SARS-COV-2 RNA Vaccines: A New Technology Leading the Way In COVID-19 Immunity

William Bochuan Hu - G11 Student at the University of Toronto Schools , Sunlifegene Academic Program in Medical Science

Supervisor: Dr. Allina Wang (Sunlifegene Academic Program in Medical Science, Faculty of Medicine, University of Toronto)

Table of Contents:

Abstract:

The COVID-19 pandemic has struck nations across the world, infecting 82.6 million people worldwide, killing 1.8 million people as of December 31st, 2020 and impacting the daily lives of billions of people through public health measures and economic repercussions (1). The COVID-19 disease is caused by the SARS-COV-2 virus, an RNA virus that infects human cells, leading to fever, pneumonia, Acute Respiratory Distress Syndrome (ARDS) and potentially death for patients (2). Many quarantining, physical distancing and personal protection measures taken to combat the pandemic come at the cost of great disruption to economic and social activity. Therefore, developing and distributing a vaccine to counter SARS-COV-2, the virus that causes COVID-19, is instrumental in providing herd immunity to the world and allowing for a return to pre-pandemic life and business. RNA vaccines have emerged as some of the most promising candidates for providing large scale immunity to COVID-19 due to their efficacy, safety and ease of manufacture.

The goal of this paper is to present the scientific concepts behind SARS-COV-2 vaccine research in an understandable manner. To do this, the paper will first describe the **1)** biology of a virus, **2)** the vaccine testing phases, **3)** explain differences between the five major vaccine types, and finally **4)** discuss the structure, production, advantages, and disadvantages of an exciting new technology: RNA vaccines.

Keywords: RNA vaccines, SARS-COV-2 Vaccines, COVID-19, RNA virus

Introduction to the Virus:

SARS-CoV-2 is a coronavirus composed of 16 Non structure proteins and 4 structural proteins: the Envelope, Membrane, Nucleocapsid and Spike proteins and internal 29.9kbp mRNA genetic information.

The genome of SARS-COV-2 is divided into two sections: **1)** non-structural protein genes (which code for proteins involved in infiltrating and replicating the virus in host cells), and **2)** structural protein genes (which code for proteins that make up the capsid of the virus) (3).

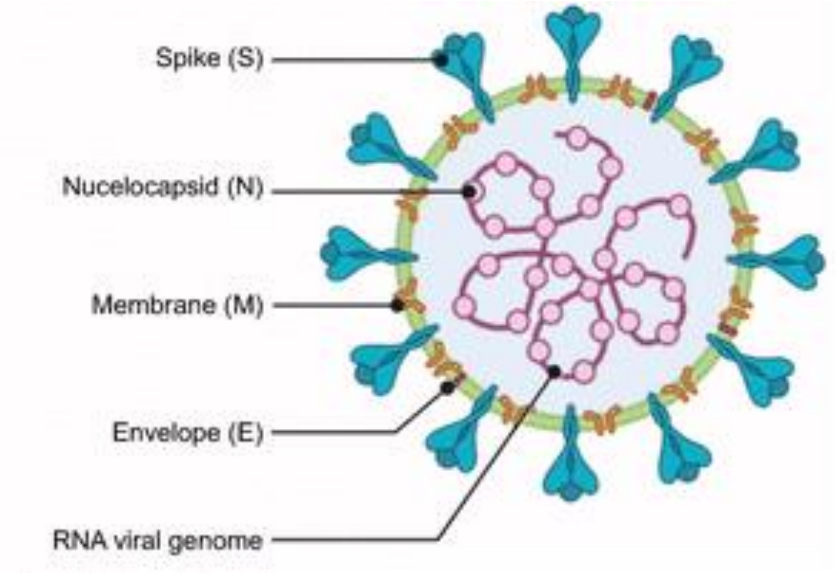

Figure 1: Diagram of the 4 Structural Protein Components of a SARS-COV-2 RNA Virus (4). The SARS-COV-2 virus is made up of four structural proteins that protect the RNA of the virus and allow it to enter host cells. In turn, the RNA itself is divided into sections coding for nonstructural and structural proteins that are translated by host cells' ribosomes into the specific proteins during reproduction.

