact that one person cannot contract the disease will reduce the instance of the transmission of the disease, thus reducing the likelihood of others contracting the disease despite their immunity. This is the premise that herd immunity relies upon. If enough people in a community are vaccinated the likelihood of those that are not vaccinated becoming ill significantly decreases.

Within a population there are people that cannot be vaccinated. The case may be that of age, too young or too old. Another reason is that the individual is immunocompromised because of disease and cannot be vaccinated as it stimulates the immune system. There are also instances wherein people are allergic to the vaccinations. The instance of increased immunity for those that have not been vaccinated because of those that have within the same population can be substantiated by a reduction of infections within the non-vaccinated portion of the population. Herd immunity helps to protect those that cannot be vaccinated, hence the phenomenon that a single individuals immunity increases the immunity of others within the community.

In general if 80% or more of the population is immune to a disease then the herd immunity threshold has been reached. For the purposes of the classroom one can use the 80% or greater rule. The threshold for diseases does vary from disease to disease based on how infectious the disease is, namely how many people are likely to be infected by an infected individual. The herd immunity threshold for small pox is 80-85%, for polio 80-86%, and rubella 83-85% while measles calls for 83-94% and pertussis 92-94%.[1] One can see that diseases with higher propensity to spread warrant a higher threshold. The metrics for determining these thresholds are beyond the scope of this unit.

Vaccines: A Likely Future, the DNA Vaccine

DNA vaccines hold promise as the most viable vaccine delivery method in the near future. There are specific health concerns with today's methods and DNA vaccine technology, when fully realized, will naturally circumvent those concerns. Furthermore there are limitations to today's vaccines concerning ease of production, transport, and storage.

Recall that non-live, killed or inactivated, vaccines are typically not providing life-long immunity. They work, but do not effectively activate cellular immunity. Live attenuated vaccines provide longer protection but their immunogenicity is linked to their level of attenuation. That means that the less attenuated, the better they work, which has inherent risk. Furthermore, with live attenuated vaccines there is the threat that mutations occur and new subtypes and variants arise. Generating copies of the pathogen, whether it is bacterial, fungal, or viral provides the opportunity for mutation and the incidence of new variants. These new variants may not respond to attenuation the same manner as their predecessor, thus the risk of inoculating people with pathogen that is not attenuated to the degree that was assumed.

Current vaccine technology is also severely limited by issues with temperature stability, impacting storage and transport. Maintaining vaccines at temperature during all times of transport and storage is difficult and consequently increases costs. Antigens are proteins and any given protein will have a temperature range in which it is stable and will maintain its structure. Exceeding the temperature thresholds for a protein will cause it to denature as the bonds that ensure its conformation of structure are compromised. Since antigen recognition is based on shape conformation by a receptor or antibody it is imperative that the shape of the antigen is not jeopardized and altered. This adds many levels of complexity to the distribution and storage of vaccines in the US and other first world countries and is a significant barrier in third world countries. Students may wonder why diseases that we have vaccines for are still prevalent in the world and the matter is sometimes as straightforward as transport and storage. Ultimately, one must question the usefulness of a vaccine if it cannot be delivered to the patient.

DNA vaccines are using the nucleic acid code for the antigen. The code is taken from the pathogens DNA or RNA. This section of nucleic acid is then packaged within a plasmid and adjuvants to be delivered to cells to generate immunity. A plasmid is a circular piece of DNA derived from bacteria. The plasmid enters the nucleus of the target cell and is transcribed and then translated into proteins, the antigens. Nucleic acid has much higher temperature stability than proteins, thus transport and storage barriers are not an issue. The fact that only the instructions for the antigen are even introduced to the patient eliminates any concern of virulence and is inherently extremely safe for the patient.

With DNA vaccines the actual antigen is not being used for inoculation, just the code. The fact that the recipients cells are translating and expressing the antigen themselves helps to increase the immunogenicity of the vaccine because the threat of antigen structure being compromised by any of the conventional vaccine processes has been diminished. Quite simply, the antigen is not even produced until it is within the patient therefore it is not subject to degradation or denaturation before performing its intended function.

DNA vaccines are delivered to somatic cells as well as APC's and there is evidence they result in long-term immunity by effectively activating B-cells which results in memory B-cells and antibodies. The vaccine must enter the patients cells and make it into the nucleus where it can be transcribed into RNA, processed, and then translated. Adjuvants, like eurkaryotic promotors and enhancers are used to elevate the expression. The

delivery methods do vary from the typical vaccine because needle delivery has not proven effective. The delivery methods for DNA vaccines aim to get the product into the cells because the whole process relies on the production and presentation of the antigen.

