The Evolution of Vaccines in the face of evolving disease. Is the mRNA vaccine all that different?

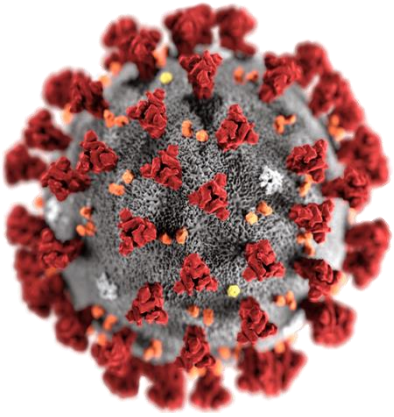
When the body is exposed to a germ, there is a portion of the germ that the body reacts to. This portion is called the antigen. Vaccinations work by pre-exposing the body either to a weakened germ or to the antigenic portion of that germ. This gives the body the opportunity to build antibodies and prepare the body to fight a future potential infection from that pathogen. For the sake of simplicity, the focus here will be on vaccines against viral infections specifically.

The first traditional vaccines have been the form of weakened (attenuated) viruses.
Think of these vaccines as a mosquito that is missing its wings and the straw-like tip of its mouth has been bent. It is still a mosquito to be sure. It could possibly still bite you, but it would be rather unlikely. Likewise, the body is still able to recognize the antigenic portion of the virus and mount a response, but the ability for the virus to infect has been diminished.

The first vaccines for polio, smallpox, and even influenza were all live, weakened viruses. The MMR is still a live, weakened (attenuated) vaccine. These vaccines are highly effective because they so closely mimic the actual disease. However, they have the potential of making some people feel ill as though they had the disease itself. Actually, this can be a great indicator that the vaccine was effective because the body is responding to the vaccine. They might also be talking about a reaction to the live, attenuated vaccines that were common years ago. However, it is rare that these vaccines actually cause infection in people.

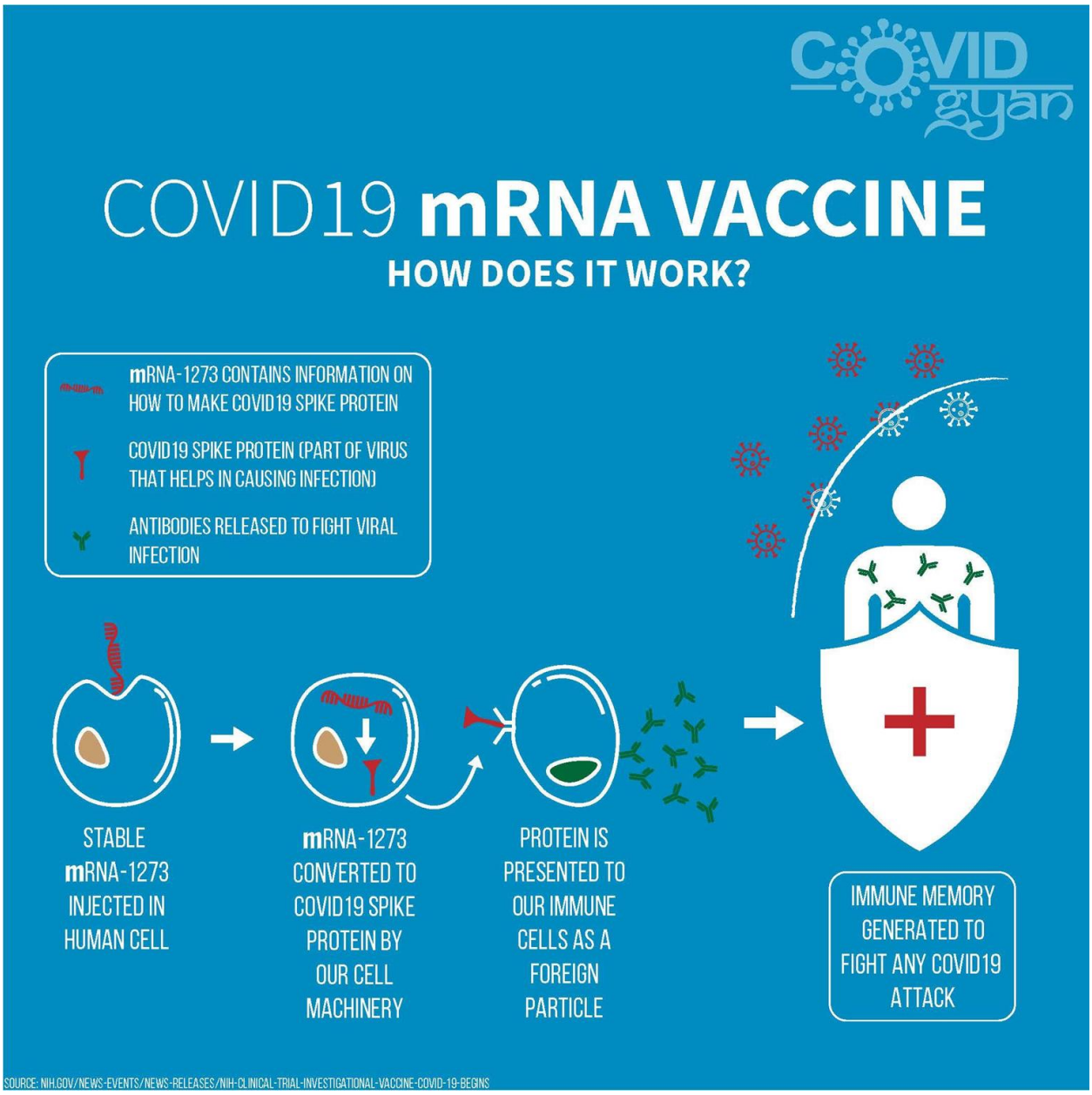
Subsequent vaccines that were developed were called “inactivated vaccines” and were made of a very specific portion of the viral protein. Think of these immunizations as a completely smashed, dead mosquito missing its wings, legs, and straw-like mouth. It is still a mosquito. However, it is impossible for that mosquito to bite you or to cause any infection in your body. The potential for the mosquito to come back to life is impossible. It has been completely disarmed. However, we still can recognize that it is a mosquito.
That is important because similarly even though we are only injecting a very small antigenic portion of the virus, the body still recognizes it as an invader and mounts an immune response to it. This is the most common form of immunizations we use today. Even though the body is only exposed to a very small portion of the virus, the body will immediately recognize the virus whenever re-exposure occurs. This type of immunization cannot cause infection because it is like a dead, smashed mosquito missing most of its parts. This has been the model for most of the vaccinations we give in the United States. The problem with these vaccines is the production process is lengthy. The first step in production is producing a hybrid of the virus. Then, enough virus has to be produced with the eggs of hens. Only then can the antigenic portions of the virus be removed and purified. If the strain of a virus mutates, it is near impossible to change the vaccination quickly to match that change.