The 16 nonstructural proteins perform functions critical to the virus' survival and replication in host cells by disguising viral RNA, cleaving necessary protein sections and replicating the genome itself. The 4 structural proteins perform functions to protect the viral RNA. Nucleocapsid (N) proteins are bound to the RNA and aid the viral replication cycle while membrane (M) proteins determine the shape of the viral envelope and stabilize the N-protein-

RNA complex. Envelope (E) proteins aid production and maturation of the virus and spike (S) proteins are transmembrane proteins attached to the outside of the membrane to aid in penetration of host cells (3).

Because SARS-COV-2 is a novel coronavirus, the human body has had no previous exposure to viruses of this exact type. As of now the majority of the world's population has not contracted COVID-19 and therefore does not have immunity to the disease. Under these conditions, it is imperative that a vaccine be developed in order to provide immunity to citizens to prevent the spread of COVID-19.

SARS-COV-2 Vaccine Candidates:

The SARS-COV-2 Spike Protein:

Most SARS-COV-2 vaccines in development induce immunogenicity (an immune response) to the Spike (S) Protein. Most vaccines currently in Phase 3 clinical trials or past approval work by inducing a human immune response to the S protein antigen. Normally, the S protein on the transmembrane surface of SARS-COV-2 membranes acts as an adhesin and interacts with ACE2 receptors in host cells to allow the virus to enter human cells. Early clinical studies found that the S protein antigen was highly immunogenic compared to M, E and N protein antigens. For this reason, many vaccines aim to deliver the S protein antigen (or mRNA coding for this antigen) into the human body, where it will induce an immune response and long-term immunity. If the patient is infected with SARS-COV-2, the elevated levels of leukocyte memory cells and antibodies specific to the S protein will help fight off the disease more effectively (5)

Current SARS-COV-2 Vaccine Development:

There are currently 78 vaccines in human clinical trials, with many more in preclinical development. Out of these, 7 vaccines (including 2 RNA vaccines) have gained limited or full approval and are the closest to mass distribution (see Table 1).

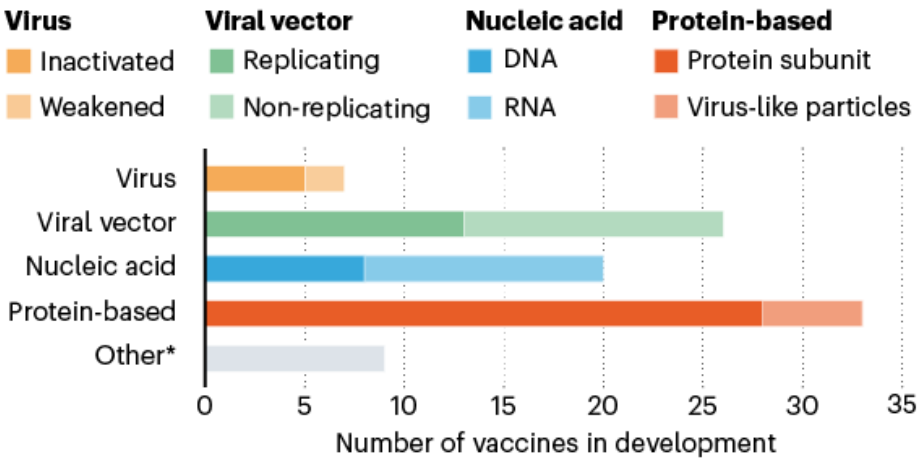

Figure 2: 16 SARS-COV-2 Vaccines in Development By Vaccine Type (6). Protein and inactivated (viral vector) vaccines predominate among vaccine currently being developed. The vaccines shown here include those in clinical trials (Phase 1, 2, 3) and preclinical development.

Five major vaccine types predominate among prototypes currently in testing. These are Genetic vaccines, Protein-based vaccines, viral vector vaccines, attenuated vaccines and Repurposed vaccines. Exploring the functions, relative advantages and disadvantages of each vaccine type is useful in understanding promising directions in future vaccine research.

Genetic Vaccines are vaccines made of nucleic acids (DNA or RNA) coding for a SARS-COV-2 antigen (usually the S protein) enclosed in a nanoparticle capsule. This type includes both DNA

and RNA vaccines. These vaccines have the advantages of being easier to manufacture than attenuated or viral vector vaccines (as they can be manufactured chemically and do not require growth of a live virus) and have less risk of inducing an overreaction in the immune system. However, they also have the disadvantages of lower immunogenicity (requiring multiple doses) and the possibility of causing mutations in human cell's DNA (DNA vaccines only).

