A Theoretical and Statistical Comparison of Major COVID-19 Vaccines

Krishna Iyer

Redmond High School, USA

ABSTRACT

The Coronavirus (COVID-19) is the first major virus to spread across the world and cause a catastrophe in decades. Vaccines are a tried and tested method of preventing the spread of viruses and have hence been used to halt the outbreak. On the surface, many of the vaccines are indistinguishable, prompting the following question: What are the differences between COVID-19 vaccines, and how well can they protect and individual? The objective of this research paper is to reveal the differences between types of COVID-19 vaccines and the processes they use to function. A comparison of each vaccine's advantages/disadvantages along with an analysis of their efficacies and safety will be used to determine the protective power of each vaccine. This paper will go over four different types of platforms available: mRNA, Recombinant protein, Inactivated Whole Virus and Viral Vector vaccines along with 5 different vaccines: BNT162b2, mRNA-1273, NVX-2373, BBV-152, AD.26.CoV2.S.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causal agent of COVID-19, began spreading throughout China in late 2019, immediately making international headlines. COVID-19 patients suffered from a wide variety of symptoms, the worst of which affected lung function. Researchers from hundreds of organizations and companies across the globe began the race to complete an effective vaccine. Speed was of the utmost importance, as the pandemic posed significant health and socio-economic challenges worldwide. Various COVID-19 vaccines have been developed utilizing different platforms, each incorporating a unique combination of ingredients. The vaccines were crucial in the prevention of the virus and protection of those who are in high-risk situations. After only slightly longer than a year after the virus emerged, there were 184 vaccine candidates in pre-clinical testing. *(Nagy et al. 2021)*

Background on COVID-19

The COVID-19 pandemic was caused by a virus known as SARS-CoV-2. SARS-CoV-2 is part of the Coronaviridae family, which is known for its crown-like appearance, coming from the protruding glycoproteins. Due to its taxonomy, SARS-CoV-2 is comparable to SARS-CoV and MERS-CoV. The virus was first discovered when groups of Chinese patients arrived at hospitals with pneumonia, from a seemingly unknown cause. As weeks passed, an increasing number of patients sought treatment for their SARS-like symptoms, including fever, cough, and chest discomfort, and in severe cases dyspnea and bilateral lung infiltration. Many of these cases were epidemiologically linked to a seafood market located in Wuhan, Hubei Province, China. By using four samples of bronchoalveolar lavage fluid from patients, groups of scientists were able to reveal an unknown type of betacoronavirus. *(Hu et al. 2020)*

Countless hours were put into developing the wide variety of COVID-19 vaccines available today. The moment the SARS-CoV-2 genome was sequenced, pharmaceutical companies and researchers began their studies and

research. To ensure safety and effectiveness, countless tests were done on all vaccines. Evaluation begins with pre-clinical studies, which are tests done in laboratories or with small animals, designed to study the processes involved with the vaccine. After preclinical trials prove successful, researchers administer the dose to an increasingly greater number of volunteers in multiple phases. The goal of these tests is to investigate dosage amounts, immune response elicitation and efficacy. If the vaccine passes all testing and is deemed safe and effective by governments, it can be approved for emergency use authorization or full authorization.

The four types of vaccine platforms that are to be discussed in the paper are mRNA, Recombinant protein, Inactivated Whole Virus and Viral Vector vaccines. A list of each specific vaccine to be discussed is detailed below:

Table 1. COVID-19 Vaccines with their respective platforms

mRNA	Recombinant Protein	Inactivated Whole Virus	Viral Vector
BNT162b2: Created by Pfizer/Biontech	NVX-CoV2372: Created by Novavax	BBV-152: Created by Bharat Biotech	Ad26.COV2.S:Created by Johnson & Johnson
mRNA-1273: Created by Moderna			

mRNA-Based Vaccines

Both the BNT162b2 and mRNA-1273 vaccines use lipid nanoparticles along with mRNA. The BNT162b2 vaccine is a joint effort by German pharmaceuticals company BioNTech and Pfizer. American pharmaceutical company Moderna created the mRNA-1273 vaccine. The two vaccines contain the SARS-CoV-2 spike protein information encoded in the mRNA to promote its early recognition. *(Fernández et al. 2020)*

Messenger RNA (mRNA) is an agent used to prevent and treat various diseases. LNP-mRNAs are particles where lipid nanoparticles are used as a protective shell for the mRNA, preventing it from degrading while traveling through the body.

