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Advancements in Vaccine Development: Measles vs. COVID-19

Sarah Ziegler

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Abstract

As an ever-progressing field of study, vaccine development has made headway over the past decades. By doing a comparative study between development of the measles vaccine in the mid-20th century, and the ongoing development of the COVID-19 vaccine in 2020, many of the insights and advancements in the field can be easily highlighted. First, the knowledge and experience gained over those decades has helped the vaccine developing process become more efficient. With more vaccines in production, or at least under study, it is more likely to have a related precedent to build upon, as opposed to relying on a successful vaccine of some unrelated disease. More to the point, different vaccine types have altered the way researchers attempt to formulate future vaccines. No longer are inactivated and attenuated vaccines the only option; subunit vaccines, as well as innovative, (though yet to be proven), nucleic acid vaccines are now additional approaches. These advancements have opened doors for researchers in their quest to fight diseases. This paper will explore the advancements and their impact on the present-day COVID-19 vaccine development.

Keywords: Vaccine, Measles, COVID-19, mRNA Advancements in Vaccine Development: Measles vs. COVID-19

Though the majority of successful vaccines were developed in the 1900s, the challenge to develop vaccines still exists today, with both known diseases, such as cancer, as well as with novel infections that sweep the world. Measles used to be a common childhood disease; one which everyone contracted and with the majority of patients recovering completely. It was practically inevitable until the late 1900s, when a measles vaccine was introduced to the public. In the mid-1950s, after weeks of trying, John Enders's lab successfully isolated the measles virus. Eventually, through implementation of routine measles vaccine—one dose at 12-15 months, and a second at 4-6 years—measles was successfully eradicated from the U.S. in 2000, and from the Americas in 2016 (The College of Physician of Philadelphia, n.d.). However, that milestone of eliminating measles was not yet to be reached, as it was another ten years from the isolation of the virus until the measles vaccine officially debuted.

Contrastingly, it took Chinese researchers weeks to sequence the genome of SARS-CoV-2, a feat way beyond the simplicity of merely isolating the virus. Even more so, a projected release date for a safe and effective COVID-19 vaccine is only 12-18 months from the start of development, and one can only hope that the vaccine will eradicate the virus. Normally, vaccine development with FDA approval can take anywhere from 5-10 years. Obviously, vaccine technology has critically advanced in the decades since the measles vaccine, thus allowing researchers to expedite the vaccine development process for COVID-19 and all future pandemics. This paper will explore some of these advancements and their potential impact on the COVID-19 vaccine development.

Methods

All of the information discussed in the paper was obtained through the PubMed database, as well as via Google searches which led to government sites, like the

CDC and NIH, and also to known and established medical sciences related sites, like CHOP and The College of Physicians of Philadelphia.

The majority of the amassed information pertained to the techniques involved in developing both the measles vaccine and the potential COVID-19 vaccine, so that I could compare and contrast the respective availability of resources.

One study explored in the paper included vaccine trial studies in which the efficacy of various measles vaccines were tested either alone, or in a series with other forms of developing measles vaccines. At a designated interval after each trial, measles titers were measured and eventually, the most effective vaccine was sought out.

There are currently over one hundred biotechnology companies and universities developing vaccine candidates for COVID-19. For the vaccine studies that are not yet ready for human test trials, i.e. majority of the COVID-19 studies, this paper analyzed selected studies which elaborated on the numerous approaches towards an effective COVID-19 vaccine.

Discussion

An Overview of Vaccines

How vaccines work

The purpose of a vaccine is to trigger the immune system to stimulate an initial immune response and ultimately create a cellular memory mechanism to fight future attacks by the pathogen. This way, when the body is exposed to the actual disease in the future, the body will produce an immediate secondary immune response and not a primary response (Clem, 2011). Secondary immune responses are quicker and more specific, and are therefore better than a primary immune response.