Protein based vaccines deliver SARS-COV-2 proteins directly into the body to trigger an immune response. Many such vaccines store these proteins in nanoparticles. Protein-based vaccines are often simple to manufacture due to the small size of their peptides and established manufacturing methods already in use to create vaccines for other illnesses. However, the selection and modification of appropriate antigens that are both immunogenic and can bind with the CD4+ glycoproteins on T cells is often time-consuming and challenging (7).

Viral vector vaccines place genetic material coding for SARS-COV-2 antigens (again, usually the S protein) into non-SARS-COV-2 viruses. For example, many viral vector vaccines use Adenoviruses as capsids to contain SARS-COV-2 RNA. Viral vector vaccines are relatively complex to manufacture (due to the necessity of growing viruses on a substrate and the high chance of contamination) and can have reduced effectiveness if the recipient has already been exposed to the vaccine (8).

Attenuated vaccines inject SARS-COV-2 viruses grown in culture and attenuated (rendered unable to reproduce and cause disease) using chemicals and/or heat into the body. Because these vaccines are weakened versions of live viruses, they can often provide strong and long-lasting immunity with one dose (as compared with two doses for genetic vaccines). However, the

possibility of an overreacting immune response, especially in immunodeficient recipients, is a disadvantage that must be considered (7).

Repurposed vaccines are vaccines used to combat non-SARS-COV-2 viruses that have seen some success in inducing immunity to this coronavirus. These vaccines may be faster to deploy due to established processes for manufacturing and delivering them, but they may also induce lower immunogenicity to SARS-COV-2 compared to other vaccine types due to the fact that they were not explicitly designed to provide SARS-COV-2 immunity (8).

Vaccines, like most medications, are high-risk high-reward enterprises, with a possibility of success, but also potential adverse side effects on humans (or a specific category within the population, like the elderly or those with preexisting health conditions) that can end a vaccine research project. To be approved, vaccines must demonstrate two qualities: efficacy (the ability of the vaccine to induce a timely and sufficiently immunogenic response) and safety (the lack of extremely harmful side effects for all demographics within the population).

Clinical Trial Process:

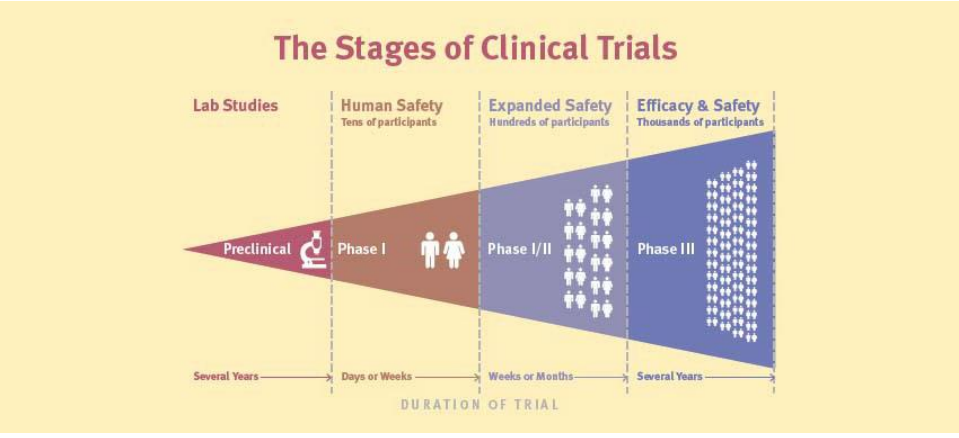

Figure 3: The Four Phases of Clinical Trials for SARS-COV-2 Vaccine Approval (9).

The goal of the four central phases is to ensure that the efficacy and safety of vaccines are above the FDA's requirements. In practice, researchers send reports of clinical trials along with details such as vaccine structure and biochemistry to the FDA, where they are assessed and given an approval, rejection, or conditional approval.

Because of these stringent requirements, vaccines must pass through several levels of trials. First, **Preclinical Trials** on animal subjects determine the basic efficacy of the vaccine, its immunogenic ability (ability to trigger immune response and antibody protection) and clear out any vaccines that demonstrate extreme safety risks. Next, vaccines enter **Phase 1** tests on small groups of humans to determine basic safety and narrow down the necessary dosage for efficacy. Then, vaccines start **Phase 2**, with larger groups including special demographics such as the children and elderly. These trials determine the exact needed dosage and any side effects that only occur with special demographic groups. Finally, vaccines go through **Phase 3**, placebo-controlled tests on large populations in order to determine any side effects that may have gone unnoticed in smaller trial tests. Only after these steps are vaccines approved by the FDA (or equivalent agencies) and mass-manufactured for public use.