While the exact location of the mRNA in the LNP-mRNA structure is not precisely known, the most commonly accepted model is the core-shell model. In this proposed figure, mRNA is usually located closer to the core of the structure, while the siRNA is located towards the outside. There is also evidence stating that mRNA forms “blebs,” for which the exact composition is up to debate. The nanoparticles have an amorphous, isotropic core containing water pores surrounded by inverted cationic lipids. *(Schoenmaker et al. 2021)*

Two main challenges exist when attempting to insert external mRNA into a cell: mRNA is broken down rapidly by ribonucleases and intracellular RNA sensors are able to detect the internalization of the mRNA inside the cell, activating host defense receptors and in turn, antiviral responses from neighboring cells. Additionally, the mRNA needs to consistently reach the target tissue and escape endosomes when reaching the cytoplasm. The core-shell model mentioned above keeps the mRNA free from harm from the body and allows delivery to the target. *(Schoenmaker et al. 2021)*

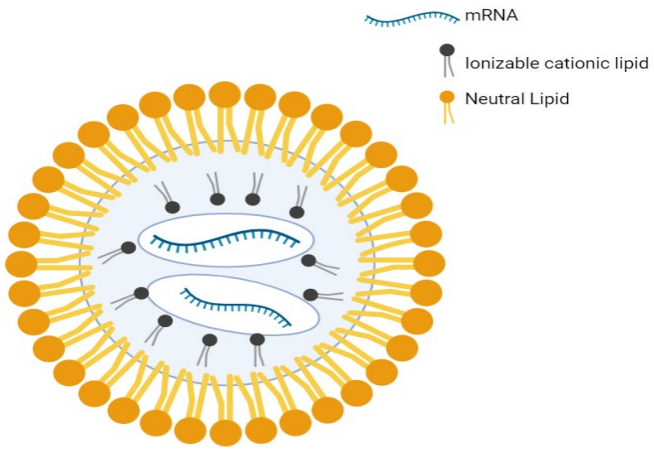

Figure 1. Proposed lipid-nanoparticle structure

The concept of using mRNA for vaccines has been drawing more attention in recent years. mRNA vaccines involve delivering nucleic acid to a cell in the human body. The molecule contains the instructions for creating a needed antigen, allowing the cell to produce these antigens, should it encounter the target virus. The body then has a significant advantage against said virus, potentially saving the infected individual. Like most vaccines available, mRNA vaccines are injected intramuscularly, intracutaneously, or subcutaneously. After entering the body, the particles travel to either non-immune cells at the injection site, immune cells at the injection site or immune cells in the peripheral lymphoid organs. mRNA's negative charge and low structural stability require the use of lipid-nanoparticles. LNP-mRNA particles enter the cell using endocytosis, creating an endosome. The newly created endosome is then directed towards a lysosome for degradation. Again, lipid nanoparticles play a role in protecting the mRNA from the acidic conditions inside an endosome. The mRNA inside the lipid nanoparticle is then taken in by ribosomes and translated into protein. These proteins cannot directly strengthen the immune system in this current state, so they are degraded by the proteasome into peptides and are presented as antigens on the surface of the cell where they can be utilized by T cells. Alternatively, the proteins can be sent to the exterior of the cell, where antigen-presenting cells can consume them and turn them into peptides, which present themselves on the surface of the cell. It is important to note that the complete set of processes that occur inside and between cells are fully clear to scientists and some of these mechanisms are only proposed. *(Ilyichev et al. 2020)*