The inoculation methods are quite advanced. One method utilizes high pressure steam to deliver the plasmid vaccine on microscopic heavy metal particles. Other methods are using pathogen like nanoparticles that can be recognized by a phagocyte and engulfed. Still another method is to use electrical pulses to disturb intramuscular tissue to encourage uptake of the vaccine. Lastly, methods are using liposomes to package the plasmid. Overall, the difficulty in the development of DNA vaccines has been with the delivering the package to the nucleus of the cells.

The DNA vaccine does show promise when it is effectively delivered to the nucleus of the patients cells. Somatic cells are presenting the antigen with a class 1 MHC pathway, that which is recognized by T-cells, confirming cell-mediated immunity. Plasmids are also found to enter APC's, making them transfected, and initiating immune pathways at both the cellular and humoral level. Furthermore, transfected somatic cells are phagocytosed and the antigen is presented to T-cells.

DNA vaccines also show promise in clinical studies for the treatment of cancers. This is based on the premise that a cancerous cell will display a surface level protein unique to the cancerous cell and not utilized by other cells. The immune system can be alerted to this antigen through DNA vaccination, mobilizing the body's immune system against the cancer. This is significantly more promising as a treatment as opposed to chemotherapy and transplant which both have some extreme side-effects and risks. Furthermore, research is underway for immunization against cancers such as HIV and HPV.

Vaccines: Non-Physiological Barriers

The science classroom should not ignore the barriers to vaccine success that have nothing to do with the science. Recall that vaccine success is most accurately measured at the population level, the determination being whether the vaccine is effective at eliminating disease outbreak. A vaccine that creates life-long immunity, protecting people from a debilitating or deadly disease, can be for naught if the community does not adopt the practice. Herd immunity is needed for a vaccine to be effective, herd immunity relies on widespread adoption of the vaccine protocol by the community. Some barriers that have presented themselves are the public concern with vaccine safety, whether based on false information or hearsay, people have been known to choose not to vaccinate themselves or their children based on a perceived level of safety risk. There are also populations of people that refuse vaccinations based on religious beliefs, the premise being that we are born with all we need within our bodies already. Factions of populations refuse vaccination simply because they are perceived as government mandates and they believe strongly in their autonomy. Lastly, vaccines may be turned down because there is no perceived risk of the disease that the vaccine prevents. The fact that someone had never encountered a person with polio or measles gives the false sense that the diseases are not a threat.

Classroom Activities

Modeling the Immune Response

It is recommended that this unit begin with readings and lecture on the human immune system. There are some class activities that I use to support the content. One such activity involves students creating antibodies for different antigens, modeling the immune response. Allow students to use playdough and markers to model how the immune system first interacts with a pathogen, processes the pathogen, presents the antigen, creates antibodies, and subsequently interacts with the same antigen during future interactions. Students can draw from the conceptual understanding of enzymes and proteins interacting in a lock and key fashion. The antigen is a “key” and the antibody is the “lock”. Allow students to create unique pathogens with differing antigens and then allow them to create antibodies for those antigens. This all occurs in as a large modeling activity wherein all of the necessary immune system players are involved and justified either in writing or verbally. I find it effect for students to orally present their models to other students. The necessary components of this modeling activity are: pathogen (student created), macrophage, helper T-cell, memory T-cell, plasma cell, B-Cell, cytotoxic T-cell, memory B-cell, antibodies, and platelets.

Vaccination Pamphlets

Students can create pamphlets promoting vaccinations. The pamphlets should include all necessary vaccinations including when and how they are administered. The pamphlet must also include facts about the impact on public health that avoiding vaccination poses. Students should incorporate an explanation of herd immunity. It is important that data on recent outbreaks of contagious diseases that could have been mitigated with more universal use of vaccinations. Lastly, students should address vaccination myths in their pamphlets.

Research Project

A research project and report on either an autoimmune disease or allergy helps students to gain a deeper understanding of the immune system. The report should focus on the actions, albeit inappropriate, of the immune system. This helps with understanding how the immune system works because in the case of autoimmune or allergy the immune system has incorrectly identified something as a threat to the body.

Notes

1. Fine, Paul E.M., “Herd Immunity: History, Theory, Practice,” Table 1, 268.

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