Classically, vaccines are created by deactivating or attenuating the virulent part of the pathogen, while leaving the antigenic portion of the pathogen intact so that the vaccine can induce an immune response without causing the disease itself (The College of Physicians of Philadelphia, 2018). When the body detects a foreign antigen, the innate immune system goes into action first (Clem, 2011). The

innate system includes non-specific white blood cells (i.e., macrophages and natural killer cells), which can either destroy the invader or process the pathogen and present its antigen to aid in the adaptive immune response. Both the humoral and cell-mediated immune responses are part of the adaptive immune response. The humoral response consists of B-cells, which detect the foreign antigen and then self-mutate to find the antibody that best fits the antigen. After that is successfully accomplished, the B-cell that is able to produce the most effective neutralizing antibodies replicates and becomes either plasma cells, which secrete antibodies to help fight the current infection, or it creates memory B-cells specific to that antigen, so that upon future infection the body will have an antibody that targets and destroys the specific disease pathogens. The cell-mediated immune response contains two types of cells, T-killer and T-helper cells, which are either activated by major histocompatibility complex I (MHC I) or major histocompatibility complex II (MHC II). MHC proteins are expressed on the surface of all bodily cells to signal that the cells belong in the body. However, when the cells become infected with a pathogen the MHC will take the processed antigen and present it on the surface of the cell, so that the T cells of the cell-mediated immune system can respond. T-killer cells recognize the antigen presented by MHC I molecules and subsequently advance to kill the invading cell. On the other hand, T-helper cells recognize the antigen presented by MHC II molecules, and T-helper cells aid in the activation of B cells as well as T-killer cells. Regardless of their function, either T cell can replicate and form T-memory cells in preparation of future infections (Clem, 2011). In all, the job of a vaccine is to prime the body for a future encounter with a specific pathogenic agent.

Stages of Vaccine Production

Before any vaccine can be mass produced for public use, it must go through a series of developmental phases to assess first and foremost its safety, in addition to the vaccine's efficacy, required dosage and dose frequency, and screenings for any harmful side effects (The College of Physicians of Philadelphia, 2018). Prior to these phases though, researchers study the specific disease and attempt to identify its immunogenic parts. Once that has been done, researchers can either isolate the antigenic portion, or inactivate the virulent part, depending on what type of vaccine they propose to create.

Following those preliminary steps, the candidate vaccine can then enter the preclinical phase of study. In this stage, researchers test the vaccine safety and immunogenicity on animals (The College of Physicians of Philadelphia,

2018). Also during this preclinical stage, researchers may conduct what are known as challenge trials. In these tests, researchers inject their candidate vaccine into the lab animals or human volunteers, wait an amount of time so that the vaccine can elicit an immune response and create memory cells, and then finally, they inject the targeted virus into the subjects to determine if the vaccine can do its job. Based on the challenge trial results, researchers will adjust their vaccine development accordingly. During this phase, there may be a bit of trial and error in determining a safe starting dose, i.e. how many viral particles are needed to elicit an immune reaction, and method of delivery for human subjects of the next phase (The College of Physicians of Philadelphia, 2018). For the COVID-19 mRNA vaccine trials conducted by Moderna and the NIAID, three trial groups have been set up each with a different dosage. One group is testing the low dose of 25mcg, a second group is receiving the midrange amount of 100mcg, and the third group is receiving the highest dose, 250mcg (National Institute for Allergy and Infectious Disease [NIAID], 2020).

In order to advance from the preclinical stage to the clinical phases, the research group must submit an investigational new drug (IND) application to the FDA for approval to further their studies (The College of Physicians of Philadelphia, 2018). Once the researchers receive authorization, they can proceed to phase I clinical trials. At this juncture, researchers experiment with human subjects once again to test safety and immunogenicity of the proposed vaccine. This step starts with healthy adult subjects and if the vaccine is intended for younger or older age groups, the trials gradually trend towards the desired group. During this phase, researchers may conduct human challenge trials as well (The College of Physicians of Philadelphia, 2018). With regard to COVID-19, Moderna has reported that after two doses of their potential mRNA COVID-19 vaccine, participants in the low and mid groups have expressed immunity at or above the level in which someone who was naturally infected would have. This seems to be a promising result for phase I trials, especially since it seems that once someone contracts COVID-19 they do not get it again, and so the natural amount of antibodies should be sufficient for vaccine induced protection (CBS News, 2020).