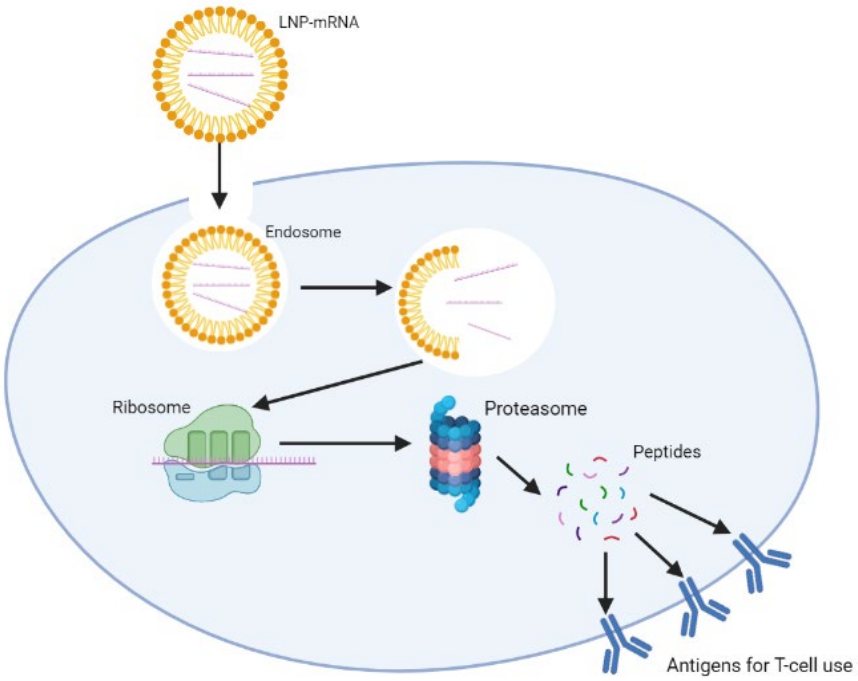

Figure 2. SARS-CoV-2 Antigen production processes

Recombinant Protein Vaccines

Recombinant nanoparticles mimic the spike proteins that exist on the surface of SARS-CoV-2 viruses. This helps the body recognize the molecule beforehand. Because of the lack of replication and infectious components, they are considered a less harmful platform than the use of live viruses. Recombinant nanoparticles are also adaptable, allowing for a faster new vaccine should a variant of the original strain emerge. *(Pollet et al. 2021)*

The spike protein for the SARS-CoV-2 consists of two parts: The S1 and S2, which both are responsible for binding with the angiotensin-converting enzyme 2 [ACE-2]. Through access to the ACE-2, the virus can insert its genetic information into the cell, harming, and eventually killing it. The S-protein involves 3 S1 heads sitting upon 3 S2 heads. The S1 subunit is responsible for binding to the host cell, docking onto the receptors using the receptor-binding motif which is contained in its receptor-binding domain. The S2 subunit connects the S1 subunit to the main part of the virus. When binding to a cell, the S-protein uses only one of its 3 heads, while the rest are folded, hiding from the immune system. Soon after binding to the host cell, the virus takes advantage of the TM protease serine 2 located on the cell's surface to allow access inside the cell and eventually exploitation of the cellular reproduction process. *(Huang et al. 2020)*

The vaccines involving recombinant proteins contain a variation of the SARS-CoV-2 spike protein. Specifically, the particle that Novavax utilizes is known as the NVX-CoV2372 trimeric nanoparticle. The nanoparticle contains 3 mutations from the original spike protein, to increase protease resistance and to increase the stability of the antigen. One of the most important factors of a vaccine is its cost. In order to minimize the cost of producing the proteins, Novavax uses insect cells, specifically from moths. The insect cells come at an advantage because they are well-folded, soluble, and often contain the desired post-translational modifications (PTMs). Novavax delivers their recombinant proteins via the Baculovirus Expression Vector System (BEVS) promoting high manufacturing speed, speed, safety and scalability. Their patented Matrix-M adjuvant encourages antigen-presenting cells to enter the site of injection, eliciting a greater immune response. *(Pollet et al. 2021)*

