# Chapter 1 The History of Vaccines and their impact on medicine.

## The History of the live virus vaccine

Vaccines are one of medicines greatest invention something that has revolutionized the way we treat infectious diseases. Like all great invention they had to start somewhere the history of vaccines begins in the late 1700's. Here we find Edward Jenner, a biologist working on his farm in the United Kingdom. During this time there was a smallpox outbreak that was ravaging the United Kingdom, but Jenner found that his milkmaids had immunity to smallpox. He concluded that this immunity came from them catching the mild cowpox disease, a disease that is very similar to smallpox. Because of this he began his experiments by inoculating people with mild cowpox hoping they would have the same immunity. His idea worked and the first vaccine was born. This vaccine remained the only one available for about 80 years. The second vaccine was developed by a Louis Pasteur as a way to combat rabies. He developed his vaccine by drying the spinal cord of infected rabbits as rabies effects their central nervous system. He would then feed them to another rabbit so they would get a portion of the disease and begin to develop immunity. Pasteur also took a risk and started testing on human subjects that were willing to be treated. Again, it paid off the procedure worked, and the second vaccination ever made was created. Pasteur went on to create more vaccination using this same method improving it as time went on. These early vaccines laid the ground work for the basic concept behind the vaccines that we have today. This research was valuable in giving scientists a head start when developing new technologies like the DNA vaccine.

## The history of DNA

DNA (deoxyribose nucleic acid) was first discovered all the way back in 1869 by Swiss chemist Friedrich Miescher. He was looking into white blood cells when he discovered something he called nuclein. After making this discovery Miescher then requested used bandages from the local surgeon so he could filter out the leukocytes, leukocytes are a very common type of white blood cell. After looking over these cells and finding the nuclein again he realized that he had discovered a new substance unlike any protein he had found before. This event marks the first discovery of DNA within a cell even though Miescher name was barely associated with the discovery. It was not until 100 years later that the next major advancement was made in the field of DNA research. It was the discovery of a structure, specifically the double helix that we all think of when we hear DNA. It was discovered in 1953 by the American biologist James Watson and English physicist Francis Crick. The discovery came to light after many failed attempts to create a three-stranded version of DNA. After some advice from a visiting chemist Jerry Donohue, he put the two nucleotide bases Adenine and thymine together. He soon realized he could do the same with the other two bases of Guanine and Cytosine. With these bases connected to each other they held the backbones of DNA making the double helix that we know today. This was a huge leap forward in the science of molecular biology. To this point we had been using live virus vaccines ever since their discovery in 1796 by Edward Jenner. Moving forward in the 1970's and 1980's this new discovery helped produce new technology such as genetic engineering and rapid gene sequencing. This time of advanced research eventually led to the questions of what this research could apply to and how it could help humanity. That question was answered in the 1990's when several groups worked to make a new type of technology. In 1992 multiple groups worked to create the first vaccine using DNA expressed proteins. After about 5 years of clinical trials these vaccines were finally decided to be safe for human use.

### Why is DNA different?

There are many differences between the live virus and DNA vaccines. the biggest of them being the raw material within the vaccine itself. As well as where the material goes once it is inside your body. As we saw earlier the live virus vaccines uses a very potent version of the disease to start with. While the difference with the DNA vaccine is in the fact that it needs a live unpowered version of the virus in order to work and create antibodies in your body. Because of the supporting proteins in the DNA vaccines it does not have to use the potent version of diseases to get results. But this means it needs a template to base its antibodies off of this is where the virus comes into play. That is just a main difference between the live virus version of the vaccine. The other reason and the main reason why DNA vaccines are being used is the transportation of the vaccine. When the vaccine is injected, it works its way through the bloodstream and into the cells. The previous version of the live vaccines were usually given by mouth as syringes were yet to be developed. While this method worked for the time it was not the most efficient method at distributing the vaccine. The DNA vaccine was also discovered to have its own major problem. These DNA vaccines have a chance to enter the nucleus of the cell and possibly interfere with the DNA already in the cell. While there have been very few cases of this happening. This was a risk that no scientist wanted to take. This is what opened the doors to look for an alternative that was safer and more effective than the DNA vaccine.