After successful phase I trials, the vaccine can move on to phase II clinical trials. Here, researchers study a larger test group including a control group and the main point of this phase is to further characterize dosage, frequency of immunization, and method of delivery (The College of Physicians of Philadelphia, 2018). In this phase, the clinical studies will also ascertain whether the vaccine shows any

Advancements in Vaccine Development: Measles vs. COVID-19

efficacy. Safety of the vaccine is monitored as well.

Next, there are phase III clinical trials. This is where the potential vaccine is determined to be effective by recruiting hundreds or thousands of volunteers to help quantitate how effective the vaccine is in a large cohort (The College of Physicians of Philadelphia, 2018). The large subject group also allows for the detection of rare side effects. During this phase, vaccine safety and dosage are still monitored for necessary corrections. Vaccines are never 100% effective. Measle vaccine is thought to be about 85% effective. Therefore, phase III trials must assess vaccine effectiveness.

Finally, after the vaccine has successfully passed through all phases of clinical testing, the researchers can submit a biologics license application to the FDA for licensure of their candidate vaccine (The College of Physicians of Philadelphia, 2018). If the FDA approves, and the CDC subsequently recommends this vaccine for routine administration, the researchers will be able to manufacture their vaccine and enable mass population immunization.

At this point, researchers can conduct an optional phase IV clinical trial to further monitor the vaccine's safety and efficacy (The College of Physicians of Philadelphia, 2018). Studies can also be done to learn if the vaccine has potential for any alternate uses (i.e. other than for protection of the targeted pathogen).

Post licensure, the FDA and CDC continue to monitor the vaccine (The College of Physicians of Philadelphia, 2018). In 1990, the FDA and CDC established the vaccine adverse event reporting system (VAERS). The VAERS allows for anyone to report adverse side effects, which seem to be caused by a particular vaccine. The CDC then analyzes all of the input data to determine several conclusions. Among those conclusions are whether a new adverse side effect has indeed been detected, and whether certain health conditions place a patient at a greater risk of developing an adverse side effect. Also in 1990, the CDC established the vaccine safety datalink (VSD). This system provides access to numerous databases listing which vaccines were given to a particular patient on the reported date. The VSD conducts vaccine safety studies based on questions raised in medical literature or reports from the VAERS. In addition, the VSD monitors the safety of new vaccines.

Advances in Vaccine Development

In the sixty years since the development of the measles vaccine, the technologies used have improved as well as increased. For example, while Enders, Hilleman, and all the other researchers of that time were experimenting with either inactivated (dead virus) or live-attenuated vaccines,

researchers of today can work with a greater variety of vaccine types ranging from pathogen subunit vaccines to nucleic acid vaccines (NIAID, n.d.). Both forms of the newer vaccine methods aim at inoculating with only the antigenic portion of the microbe as opposed to injecting the whole pathogen, which is what is done with inactivated and attenuated vaccines. In an inactivated vaccine, the entire pathogen is killed and then subsequently administered to the patient (Clem, 2011). Attenuated vaccines, on the other hand, leave the pathogen partially alive, and then upon administration, induce a stronger immune response than inactivated vaccines. However, because the attenuated vaccine is slightly live, it does present a greater risk to the immunocompromised community (Clem, 2011). The challenge in designing inactivated viruses or attenuated viral particles is that there is no set formula for how to kill or attenuate the virus. Each virus is different. That is why it can take months, or even years, to generate an effective candidate vaccine.