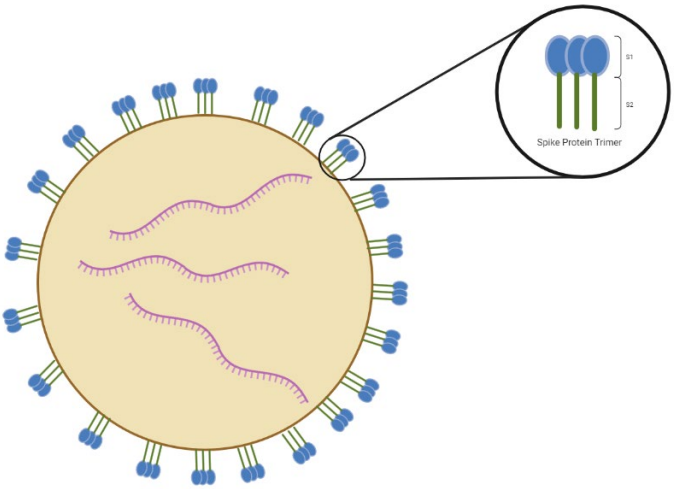

Figure 3. Structure of a SARS-CoV-2 S-protein

Inactivated Whole Virus Vaccines

Inactivated whole virus vaccines have been used for decades, having a lot of effort done for its research. Countless tests have proved its safety and reliability. Due to the use of whole viruses, vaccine users display symptoms of the virus, although not to the same extent. Inactivated whole viruses work by introducing the body to an inactivated version of the target virus, allowing the body time to learn and build immunity, so if the cells were to encounter said virus, they would have a significantly higher chance of killing it. The viruses are killed using different methods including, but not limited to: Temperature, Formaldehyde (CH_2O), Gamma Rays, or pH. These inactivated cells along with other chemicals are then injected intramuscularly where the body can react with them. *(Khoshnood et al. 2022)* Normally, when an individual contracts COVID-19, the virus starts by entering the body and replicating by exploiting intracellular processes. Antigen presenting cells then ingest the virus and Th cells recognize the antigens, calling other nearby immune cells. B cells produce the antibodies needed to harm and kill the virus, while T cells use their cytotoxicity to tear apart the virus' structure. After the virus has been eliminated from the body, small amounts of B cells and T cells remain. These cells are used for immunological memory and can aid the body in the future. *(Khoshnood et al. 2022)*

When BBV-152 is injected into a human body, the cells will instead encounter a destroyed version of the original virus. The organic compound β-propiolactone is used to inactivate the strain. High dosages of the virus and naturally occurring adjuvants are needed to stimulate an immune response. BBV-152, uses the Algel-IMDG adjuvant that induces a Th-1 and Th-2 immune response. *(Hotez et al. 2021)* When observed under a transmission electron microscope, the inactivated virus appeared very similar to the original; a relieving find due to the destructive properties of β-propiolactone. *(Ahmed et al. 2022)*

Viral Vector Vaccines

Although viral vector vaccines have been used since the 1970s, they have seen more attention in recent years, with an increased interest in genetically engineered vaccines. These clever vaccines use the invasive properties of other viruses to deliver genes encoding antigen creation processes to cells. These viruses are known as 'viral vectors.' Scientists and specialists use different kinds of viral vectors based on many factors, such as protein expression capabilities and

cell entry kinetics. Some commonly used viral vectors include the adenovirus, measles, and influenza virus. *(Deng et al. 2022)*

Scientists begin by stripping down most of the virus's harmful genes and leaving behind only its infectious capabilities. The new modified virus can only enter cells and deliver the genes and cannot destroy cells or replicate. They then enter the cell much like any other virus and are able to deliver the genes to the DNA polymerase, resulting in antigen creation. *(Deng et al. 2022)*

The Johnson & Johnson vaccine (Ad26.COV2.S) encodes and transports the SARS-CoV-2 spike protein information using the human adenovirus type 26 vector (Ad-26). This well-studied virus is known for causing the common cold. Ad26 is a double-stranded non-enveloped DNA virus known for having low seroprevalence rates, making it a useful asset for gene delivery. Pre-clinical trials involving hamsters and rhesus macaques have shown highly effective SARS-CoV-2 protection and later trials have shown that only a single dose is enough to eliminate the most severe or deadly symptoms. It is important to note that Ad26.COV2.S faced a restriction period on May 6, 2022 after 6 individuals developed severe blood clots and saw thrombosis with thrombocytopenia syndrome a few days after receiving the vaccine. *(Deng et al. 2022)*

A Theoretical Comparison of Vaccine Platforms

When determining the theoretical best vaccine for COVID-19 protection, multiple factors in favor and against must be assessed. For comparing the vaccines highlighted in this paper from a purely theoretical standpoint, only the biological processes and production ability will be considered.