## What is mRNA?

mRNA (messenger RNA) is the RNA that tells the DNA in your body how to make specific proteins on the ribosome. These proteins then trigger a response from your immune system allowing your body to make antibodies. This process starts in the nucleus where the mRNA waits for the DNA to transcribe a copy of itself. It then takes that transcribed copy out of the nucleus into the cytoplasm. Here it is read by protein structures in order to produce amino acids from the corresponding codon base. These proteins structures exist in things known as ribosomes. The ribosome is the one and only place in the cell where these proteins are produced from mRNA. mRNA is a carrier of information it does not alter the information it carries in any way. Hence why it is called the messenger think of it almost like a mail man. It delivers packages from the place it was made, in this case the nucleus to the place where it is opened the protein structures. This is what allows our body to make different proteins that are essential to our bodies everyday systems. MRNA is a very important part of our bodies which is what lead researchers and scientists to study it. They hoped to find a way to expand its uses so that we could use it on a more efficient and larger scale. Eventually these scientists were able to find a way to use this newly discovered mRNA in order to help millions of people.

### The History of mRNA

The history of mRNA is one that goes way beyond vaccines. MRNA was first discovered in May of 1961 by Francois Jacob in the article titled Nature which earned him a noble prize. It struck his interest because of how the messenger carried the DNA and genes. At this time how the DNA was carried out was unknown. There were many theories on it, but none had solid evidence that could back them up. That was until an experiment that was carried out by Francois Gros where he used an RNA inhibitor to halt the production of proteins. This confirmed that

RNA played a role in the synthesis of proteins. Its use in medicine was not discovered until 1978 by Robert Malone. Malone discovered that human cells could absorb mRNA. He realized that RNA could be treated almost like a drug that can be molded to change its effects. At first it wasn't even considered for any medical purposes it was instead used for research. It wasn't until 1984 when a team of biologists were able to produce active mRNA in a lab. They did this by being able to both produce and prevent proteins from producing. This opened the door to many experiments involving animals. For example, it was used to treat the Flu and cancers in small animals like rats and rabbits. With this newfound knowledge this team took this to a company called Oilgogen. They worked with this company to find ways that RNA could be used to stop gene expression, the aim of doing this was to stop and treat different diseases but it was here that mRNA vaccines ran into issues the first being that RNA is very challenging to work with making production very difficult. The other issue being that in order to efficiently make these vaccines it was going to be very expensive. Researchers estimated it was going to be around 119 million dollars to begin work on a large scale. None of the larger vaccine companies were willing to invest this amount of money in a vaccine they were unsure about. Then finally in 2000 a researcher by the name of Ingmar Hoerr was able to get results after injecting mice. Shortly after these results were published belief in these new vaccines grew and money started trickling in. The larger vaccine companies were starting to believe that these mRNA vaccines could be the next advancement in vaccine technology. This is when clinical trials were able to be held as well as human experiments. The trials tested against some of the common diseases that DNA encoded for the like influenza and rabies. As well as some that DNA could not even start to process like Aids and the HIV virus. These trials were the first major step for the vaccines companies as they started developing trust in these scientist. It paid off as it lead to some of the medical marvels we have today like the covid 19 vaccine.

## Why are mRNA vaccines different?

mRNA vaccines differ greatly from the traditional DNA vaccines. They differ because they do not contain a live version of the virus. This is because mRNA uses proteins in order to teach cells how to react if they become infected. While DNA still contains a live weaker version of the virus so the cell can learn how to make antibodies. Another advantage of mRNA is the fact that it can not interfere with your genetics even if it tried too. This is because the mRNA vaccines will not enter the nucleus of a cell where the DNA is stored. Making this type of vaccine much safer because it does not enter the core of the cell. Another advantage of mRNA over the traditional DNA vaccine is the timeframe it takes to make one. Because mRNA does not require a live version of the virus and can be made in a lab. Its time frame to be made is much shorter than the traditional DNA vaccine meaning it can be distributed rapidly. This was a major reason why mRNA was so prevalent during the covid 19 outbreak because of the speed it was able to be distributed. Another major difference of the mRNA vaccine to the others is that it is programmable. This means that scientists can put what they want on the mRNA strand before they inject it. So, when it enters that body and begins to make proteins and antibodies it will make exactly what those scientists told it to make.

## Pre covid mRNA

mRNA really got its name out in public space during the span of the covid 19 virus. During this period, it was used to create the famous Pfizer and Moderna vaccines that helped slow the spread of covid 19. But where was this technology before the outbreak? It was still in

clinical trials as a solution for other unrelated diseases. Some of these notable diseases are HIV, rabies, and the influenza virus. None of these vaccines have been realized to the public yet as the covid vaccines took priority over it. Regardless of covid mRNA vaccines have been the forefront of mRNA research ever since they were discovered. Once we discovered we could have a vaccine without having to use possible dangerous live versions of disease. mRNA vaccines are still a very new science that need to be developed. These vaccines aim to have the amount of success of the mRNA vaccines during the covid outbreak. The other major goal of these vaccines is to eventually replace the widely used DNA vaccine. Because of the small safety issues that are present in these vaccines as well as the time period to produce them.