The length of trials combined can span from 1.5-12 years, a fact that would make a SARS-COV-2 vaccine unavailable until the summer of 2021 using the traditional vaccine development timeline (11). However, regulatory agencies have responded to the urgent need for immunity by allowing adjacent phase trials to be run simultaneously (e.g. Phase 1/2 and Phase 2/3 trials)

through the Fast Track Program and in some cases even permitting manufacture and use of vaccines before Phase 3 trials have finished. For example, BioNTech/Pfizer's RNA vaccine is currently undergoing a Phase 2/3 trial through the Fast Track Program, but has also been approved for early use by several countries (12).

These reforms have allowed researchers with successful prototypes to push ahead and aim for vaccine deployment by the beginning of 2021. Table 1 (see Tables section) describes the 17 vaccines in Phase 3 or limited/full approval, and hence those most likely to provide large scale immunity to COVID-19, in more detail (12).

SARS-COV-2 RNA Vaccines - A Promising Vaccine Against COVID-19 Infection:

RNA vaccines stand out as one of the newest and most promising additions to the immunogenic arsenal to counter SARS-COV-2. The use of mRNA as a vaccine to create an immune response was first proposed in 1994 by Zhou & Berglund. Researchers throughout the 1990s and 2000s improved RNA vaccine technology, for example adding modified nucleosides to vaccines in order to introduce foreign genetic material into the body without being targeted by the immune system. Companies such as Moderna (founded 2010) and BioNTech (founded 2013) were later founded to capitalize on this technology by developing RNA vaccines to treat real-world diseases (13).

Early attempts to use RNA vaccines against cancer, cardiovascular and renal diseases reported serious side effects, but the efficacy and safety of top RNA vaccines for SARS-COV-2 has been

rapidly improving. Although RNA vaccines are still a relatively new and untested innovation, the urgency of the COVID-19 pandemic and the potential benefits in safety and fast, low-cost production has spurred rapid RNA vaccine innovation. On December 2nd 2020, BioNTech/Pfizer's vaccine BNT162b2 was accepted for limited approval in the UK, becoming the first mRNA vaccine ever to gain approval for medical use! Bahrain (Dec. 4, 2020), Canada (Dec. 9, 2020) and Saudi Arabia (Dec. 11th, 2020) have soon followed (14).

How RNA Vaccines Work:

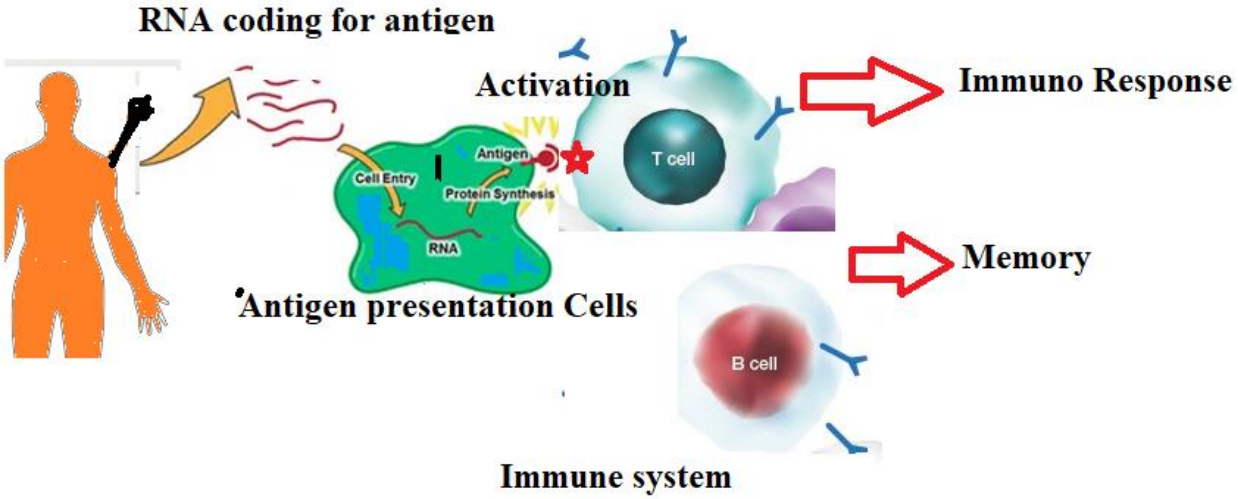

Figure 4: RNA Vaccine Translation, Antigen Presentation and Immunization Process (15).RNA vaccines work by introducing artificially produced SARS-COV-2 RNA into human antigen-presenting cells, where they are translated by cells' own ribosomes into proteins, which are presented to lymphocytes to induce an immune response.

RNA vaccines take advantage of body cells' own protein production systems to produce viral antigens in human cells themselves. An RNA vaccine contains 4 internal components. An mRNA strand coding for the SARS-COV-2 S protein (also known as the antigen) is capped on

either end by the 5' Untranslated Region (UTR), 5' cap, 3' UTR and a PolyA Tail for extra protection. All of these components are surrounded by a lipid nanoparticle capsule.

In the first step **(1)**, the lipid capsule, being made of the same structure as the cell membrane, binds with the membrane and releases the internal components into the cytoplasm. Then, **(2)** the cell's own ribosomes translate the mRNA into corresponding S proteins. Next, **(3)** the cell, an antigen presenting cell (APC), binds the SARS-COV-2 Spike protein, specifically the S protein's Receptor Binding Domain (RBD) with the Major Histocompatibility Complex (MHC). **(4)** The MHC presents the antigen on the extracellular side of the cell's membrane to inactive T cells. **(5)** The binding of T cells to the antigen creates antigen-specific CD4 T cells. These antigen-specific CD4 T cells act as a trigger to activate the primary immune response. **(6)** Activated CD4 T cells will further activate other immune cells that specialize to play various roles in the immune system: some disgorge neutralizing antibodies (effector B cell/plasma cells) and generate antigen-specific memory T cells and memory B cells. Once this process is complete, the body will have developed a robust, long-lasting immune response that can be reactivated when a real SARS-COV-2 virus arrives (16).

Advantages and Disadvantages of RNA Vaccines:

RNA vaccines have several advantages and disadvantages that regulators must weigh when deciding on approval.

The first advantage is high efficacy rates for the top RNA vaccine contenders (94.5%-95%). FDA vaccine approval generally requires a minimum efficacy of 50%, meaning that top RNA vaccine efficacy goes above and beyond this most important threshold.

Secondly, RNA vaccines are comparatively easy to manufacture. Since RNA and its lipid nanoparticle capsule are both essentially combinations of chemicals, they can be manufactured relatively easily in a lab (unlike, for example, attenuated vaccines which require time-consuming growth of virus samples in egg cultures). This reduces production cost and time and allows for faster vaccine production to counter new virus strains (14).

Thirdly, RNA vaccines are potentially safer for the body then the alternatives. Since only genetic material coding for a virus, and not an actual (attenuated) virus itself is being injected into the body, the risks of an overreacting immune response are relatively low. Furthermore, RNA generally will not integrate itself into the patient's genome the same way DNA from a DNA virus would, reducing risks of lysogenic aftereffects or mutations. This makes the vaccine safer for those taking it (14).

However, RNA vaccines do have some disadvantages. Firstly, there is the risk of vaccine degradation. Since RNA tends to be more volatile compared to DNA and especially compared to proteins, RNA vaccines may risk degradation in transport. Because of this, many RNA vaccines have to be shipped at low temperatures in order to preserve stability and effectiveness.

Secondly, the fact that RNA vaccines generate milder immunogenicity compared to alternatives, many RNA vaccines require 2 injections. This makes it harder to achieve herd immunity using these vaccines. For example Canada, which has ordered 6 million RNA vaccines for the first quarter of 2021, will only be able to vaccinate 3 million people as two doses are needed per person (17).

Despite these challenges, scientists are creating techniques to reduce degradation of RNA vaccines. These include changing structures in RNA to increase stability or combining RNA vaccines with RNA polymerase to amplify RNA copy numbers. These innovations have the potential to increase stability of vaccines so that they can be stored for up to 18 months without degradation.