The greatest advantage to mRNA-based vaccines is their inherent safety when compared to more traditional inactivated or live-attenuated vaccines. Normal virus-based vaccines have an infectious aspect, which at times can be harmful to cells. mRNA vaccines deal with the transportation of usable instructions only, so they have low reactogenicity. Unlike viral vector vaccines, mRNA vaccines can be used multiple times, because of the lack of vector resistance. When transporting vaccines, acceptable storage temperatures are one of the most difficult challenges to overcome. mRNA vaccines need to be kept at extremely low temperatures to maintain stability. BNT162b2 needs to be kept at -90 to -60 degrees Celsius and mRNA-1273 needs to maintain a temperature from -50 to -5 degrees Celsius. Many places, especially remote or underdeveloped regions, do not have the resources required for extended vaccine storage. *(Fang et al. 2022)*

Similar to mRNA-based vaccines, recombinant protein vaccines do not contain live or infectious components that could cause damage. Since the particles interact minimally with immune defenses, NVX-CoV2373 causes few symptoms. The body's immune reactions after vaccination have been shown to be strong and safe because of the Matrix-M adjuvant. Unlike mRNA-based vaccines, recombinant protein vaccines like NVX-CoV2373 are quite easy to store and transport, making them a promising option for developing countries. New production processes also make recombinant protein vaccines relatively cheap to produce. NVX-CoV2373 uses Sf9 cells from moths and the insect baculovirus to create mass amounts of the recombinant antigen protein. However, recombinant proteins are a relatively new technology. Because of this, funding has been focused towards DNA, mRNA and vector vaccines, making recombinant protein is a less popular option. Many are confident that it will eventually become better known, and that the public's hesitancy will diminish as time goes on. *(Hotez et al. 2020)*

Inactivated whole virus vaccines were some of the first vaccines ever formulated, having more than 50 years of research done in its name. They are well trusted by both the public and vaccine specialists. The vast amount of information regarding inactivated whole virus vaccines allows a high development speed for new similar vaccines. The vaccine's structure permits transportation at around 2-8 degrees Celsius, making it a more viable option when infrastructure does not support most other vaccines. Infamously, inactivated whole virus vaccines produce a large and unpleasant immune reaction. The body's response to the inactivated SARS-CoV-2 virus particles is similar to the reaction when encountering live SARS-CoV-2, discouraging vaccine users from further vaccination. When SARS-

CoV-2 is inactivated, often the virus's structure is damaged resulting in damaged epitopes and surface antigens, leading to a weaker immune response. *(Khoshnood et al. 2022)*

Viral vector vaccines demonstrate high adaptability for variants of viruses like the Delta and Omicron variant of SARS-CoV-2 as well as optimization capability. Genetic engineering allows scientists to quickly modify existing viral vectors for additional purposes. They can also be stored at 2-8 degrees Celsius for around 6 months, increasing the accessibility of the vaccine. The elimination of virulence genes from the vector results in a safe immune reaction. The main flaw with the viral vector vaccine design is the body's eventual resistance to the vector. Repeated use of the same viral vector for multiple different vaccines can prevent it from entering cells by prematurely destroying the vector. Vaccine users may also have pre-existing immunity to vectors like the adenovirus used in Ad26.COV2.S, preventing the dosages from being effective. *(Travieso et al. 2022)*

A Statistical Comparison of COVID-19 Vaccines

To compare the vaccines, two measures are used: Efficacy and Safety. Efficacy refers to how well a vaccine can provide expected results in ideal conditions. A vaccine with high safety will have minimal adverse impacts, but avoiding light, common effects is a demanding request. Vaccine producers have a greater focus on reducing severe effects of vaccines, so this paper will only highlight the probabilities for serious adverse effects that hold the possibility of serious damage.

Search Methods: To find the information listed below, studies found on the National Library of Medicine, The Lancet, and an FDA meeting briefing document were utilized.

