RNA, Viral Vector, and Inactivated Virus are the most effective COVID 19 vaccine types in progressing through clinical-stage development.

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Abstract

The creation and efficient approval of medical solutions is imperative to address the growing health, socio-political and economic detriments of the Coronavirus Disease 2019 (COVID-19) pandemic. Vaccines prove to be the most effective and proactive method in reducing the likelihood of populations contracting, spreading and becoming ill with the virus.[1] Vaccine groupings have varying functionalities, and as a result, typically will have varying speeds of development. The objective of this investigation was to determine which vaccine type passes through clinical-stage development most efficiently. We compared 7 different vaccine categories and categorized their developmental capacity based on aggregate stage of development. Furthermore, reasoning for varying speeds of progression for vaccine typings was explored based on developmental characteristics of vaccine types and existing established technologies for the vaccine. The Milken institute was used to collect vaccine type and stage of development for over 200 COVID-19 vaccines. This investigation determined that inactivated virus vaccines had the highest aggregate stage of development. Furthermore, RNA and Non Replicating Viral Vector vaccines were the only vaccine groupings that progressed to stage IV development.

Introduction

The rise of the COVID-19 caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS - COV - 2) following an outbreak in Wuhan, China resulted in one of the most challenging historical global pandemics. Over 120 million people have been infected with the virus since the beginning of the

[1] Greenwood, B. (2014, May 12). The contribution of vaccination to global health: Past, present and future. Retrieved March 25, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4024226/

pandemic.[2] A viable and effective vaccine is crucial in reducing the virus's high mortality rate and lessening the detriments the pandemic has caused to nations worldwide. Thus, a comprehensive analysis of various treatment types is needed to better understand which treatments are the most beneficial to research and should be invested in. Identifying the treatments that develop faster through clinical stages may indicate which treatments have the highest efficacy and can help predict which treatments should be employed first. In this investigation, by focusing on proactive measures, we gathered a group of prevalent COVID-19 vaccine variants and categorized them into 7 groupings: DNA - based vaccines, Inactivated Virus, Non-Replicating Viral Vector, Protein Subunit, Replicating Viral Vector, RNA - based vaccine, and Virus-like Particles.

Different vaccine types function in different manners. For example, subunit vaccines carry specific purified viral antigens that effectively stimulate the immune system in conjunction with vaccine adjuvants to prolong a pathogen-specific immune response.[3] In comparison, whole-pathogen or inactivated vaccines contain pathogenic bodies that have been grown and cultured but are neutralized before injection.[4] As a result of their varying properties, different vaccine types progress through developmental stages at varying levels of efficacy. Comparatively, despite having well established technology, the approval of a subunit vaccine is wholly contingent on when the best antigen combination for the vaccine can be determined. This makes it considerably more taxing to develop a subunit vaccine in comparison to inactivated or live-attenuated vaccines.[5] On the other hand, despite being a vaccine type that has only recently been available for widespread public use, mRNA vaccines have risen to the forefront of COVID-19 treatment during the pandemic because they do not require large production developments to

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[2]Elflein, J. (2021, March 22). COVID-19 cases, recoveries, and deaths by country. Retrieved March 25, 2021, from https://www.statista.com/statistics/1105235/coronavirus-2019ncov-cases-recoveries-deaths-most-affected-countries-worldwide/

[3] Vaccine types. (n.d.). Retrieved March 30, 2021, from https://www.niaid.nih.gov/research/vaccine-types

[4]Sanders, B., Koldijk, M., & Schuitemaker, H. (2014, November 28). Inactivated viral vaccines (1270613603 938515045 B. Nunnally, 1270613604 938515045 V. Turula, & 1270613605 938515045 R. Sitrin, Eds.). Retrieved March 25, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189890/

[5]What are protein Subunit vaccines and How could they be used against COVID-19? (n.d.). Retrieved March 25, 2021, from https://www.gavi.org/vaccineswork/what-are-protein-subunit-vaccines-and-how-could-they-be-used-against-covid-19

mass produce the vaccine.[6] Furthermore, the vaccine type can be easily developed, as creating synthetic mRNA is relatively straightforward once the virus's genetic sequence is determined.[7] This investigation determined which vaccine type is the most efficient in passing through clinical-stage development.