Over the past decade, new innovative technologies have been instituted to develop effective vaccines. Subunit vaccines are one example where a mere pathogenic unit—a protein, or sugars on the microbe's outer coat—are administered into the patient to elicit an antibody response, thus allowing a person to attain immunity (NIAID, n.d.). However, subunits vaccines are often not effective enough on their own and require an adjuvant to enhance their immune response (NIAID, n.d.). While historically composed of only aluminum salts, adjuvants today come in many more varieties like MF59 (oil in water emulsion composed of scalene), CpG 1018 (cytosine phosphoguanine, a synthetic form of DNA that mimics bacterial and viral genetic material), and others (Centers for Disease Control and Prevention [CDC], n.d.-a). All of these adjuvants serve to aid in the immunogenicity of the vaccine, hopefully providing a stronger response and longer lasting protection. The inclusion of adjuvants in vaccine formulation requires researchers to carefully assess where these added compounds elicit unwanted side effects.

Contrary to the aforementioned vaccines, nucleic acid vaccines do not inject any physical part of the pathogen into the body. Rather, these vaccines inject a lab synthesized DNA or mRNA sequence that codes for one or more antigenic proteins (NIAID, n.d.). Once inside the body, the nucleic acid is taken up by the virally targeted cells and instructs those cells to synthesize and secrete the desired protein. Only then, after the protein is in the body, will the body generate an immune response and acquire antibodies to that specific disease (NIAID, n.d.). With this method of inoculation, the body itself is an integral part in creating the immunogenic portion of the

vaccine. An mRNA strand alone will do nothing. However, when acted upon *in vivo*, the body completes the last step in the vaccine synthesis, creating the protein to which it needs to attain immunity.

Nucleic acid vaccines have a quicker production time than traditional whole-pathogen vaccines (NIAID, n.d.). This is because a pathogenic specimen does not need to be grown for the creation of the vaccine (Park, 2020). Under normal circumstances, the microbe can take a few months to grow to the desired quantity. Thus, nucleic acid vaccines may be favored over whole-pathogen vaccines, especially in situations where time is a consideration.

Additionally, though nucleic acid vaccines can be injected directly into the body, another vaccine delivery mode has developed over the years. Instead of injecting the DNA or mRNA directly into the body, options now exist to use a vector for introduction of the vaccine (NIAID, n.d.). A vector is a small particle that acts as a vehicle for vaccine delivery. A viral vector, such as adeno-associated virus, can incorporate the vaccine's genetic material by replacing some of its viral genes with the vaccine's desired sequence (Robert-Guroff, 2007). Studies have proven that viral vector administration is both safe and effective, though the quantitative values vary amongst the viruses (Robert-Guroff, 2007). There are also non-viral vectors, for example, liposomes and lipid nanoparticles (LNP), which can be used to deliver nucleic acid vaccines as well. One advantage of non-viral vectors, is that they are less immunogenic than their viral counterparts. With both forms of vectors, however, the target site in the body can be specified with the help of specific receptor molecules. Like this, researchers can guide and control the vector's integration and vaccine delivery within the body.

The Measles Vaccine

In 1954, just a year before the introduction of the inactivated polio vaccine, Thomas Peebles, MD, working in John Enders's lab at Boston Children's Hospital, succeeded in isolating the measles virus from the blood of 13-year-old David Edmonston (The College of Physicians of Philadelphia, n.d.). After isolating the virus, Enders's goal was to formulate a vaccine. It took until 1960 to prove that the isolated strain could be formulated into an effective attenuated measles vaccine; it just needed additional tweaking to attenuate it further (Hendriks & Blume, 2013). Wanting other researchers to also attempt to create a measles vaccine, Enders shared the Edmonston strain. Most researchers of that time were inspired by the recent success of the polio vaccine, and tried to mimic that development in their construction of a measles vaccine (Hendriks & Blume, 2013). In countries where Salk's

inactivated polio vaccine (IPV) took credit for controlling the disease, like in Sweden and Netherlands, researchers worked at creating an effective inactivated measles vaccine. In other countries, such as the U.S. and U.K., where Sabin's recently released oral polio vaccine (OPV) was used to combat polio, researchers preferred to attempt an attenuated version of the measles vaccine.