Study Information: All of the studies listed below were done with a vaccinated group and a placebo group. The vaccinated group would receive the necessary number of doses of the vaccine, while the placebo group would receive look-alike injections which lacked active ingredients. Both groups of participants report their reaction and whether or not they contracted a virus. This type of study allows scientists to monitor the effect their vaccine has on small populations, a crucial step for its eventual approval. The efficacy is given as the percentage decrease in the probability of the two events listed in the table occurring, and the numbers in parentheses represent the confidence interval. The percentage given for severe adverse effects shows the percentage of vaccine recipients in the study who showed severe symptoms after receiving the fulfilling number of doses. These symptoms may or may not be directly linked to the vaccine.

Table 2. Efficacy of COVID-19 vaccines based on randomized controlled trials prior to the Omicron variant emergence (95% confidence interval)

Vaccine	Efficacy for Symptomatic COVID-19 Prevention	Efficacy for Severe COVID-19 Prevention	Author(s)
BNT162b2	96.2% (93.3, 98.1)	96.7% (80.3, 99.9)	*Thomas et al. 2021*
mRNA-1273	94.1% (89.3, 96.8)	100% (No Confidence Interval estimated)	*Baden et al. 2021*
NVX-CoV2373	89.7% (80.2, 94.6)	100% (No Confidence Interval estimated)	*Heath et al. 2021*
BBV-152	77.8% (65.2, 86.4)	93.4% (57.1, 99.8)	*Ella et al 2021*

AD26.COV2.S	66.9% (59.1, 73.4)	76.7% (54.6, 89.1)	*Jassen Biotech 2021*

Table 3. Serious Adverse effects stemming from vaccine usage with percentage of trial participants in the vaccinated group showing the effects

Vaccine	Possible Severe Adverse Effects	Percentage of participants with one or more Severe Adverse Effect	Author(s)
BNT162b2	Severe persistent lymphadenopathy and very rare Bell's palsy. Allergic reactions	1.2%	*Thomas et al. 2021*
mRNA-1273	Thrombotic events, Lymphadenopathy	0.6-0.7%	*Baden et al. 2021*
NVX-CoV2373	Myocarditis	1.0%	*Heath et al. 2021*
BBV-152	Lymphadenopathy, thrombocytopenic purpura, Autoimmune glomerular disorders	0.3%	*Ella et al 2021*
AD26.COV2.S	Thrombosis with thrombocytopenia syndrome,	0.4%	*Jassen Biotech 2021*

The information shown in the studies demonstrates the following: The vaccines ranked in order of highest efficacy for symptomatic COVID-19 Prevention are BNT162b2, mRNA-1273, NVX-CoV2372, BBV-152 and AD26.COV2.S. Their rankings in terms of severe COVID-19 prevention are mRNA-1273/NVX-CoV-2372, BNT-162b2, BBV-152 and AD26.COV2.S. Clinical trials for Moderna's and Novavax's vaccine saw that 0 participants in the vaccinated group had severe COVID-19 symptoms, an extremely positive outcome. AD26.COV2.S performed poorly in clinical trials with a severe COVID-19 prevention efficacy lower than that of standard efficacy of symptomatic COVID-19 prevention. The mRNA vaccines highlighted in this paper show remarkable efficacy, making them a strong choice. It is important to remember that for each vaccine, efficacy varies across many different demographics including race, gender and most importantly, age. The statistics mentioned in Table 2 may not be precise to a specific background, rather a representation of the general population.

All the vaccines listed showed low chances of severe adverse effects. Often, vaccine hesitancy stems from fear of harmful side effects, a justified cause for concern. The clinical trials showed that many of the serious adverse effects were caused by pre-existing conditions such as allergies. The rankings in terms of percentage of the vaccine group with serious adverse events are as follows: BBV-152, AD26.COV2.S, mRNA-1273, NVX-1273 and BNT162b2. Although the inactivated whole SARS-CoV-2 viruses in BBV-152 would make one assume that it results in more side effects, it proved its safety among the vaccinated group.