How RNA Vaccines Are Produced:

There are three major components that are produced to make a functional vaccine. First is the In-Vitro Transcribed (IVT) RNA itself, coding for the SARS-COV-2 Spike protein RBD. Second is the modifications and additions to the RNA in order to increase protection and protein translation. Third is the lipid nanoparticle capsule that contains the RNA (16).

Figure 5: Example of A Laboratory RNA Solid State Synthesizer (18) Repeatable processes, such as RNA translation, with the same reactants used up to produce a specific quantity or products can be made using solid-state synthesizers.

The creation of an RNA vaccine begins with production of plasmid DNA. This DNA, created through genetic engineering of plasmids, contains a DNA-dependent RNA polymerase promoter and nucleotides complementary to the desired mRNA strand (19). IVT RNA is transcribed from DNA using a bacteriophage DNA-dependent RNA Polymerase (T3, T7 or Sp6 phage) that binds to the RNA Pol promoter and base pairs DNA nucleotides one by one. This forms a complementary RNA strand that base pairs with the original DNA. The entire process happens within a solid state synthesizer (16).

After the IVT RNA has been produced, several modifications are made to increase its protein production when in the body cells. Rare codons are replaced with synonymous codons and the G:C content of RNA is enriched. Finally, additional caps are added on either end of the RNA to protect the strand. The 5' cap can be added using a vaccinia virus capping enzyme or synthetic cap or anti-reverse cap analogues. A PolyA tail is added by encoding a DNA template or using PolyA Polymerase (20).

Finally, the surrounding lipid nanoparticle capsule is constructed. This process takes place inside of a solid state synthesizer. Lipids are molecules made of fatty acids and glycerol which naturally form into agglomerations. Lipid nanoparticles are placed into a solution of water and a water miscible organic solvent. The solvent is then removed, which forms stable and equally sized (70-100 nm) lipid nanoparticles. When the nanoparticle capsule finishes forming around the mRNA,

rinsing and purification occurs. The end product of these synthesizer reactions is an RNA vaccine (21).

Comparison of BioNTech/Pfizer and Moderna Vaccines:

The two main vaccines in Phase 3 or beyond are currently Pfizer/BioNTech and Moderna/NIH. Moderna has signed contracts with the US, the EU, Japan, Qatar, Canada while Pfizer has signed contracts with the US, Japan, the EU, the UK, Bahrain, Taiwan and Canada for vaccine orders. In Canada's case, Pfizer aims to deliver 6 million doses of BNT162b2 vaccine The similarities between the Modern and BioNTech/Pfizer vaccines are evident. Both use a lipid nanoparticle shell to encase a section of mRNA coding for the S-protein of the SARS-COV-2 virus. The efficacy rates for both vaccines are also similar: Moderna's vaccine has an efficacy rate of 94.5% while BioNTech/Pfizer's has an efficacy of 95%. Both of these rates are well above the 50-90% vaccine efficacy deemed necessary by experts to provide herd immunity to the virus (12).

However, there are small differences between the two vaccines that have large implications for their relative functionality. Moderna's vaccine is encased in a more resistant lipid nanoparticle layer, meaning it can be stored at temperatures of -20°C. On the other hand, BioNTech/Pfizer's vaccine has a different lipid nanoparticle structure, meaning it must be stored at temperatures of -94°C. This has important implications for the expenditure and ease of distribution of the vaccines, especially in regions of the world where refrigeration is hard to come by (12).

Conclusion:

RNA Vaccine technology has rapidly improved from its origins in the 1990s and now has the potential to replace traditional vaccine types as the go-to solution for viral epidemics. If RNA vaccines prove to be successful in providing COVID-19 immunity on a large scale, we may see increased interest and much wider use of these vaccines to counter the seasonal flu, cancer and other ailments. For Canada, the outlook regarding vaccine orders is bright: Canada has secured the largest number of vaccines per capita out of any country in the world (21). What remains to be seen is the performance of BioNTech/Pfizer and Moderna's vaccines in comparison to each other and in comparison to traditional vaccine types. The following months will be of critical importance to the future of RNA vaccines, and the field of vaccinology as a whole. If RNA vaccine companies successfully overcome production and distribution challenges, they may play a central role in saving millions of lives easing acceptance of this technology into the industry.

Acknowledgements:

I would like to express my great appreciation to Dr. Allina Wang for her suggestions and critiques of my work. I am extremely grateful for her willingness to help at all stages of the writing process for this paper.