Regardless of the method chosen, subsequent patient trials proved the attenuated measles vaccine to be more effective than the inactive vaccine (Hendriks & Blume, 2013). Some studies created several groups, each receiving a different vaccine regimen. While one group received only inactivated doses, another group received some inactive doses followed by a live dose, while a third group received one dose of the attenuated vaccine. Though several studies tried this method, all pointed to the same results: the inactivated vaccine initiated a lesser immune response and it was not known how long those antibody titers would last. The attenuated vaccine however, generated a substantial response, making it the vaccine of choice for elimination of measles (Hendriks & Blume, 2013).

It was in 1963 that John Enders and his associates received FDA licensure for their live-attenuated measles vaccine and mass measles vaccination began (CDC, n.d.-b). However, the vaccine was not attenuated enough and thus required coadministration of gamma globulins to prevent children from developing fever and a rash following inoculation (Hendriks & Blume, 2013). Approximately five years later, in 1968, Maurice Hilleman, working at Merck labs, developed Moraten—more attenuated Enders—which eliminated the need to inject the vaccine along with gamma globulins (Hendriks & Blume, 2013). Since licensure, Moraten, a descendant of the original Edmonston strain, has been the only measles vaccine administered in the U.S. (The College of Physicians of Philadelphia, n.d.). Even today, when the monovalent vaccine is no longer on the market, the Edmonston strain is still used to create the measles component of the MMR vaccine routinely given to children (CDC, n.d.-c; The College of Physicians of Philadelphia, n.d.).

Potential COVID-19 Vaccines

The COVID-19 pandemic, rampant now in early 2020, and possibly beyond, has killed hundreds of thousands worldwide in a matter of months (World Health Organization [WHO], 2020a). As of June 1, 2020, the WHO reports that there have been 371,166 deaths globally. Researchers all over the world are racing to develop a vaccine to combat the virus and stop the ever-rising death toll.

Luckily, there is an extensive history of vaccine development, allowing researchers to base their COVID-19

Advancements in Vaccine Development: Measles vs. COVID-19

vaccine developments on the experiences and accumulated information from the past. More so, unlike the measles vaccine development, COVID-19 vaccine development has a related precedent. Coronaviruses SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), while claiming no marketed vaccine, have documented research and experimentation on vaccine development. Current researchers are using these semi-constructed vaccines and adapting them for further development towards the current strain of coronavirus, SARS-CoV-2. However, regardless of the starting inspiration, all potential COVID-19 vaccines will have to go through all phases of vaccine production before being offered on the market.

As of June 15, 2020, there are scores of COVID-19 vaccine candidates starting the preclinical stage or clinical studies phase of vaccine development. These attempts include vaccine designs containing mRNA, DNA plasmid, protein subunit, non-replicating viral vectors, or inactivated COVID-19 viral particles (WHO, 2020b). Just the breadth of these alone shows how many more resources and technologies are available now versus the 1960s, when the measles vaccine was in development.

The more recent vaccine technologies, namely nucleic acid vaccines, demonstrates how the updated and increased methods are truly playing a role in COVID-19 vaccine development. In this paper, I would like to highlight one specific mRNA candidate vaccine. (An LNP-encapsulated mRNA vaccine, co-developed by Moderna and the NIAID.) As an RNA virus with RNA-dependent RNA polymerase, SARS-CoV-2 replicates RNA from an RNA template as opposed to transcribing RNA from a DNA template (using DNA-dependent RNA polymerase). This can result in high levels of RNA present within the virus (Wang, et al., 2020). Thus, using RNA as a method of priming the body towards an RNA-rich pathogen makes sense in the overall picture of vaccine development (Wang, et al., 2020).

Also, when developing this RNA vaccine, researchers opted to use the spike protein as the vaccine's target sequence. Though there are other targetable proteins on SARS-CoV-2, such as the envelope, nucleocapsid, and membrane proteins, the spike (S) protein is the subunit of the virus that binds with the body's ACE2 (angiotensin converting enzyme 2) receptor, and therefore the S protein comes across as a more effective vaccine target (Wang, et al., 2020; Zhang, et al., 2020). Figure 1 shows the location of all four proteins on the virus as well as the binding of the spike protein to the ACE2 receptor.