Conclusion

For around 50 years, vaccines have proved to be the most effective tool for stopping the spread of deadly viruses. Recently they have been utilized to combat COVID-19, a disease caused by the SARS-CoV-2 virus. Many different vaccines have been formulated and distributed to billions, halting the spread of the virus. All vaccines have major and minor differences, which can be confusing.

mRNA vaccines use lipid nanoparticles to deliver information to cells on antigen creation processes. Recombinant protein vaccines introduce cells to a modified SARS-CoV-2 spike protein. Inactivated whole virus vaccines encourage a cellular response with a destroyed version of SARS-CoV-2. Viral Vectors use another crippled virus as a path into cells to transmit genetic information. All types of vaccines have their own advantages and disadvantages making them more suitable for different needs. BNT162b2 showed the highest efficacy for preventing symptomatic COVID-19 (96.2% (93.3, 98.1)), mRNA-1273 and NVX-2372 had the greatest efficacy for preventing severe COVID-19 (100%). Finally, the lowest risk of potential severe adverse reactions to a vaccine was displayed by BBV-152 (Covaxin), having only 0.3% of the vaccinated group showing serious symptoms. mRNA-1273 claimed the best overall safety and efficacy ranking.

As of publishing this paper, vaccines are still the most effective measure for preventing the spread of COVID-19. Hopefully COVID-19 will be completely eradicated, similar to smallpox and rinderpest. Variants of the original virus strain are still emerging, prompting more research into vaccine efficacy in new conditions.

Limitations

This analysis was not without limitations and imperfections. When coming to a conclusion based only on theoretical comparisons, subjectivity may come into play. An individual may value the benefits of one vaccine over the benefits of another differently than someone else. While some studies such as that of BNT162b2 cover many different demographics, others may have tested a less diverse set of people, such as BBV-152's study only being conducted in Indian hospitals. Also, the trials only calculated the efficacy, not the real-world effectiveness, resulting in a likely disparity between the two. Although some variants of the original strain of virus may not change the efficacy of a certain vaccine a drastic amount, others may be particularly difficult to receive

Acknowledgments

I would like to thank Dr. Rajagopal Appavu, Ph.D and Jothsna Kethar for their advice.

References

Hu, B., Guo, H., Zhou, P., & Shi, Z.-L. (2020). Characteristics of SARS-CoV-2 and COVID-19. Nature Reviews Microbiology, 19(19), 1–14. https://doi.org/10.1038/s41579-020-00459-7

Nagy, A., & Alhatlani, B. (2021). An overview of current COVID-19 vaccine platforms. Computational and Structural Biotechnology Journal, 19, 2508–2517. https://doi.org/10.1016/j.csbj.2021.04.061

Calvo Fernández, E., & Zhu, L. Y. (2021). Racing to immunity: Journey to a COVID-19 vaccine and lessons for the future. British journal of clinical pharmacology, 87(9), 3408–3424. https://doi.org/10.1111/bcp.14686

Schoenmaker, L., Witzigmann, D., Kulkarni, J. A., Verbeke, R., Kersten, G., Jiskoot, W., & Crommelin, D. J. A. (2021). mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability. International journal of pharmaceutics, 601, 120586. https://doi.org/10.1016/j.ijpharm.2021.120586

Ilyichev, A. A., Orlova, L. A., Sharabrin, S. V., & Karpenko, L. I. (2020). mRNA technology as one of the promising platforms for the SARS-CoV-2 vaccine development. Vavilovskii zhurnal genetiki i selektsii, 24(7), 802–807. https://doi.org/10.18699/VJ20.676

Fang, E., Liu, X., Li, M., Zhang, Z., Song, L., Zhu, B., Wu, X., Liu, J., Zhao, D., & Li, Y. (2022). Advances in COVID-19 mRNA vaccine development. Signal transduction and targeted therapy, 7(1), 94. https://doi.org/10.1038/s41392-022-00950-y

Pollet, J., Chen, W. H., & Strych, U. (2021). Recombinant protein vaccines, a proven approach against coronavirus pandemics. Advanced drug delivery reviews, 170, 71–82. https://doi.org/10.1016/j.addr.2021.01.001

Hotez, P. J., & Bottazzi, M. E. (2020). Developing a low-cost and accessible COVID-19 vaccine for global health. PLoS neglected tropical diseases, 14(7), e0008548. https://doi.org/10.1371/journal.pntd.0008548

Huang, Y., Yang, C., Xu, X. F., Xu, W., & Liu, S. W. (2020). Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta pharmacologica Sinica, 41(9), 1141–1149. https://doi.org/10.1038/s41401-020-0485-4

Hotez, Peter J., and Maria Elena Bottazzi. “Whole Inactivated Virus and Protein-Based COVID-19 Vaccines.” Annual Review of Medicine, vol. 73, no. 1, 12 Oct. 2021, https://doi.org/10.1146/annurev-med-042420-113212.