References:

1. Mega, Emiliano Rodríguez. COVID Has Killed More than One Million People. How Many More Will Die? *Nature News*. (2020). www.nature.com/articles/d41586-020-02762-y.

2. Coronavirus disease 19 (COVID-19): Symptoms and treatment. 2020. *Government of Canada*; [updated 2020 Nov 20; accessed 2020 Dec 13]. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/symptoms.html
3. Astuti, I., Ysafril. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. *Elsevier Public Health Emergency Collection*. (2020). doi:10.1016/j.dsx.2020.04.020
4. [Diagram of the 4 Structural Protein Components of a SARS-COV-2 RNA Virus]. (2020, May 12). Retrieved December 31, 2020, from https://www.future-science.com/cms/10.4155/tde-2020-0035/asset/images/medium/figure1.gif
5. Ong, E., Wong, M. U., Huffman, A., & He, Y. . COVID-19 coronavirus vaccine design using reverse vaccinology and machine learning. *Frontiers in Immunology*. (2020). doi:10.3389/fimmu.2020.01581
6. [16 SARS-COV-2 Vaccines in Development By Vaccine Type], (2020, April 28). Retrieved December 31, 2020, from https://www.nature.com/articles/d41586-020-01221-y
7. Keshavarz-Fathi, M., & Rezaei, N. (2019). Peptide and Protein Vaccines for Cancer. *Science*. Retrieved December 31, 2020 from https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/protein-based-vaccine
8. What are viral vector-based vaccines and how could they be used against COVID-19? (n.d.). Retrieved December 31, 2020, from https://www.gavi.org/vaccineswork/what-are-viral-vector-based-vaccines-and-how-could-they-be-used-against-covid-19

9. [The Four Phases of Clinical Trials for SARS-COV-2 Vaccine Approval], (2015, July). Retrieved December 31, 2020, from https://aanassets.azureedge.net/uploadedfiles/7a006233130349b394ae0754665f31f9/23433ae2ddde432ea16e7d183e8612a3.jpg
10. Mullard, A. How COVID vaccines are being divvied up around the world. *Nature*. (2020). https://www.nature.com/articles/d41586-020-03370-6
11. How long do clinical trials take? n.d. . *Clinical Trials And Me*; [accessed 2020 Dec 7]. https://www.clinicaltrialsandme.com/resources/how-long-do-clinical-trials-take.html#:~:text=period%20of%20time.-,How%20Long%20Does%20a%20Phase%203%20Clinical%20Trial%20Take%3F,the%20 drugs%20longer%2Dterm%20effects
12. Zimmer, C., Corum, J., & Wee, S. . Coronavirus Vaccine Tracker. *New York Times*. (2020). https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html
13. Verbeke, R., Lentacker, I., De Smedt, S., & Dewitte, H. Three decades of messenger RNA vaccine development. *Nano Today*. (2019). doi:https://doi.org/10.1016/j.nantod.2019.100766
14. Alexis H. RNA vaccines: A novel technology to prevent and treat disease. *Harvard University: Science in the News*. (2015). http://sitn.hms.harvard.edu/flash/2015/rna-vaccines-a-novel-technology-to-prevent-and-treat-disease/

15. [RNA Vaccine Translation, Antigen Presentation and Immunization Process], (2015, May 5). Retrieved December 31, 2020, from https://i1.wp.com/sitn.hms.harvard.edu/wp-content/uploads/2015/05/Fig-1-REAL.png?resize=550%2C220
16. In Vitro Transcription. n.d. . *Promega*; [accessed Dec 10 2020]. https://www.promega.ca/products/rna-analysis/in-vitro-transcription/
17. Canada expects six million COVID-19 vaccine doses early in 2021. 2020. *National Post*; [updated 2020 Nov 23; accessed 2020 Dec 13] https://nationalpost.com/pmn/news-pmn/disaster-pmn/canada-expects-six-million-covid-19-vaccine-doses-early-in-2021
18. [Example of A Laboratory RNA Solid State Synthesizer], (2020). Retrieved December 31, 2020, from https://cdn.shopify.com/s/files/1/0399/0473/products/12.Right_1024x1024.jpg?v=1404742262
19. Jackson, N. A., Kester, K. E., Casimiro, D., Gurunathan, S., & DeRosa, F. The promise of mRNA Vaccines: A biotech and industrial perspective. *Nature*. (2020). doi:https://doi.org/10.1038/s41541-020-0159-8
20. Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. . MRNA vaccines - a new era in vaccinology. *Nature Reviews*. (2018). doi:https://doi.org/10.1038/nrd.2017.243
21. Mukherjee, S., Ray, S., & Thakur, R. S.. Solid Lipid Nanoparticles: A Modern Formulation Approach In Drug Delivery System. *Indian Journal of PharmaceuticalSciences*. (2009). doi:10.4103/0250-474X.57282