After injection of the vaccine which contains the mRNA sequence for the S protein, a cell in the body should

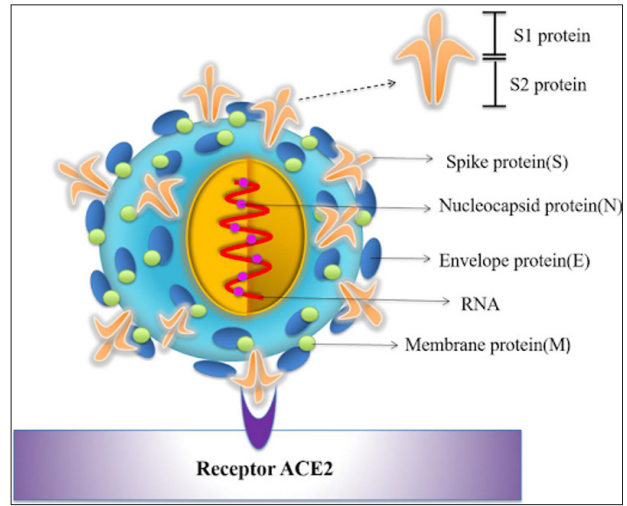


Figure 1 Proteins and Binding Site of SARS-CoV-2 Source: Zhang, et al, 2020

translate the genetic code into the functional S protein that can be secreted to allow the immune system to respond. Figure 2 depicts the process by which this COVID-19 mRNA vaccine ultimately yields memory cells in the body.

As of May 30, 2020, this candidate vaccine has advanced to phase 2 clinical trials (WHO, 2020b). Though mRNA vaccines have great theoretical potential, there are currently none on the market. However, this mRNA vaccine may successfully proceed through all phases of vaccine development, and should that happen, the Moderna/NIAID mRNA vaccine will be the first of its kind on the market

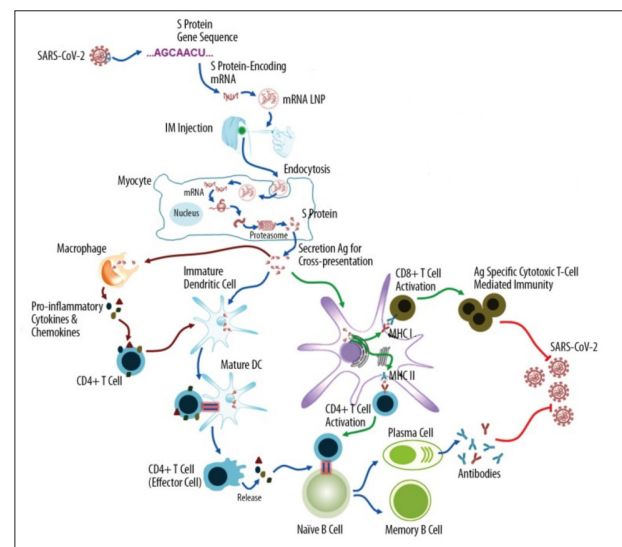


Figure 2 COVID-19 mRNA Vaccine Response

Conclusion

For the ongoing developments for a COVID-19 vaccine, it is unknown whether the vaccine's immunity will be life-long. Currently, it is unknown if natural immunity is long

lasting, though whatever that case is, I would hypothesize that the artificially induced immunity would follow suit. In my opinion, though vaccine type does play a role in duration of immunity (as illustrated in measles vaccine development), a larger portion depends upon the properties of the virus itself. Since that is yet to be determined, it is too soon to draw a conclusion with regards to any COVID-19 vaccine. Also, because all vaccines are at most in early phase II clinical trials, one cannot determine which candidate vaccine will be more effective than the others. Currently, the mRNA vaccine from Moderna is on a road to success, though results are still too incipient to make a final decision.

Finally, although the essence of a vaccine is unchanged—the goal to elicit an effective immune response still drives development—advancements in vaccines development as well as accumulation of scientific knowledge have broadened our minds when attempting to develop a new vaccine. We now have more options, some of them with more precise targeting than ever, and it is the hope that with our newfound tools, we can go on to create better vaccines and continue saving lives.

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