Khoshnood, S., Arshadi, M., Akrami, S., Koupaei, M., Ghahramanpour, H., Shariati, A., Sadeghifard, N., & Heidary, M. (2022). An overview on inactivated and live-attenuated SARS-CoV-2 vaccines. Journal of Clinical Laboratory Analysis. https://doi.org/10.1002/jcla.24418

Deng, S., Liang, H., Chen, P., Li, Y., Li, Z., Fan, S., Wu, K., Li, X., Chen, W., Qin, Y., Yi, L., & Chen, J. (2022). Viral Vector Vaccine Development and Application during the COVID-19 Pandemic. Microorganisms, 10(7), 1450. https://doi.org/10.3390/microorganisms10071450

Fiolet, T., Kherabi, Y., MacDonald, C. J., Ghosn, J., & Peiffer-Smadja, N. (2022). Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 28(2), 202–221. https://doi.org/10.1016/j.cmi.2021.10.005

Thomas, S. J., Moreira, E. D., Jr, Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Pérez Marc, G., Polack, F. P., Zerbini, C., Bailey, R., Swanson, K. A., Xu, X., Roychoudhury, S., Koury, K., Bouguermouh, S., Kalina, W. V., Cooper, D., Frenck, R. W., Jr, Hammitt, L. L., … C4591001 Clinical Trial Group (2021). Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. The New England journal of medicine, 385(19), 1761–1773. https://doi.org/10.1056/NEJMoa2110345

Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Rouphael, N., Creech, C. B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., … COVE Study Group (2021). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. The New England journal of medicine, 384(5), 403–416. https://doi.org/10.1056/NEJMoa2035389

Heath, P. T., Galiza, E. P., Baxter, D. N., Boffito, M., Browne, D., Burns, F., Chadwick, D. R., Clark, R., Cosgrove, C., Galloway, J., Goodman, A. L., Heer, A., Higham, A., Iyengar, S., Jamal, A., Jeanes, C., Kalra, P. A., Kyriakidou, C., McAuley, D. F., Meyrick, A., … 2019nCoV-302 Study Group (2021). Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. The New England journal of medicine, 385(13), 1172–1183. https://doi.org/10.1056/NEJMoa2107659

Ella, R., Reddy, S., Blackwelder, W., Potdar, V., Yadav, P., Sarangi, V., Aileni, V. K., Kanungo, S., Rai, S.,

Reddy, P., Verma, S., Singh, C., Redkar, S., Mohapatra, S., Pandey, A., Ranganadin, P., Gumashta, R.,

Multani, M., Mohammad, S., & Bhatt, P. (2021). Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. The Lancet, 398(10317), 2173–2184. https://doi.org/10.1016/S0140-6736(21)02000-6

Vaccines and Related Biological Products Advisory Committee Meeting 2021. https://www.fda.gov/media/146217/download
King, A. (2020, September 17). *Protein-based Covid-19 vaccines could overshadow rivals*. Chemistry World https://www.chemistryworld.com/news/protein-based-covid-19-vaccines-could-overshadow-rivals/4012450.article

Travieso, T., Li, J., Mahesh, S., Mello, J. D. F. R. E., & Blasi, M. (2022). The use of viral vectors in vaccine development. Npj Vaccines, 7(1), 1–10. https://doi.org/1az0.1038/s41541-022-00503-y

Ahmed, T. I., Rishi, S., Irshad, S., Aggarwal, J., Happa, K., & Mansoor, S. (2022). Inactivated vaccine Covaxin/BBV152: A systematic review. Frontiers in immunology, 13, 863162. https://doi.org/10.3389/fimmu.2022.863162