## Why mRNA vaccines are important.

mRNA vaccines are the forefront of medical vaccine research. The covid 19 epidemic really brought to light the power of the mRNA vaccine. Because both the Pfizer and Moderna vaccines are the first mRNA vaccines available to the public. While mRNA has been around for a long time the research of it in vaccines is fairly new. This means it can be further research to treat terminal diseases like different cancers or aids. The possibilities of mRNA are nearly endless whether it involves medicine or research. Because of how mRNA works it can be customized and changed in order to fight specific diseases. This means that it can be used to suppress or even cure diseases that humans have been battling for decades. The future of mRNA vaccines is a very bright one. It is highly under researched and not a lot of people know it exists as most people first encountered it during the covid pandemic. This is a whole new realm of medicine that has yet to be deeply researched, one that could hold answers to many medical problems. It will only improve as scientists get better at constructing mRNA to fight new and upcoming diseases. Leading the world into a safer future where some if not all deadly diseases can be a thing of the past. With more research and time it could be adapted to take on more than just viral diseases. It could be adapted and changed to cure different types of cancers or bloodborne diseases like AIDS or HIV. The only thing holding it back is the lack of awareness about it limiting those who want to study it. That is why the mRNA vaccine is so important because of its nearly limitless potential in all aspects of the medical field.

## Summary

Looking back at what we discussed earlier in the chapter we can see the importance of vaccines and how they have effected our society. We saw how vaccines first started all the way back in the 1700's with Edward Jenner and smallpox. How he laid the groundwork for the basic concept of a vaccine that will still use today. How this lead into the next major advancement in vaccine technology the DNA based vaccine. This new vaccine used a lesser version of the disease as well as some thing our body is familiar with, this allows our bodies to create antibodies to protect the cells. This vaccine was developed by a team of individuals in the early 1990's using the methods previously discovered by Jenner. Then the latest version of the vaccine was the developed the mRNA vaccine. This vaccine made itself know during the covid 19 pandemic where it was used to create the Pfizer and Moderna vaccines. mRNA has been around for much longer than the covid outbreak, it was just not very well known. Because before covid it was in clinical trials for other diseases, but those were out on hold because of the urgency covid had. When mRNA was discovered in 1961 it was not considered for medicine but instead for research. It wasn't until 1978 where it was applied to vaccines in the medical field. What made this vaccine stick out is that it no longer needs a piece of the virus to create antibodies.

This is because mRNA uses proteins to command the cell to make these antibodies to combat disease. With mRNA vaccines being fairly new and under researched this field has so much potential for the world of medicine. mRNA went from being unknown to one of the biggest medical advancements in the world.

**References**


1. Dolgin, Elie. “The Tangled History of Mrna Vaccines.” *Nature*, vol. 597, no. 7876, 2021, pp. 318–324., https://doi.org/10.1038/d41586-021-02483-w.
2. Melton, D. A. *et al. Nucleic Acids Res.* **12**, 7035–7056 (1984).
3. “What's Different about Messenger RNA (Mrna) Vaccines for COVID-19?” *Memorial Sloan Kettering Cancer Center*, https://www.mskcc.org/coronavirus/what-s-different-about-messenger-rna-vaccines-covid-19#:~:text=How%20do%20COVID%2D19%20messenger,response%20if%20someone%20gets%20infected.
4. “Moderna's Mrna Platform.” *Moderna*, https://www.modernatx.com/power-of-mrna/modernas-mrna-platform.
5. “How Do DNA Vaccines Work?” *Medical News Today*, MediLexicon International, https://www.medicalnewstoday.com/articles/dna-vs-mrna-vaccines-similarities-and-differences.
6. “The Discovery of The Double Helix, 1951-1953 | Francis Crick - Profiles in Science.” *U.S. National Library of Medicine*, National Institutes of Health, https://profiles.nlm.nih.gov/spotlight/sc/feature/doublehelix.
7. Fynan, Ellen F, et al. “One Group's Historical Reflections on DNA Vaccine Development.” *Human Gene Therapy*, U.S. National Library of Medicine, Sept. 2018, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6152846/.
8. Institut Pasteur. “Discovery of Messenger RNA in 1961.” *Institut Pasteur*, 23 Feb. 2021, https://www.pasteur.fr/en/home/research-journal/news/discovery-messenger-rna-1961.
9. Pray, L. (2008) Discovery of DNA structure and function: Watson and Crick. *Nature Education* 1(1):100