A new era in vaccine development began when scientists discovered the possibilities of using messenger RNA (mRNA). mRNA is genetic material already found in the cells of the body. It is the instructions from DNA to determine what proteins need to be made within the cells. Basically, mRNA functions in the body to make **proteins**. The portion of the COVID-19 virus that the body mounts an immune response to is the spike **protein**.- the red projections surrounding the virus particle.



As mentioned before, the process to grow a virus and isolate only a specific antigen from it is lengthy.
In the most basic terms, mRNA molecules can be made in a lab and production can be scaled up rapidly. mRNA vaccination utilizes the body's own processes to make antigenic proteins that previously took us many months to manufacture. This bypasses the entire manufacturing process allowing mRNA vaccines to come to market faster. Because they are made in a lab as opposed to a cell, this allows more adaptability for viruses that mutate.

Please refer to the following diagram of how the COVID-19 mRNA virus works:



With regard to the COVID-19 mRNA vaccine, once the harmless spike protein is produced in the cell, the mRNA degrades. The spike protein is then expressed on the outside of the cell activating both humoral and cellular immune responses. This process closely mimics a natural infection which generally provides for a more effective vaccination. mRNA vaccines do NOT affect our

DNA. This mRNA never even enters the cell's nucleus where the DNA is housed. This vaccine cannot cause a COVID-19 infection in anyone.

This is one of the central advantages of mRNA vaccines. Also, the process does not require amplification through hen's eggs or other cells. In a nutshell, mRNA vaccines are faster and cheaper to produce than traditional vaccines.

That might lead people to question why mRNA has not been the basis for vaccinations all along. It was not until recently that science was able to figure out how to stabilize the mRNA molecule. Not only is it sensitive to temperature, but it degrades rapidly when injected into the body. Once it was discovered that mRNA was stable once packaged within a lipid bubble, the molecule was stable enough to move forward with vaccine trials. The trials of the mRNA vaccines have exceeded expectations so far with a 95% efficacy rate after two doses.

However, the storage requirements of mRNA vaccines can make it difficult for a successful vaccination program especially in rural communities. So far, the Pfizer vaccine requires sub-zero temperatures for storage, and the vaccine is only good for 5 days once placed in the refrigerator. The Moderna vaccine requires normal freezer temperatures for storage, but is stable for 30 days in the refrigerator. It is important to remember that both of the vaccines require a booster shot at 21-28 days, and you must be vaccinated with the same manufacturer as the first dose you were given.

The mRNA vaccines are not live virus vaccines, nor do they use an adjuvant to enhance vaccine efficacy. These vaccines do not enter the nucleus and do not alter human DNA in vaccine recipients. As a result, mRNA vaccines cannot cause any genetic changes.

These vaccines are being held to the same safety standards as all other vaccines. They only came to market sooner due to scientific developments, funding, and the ability to manufacture the vaccine while the trials were going on. Drug companies cannot afford to manufacture vaccines that will not make it to market, but the federal government subsidized the costs of manufacturing so there would be no loss to the drug companies.

Both vaccines were tested in diverse adult populations, including older adults and people of color. Over 73,000 people were tested in the Moderna and Pfizer trials combined.

The vaccine will only be approved for people 16 years and older in the United States.

So far, the most common side effect has been pain at the injection site. Systemic side effects have been seen less commonly and include fever, chills, headache, muscle aches and fatigue. This was seen more commonly after the second vaccine.

No significant safety concerns were identified in the clinical trials.

As of last week, the recommendation was for pregnant women (and those who will be pregnant in the next two months) not to get the vaccine. This is only because the trials did not include

pregnant women, so this guidance may change with time. *However, as of 12/13/2020, the American College of Gynecologists and Obstetricians (ACOG) recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups.* These groups include essential workers and healthcare personnel.

Additionally, anyone who has a history of anaphylaxis should not be given the vaccine at this time. It is rare, but normal for people to have anaphylactic reactions to vaccines. This is not new and at this time, it does not appear to be a higher incidence with this vaccine than with any others.

Anyone who has had a positive COVID test in the past 90 days should not receive early doses as they have immunity for at least 90 days. That allows more healthcare workers the opportunity to get vaccinated.

We expect the vaccines to arrive next week possibly.

So far, the data provided on both mRNA vaccines are over 90% effective in preventing infection with COVID infection.
It is 100% effective in preventing vaccinated people from getting severe disease.
Full protection is expected 7-14 days after the second dose.

Abbasi J. COVID-19 and mRNA Vaccines—First Large Test for a New Approach. *JAMA.* 2020;324(12):1125–1127. doi:10.1001/jama.2020.16866

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