Tables:

Table 1: SARS-COV-2 Vaccines Currently in Phase 3 Clinical Trials, Limited or Full Approval. This table provides the current phase of development or approval, organization and a brief description of SARS-COV-2 vaccines, divided into five vaccine types (Genetic, Viral Vector, Protein-Based, Attenuated and Repurposed) as of December 13th, 2020.

Vaccine Name	Stage	Organization	Details
Section 1: Genetic Vaccines			
mRNA-1273	Phase 3	Moderna, National Institute of Health	Delivers RNA coding for S protein into the human body via a lipid nanoparticle vector.
BNT162b2	Phase 2/3, Approval (Canada, Bahrain, Saudi Arabia), Emergency Approval (UK, US, UAE, Kuwait, Mexico)	Pfizer, BioNTech	Delivers RNA coding for S protein into the human body via a lipid nanoparticle vector.
AG0302-	Phase 2/3	AnGes, Takara Bio, Osaka	Delivers DNA coding for S

COVID19		University	protein into the human body via a skin injection.
Section 2: Viral Vector Vaccines			
Ad5	Phase 3, Limited Approval (China, Military Use)	CanSino Biologics, Academy of Military Medical Science	Delivers S protein using replication defective adenovirus(Ad5) vector.
Sputnik V	Phase 3, Conditional Approval (Russia)	Gamaleya Research Institute	Delivers S protein using two adenovirus (Ad5 and Ad26) vectors.
Ad26	Phase 3	Johnson & Johnson, Beth Israel Deaconess Medical Center	Delivers S protein using adenovirus (Ad26) vector. This vector has been used in the past for Ebola vaccines.
ChAdOx1	Phase 3	AstraZeneca, University of Oxford	Delivers S protein using chimpanzee adenovirus (ChAdOx1).
Section 3: Protein-Based Vaccines			
NVX-CoV2373	Phase 3	Novavax	Introduces purified SARS-COV-2 protein antigen using liposomes.

EpiVacCorona	Phase 1/2, Conditional Approval (Russia)	The Vector Institute	Introduces SARS-COV-2 protein peptides into the body.
CoVLP	Phase 2/3	Medicago, GSK	Introduces SARS-COV-2 proteins grown in plant cells into the body, along with immunity boosting adjuvants.
ZF2001	Phase 3	Anui Zhifei Longcom, Chinese Academy of Medical Sciences	Introduces SARS-COV-2 S protein Receptor Binding Domain proteins along with adjuvants into the body.
Section 4: Attenuated Viral Vaccines:			
Unnamed Inactivated vaccine	Phase 3, Limited Approval (UAE, China)	Sinopharm, Wuhan Institute of Biological Products	Injects culture-grown SARS-COV-2 heat-inactivated viruses with low reproductive capacity.
BBIBP-CorV	Phase 3, Limited Approval (China), Approval (UAE)	Sinopharm, Beijing Institute of Biological Products	Injects culture-grown SARS-COV-2 heat-inactivated viruses with low reproductive capacity.
Corona Vac	Phase 3, Limited Approval	Sinopharm	Injects SARS-COV-2 plaque-

	(China)		purified, chemically (beta-propiolactone)- inactivated viruses.
Unnamed Inactivated vaccine	Phase 3	Institute of Medical Biology (Chinese Academy of Medical Sciences)	Introduces inactivated SARS-COV-2 vaccine.
Covaxin/BBV152	Phase 3	Bharat Biotech, Indian Council of Medical Research, National Institute of Virology	Introduces inactivated SARS-COV-2 virus into human body.
Section 5: Repurposed Vaccines:			
Bacillus Calmette-Guerin	Phase 3	Murdoch Children's Institute	Delivers live, attenuated strain of the bacteria *Mycobacterium bovis*. Previously used to treat tuberculosis.