Methods

The stage of development was analyzed through 7 selected vaccine variants. These variants included the following: DNA-based vaccines, Inactivated Virus Vaccines, Non-Replicating Viral Vector, Protein Subunit vaccines, Replicating Viral Vector vaccines, RNA-based vaccines, and Virus-like Particle vaccines. Live Attenuated, unindicated, and Replicating Bacterial Vectors were not explored in this investigation, as the sampling body for these categories was comparatively far lower than the other vaccine groups discussed in this study. First, data regarding the developmental stage of each vaccine group was collected from the Milken Institute, a non-profit and non-partisan organization that hosts one of the largest COVID-19 Treatment and Vaccine Tracking databases globally.[8] The developmental stage of each vaccine variant was then sorted into different developmental stages: Pre-clinical, Clinical, stage I, stage I/II, stage II, stage III, and stage IV.

Each stage was correlated to a specific numerical value, which was used to sort vaccine treatments for statistical analysis. Vaccines in preclinical stages were given a value of 0, stage 1 vaccines were correlated to a value of 1, stage 2 was correlated to a value of 2, etc. The highest value, 4, was applied to treatments that have already received official authorization for public use. Decimal values were given to vaccine treatments that were between developmental stages. For example, if a treatment was between clinical stage I and II, then it would be given a value of 1.5. Once the developmental stage of all vaccine types was collected and sorted, the mean stage of development as well as the standard deviation and

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[6]Anne Trafton | MIT News Office. (n.d.). Explained: Why RNA vaccines FOR Covid-19 raced to the front of the pack. Retrieved March 25, 2021, from https://news.mit.edu/2020/rna-vaccines-explained-covid-19-1211

[7] Ibid

[8]Milken Institute. (n.d.). Retrieved March 25, 2021, from https://airtable.com/shrSAi6t5WFwqo3GM/tblEzPQS5fnc0FHYR/viweyymxOAtNvo7yH?blocks=hide

variance for each variant was calculated as shown in Figure 1b. Histograms of the developmental stage across vaccines were created for each vaccine type. Additionally, a one-way ANOVA test was used to determine if the mean stage of development was significantly different across different variants. In this investigation, a tukey test cannot compare the different means due to the nature of our data. Therefore, manual analysis of descriptive statistics is required to identify specific vaccine types that are most effective at passing through the clinical stages of development. Bar plots were made to visualize the number of individual vaccine treatments that had reached a specific developmental stage for each vaccine type. A Shapiro-Wilk test was used to test the data for normality. In the analysis, the two leading vaccine types were then compared using a chi-squared test to determine statistical difference. Figure 1 was used to generate the bar graphs to generate the statistical tests used in this investigation and to visualize different types of vaccine treatments and their progression through the clinical stages of development.

Figure 1: Code used to generate bar graphs to generate the statistical tests

```
rna_vaccine_data_factor$Stage.of.Development <- as.integer(rna_vaccine_data_factor$Stage.of.Development)
viralvector_vaccine_data_factor$Stage.of.Development <- as.integer(viralvector_vaccine_data_factor$Stage.of.Development)
protein_vaccine_data_factor$Stage.of.Development <- as.integer(protein_vaccine_data_factor$Stage.of.Development)
particle_vaccine_data_factor$Stage.of.Development <- as.integer(particle_vaccine_data_factor$Stage.of.Development)
replicating_vaccine_data_factor$Stage.of.Development <- as.integer(replicating_vaccine_data_factor$Stage.of.Development)


summary(vaccine_data_factor)
summary(dna_vaccine_data_factor)
summary(inactived_vaccine_data_factor)
summary(rna_vaccine_data_factor)
summary(viralvector_vaccine_data_factor)
summary(protein_vaccine_data_factor)
summary(particle_vaccine_data_factor)
summary(replicating_vaccine_data_factor)

ggplot(dna_vaccine_data_factor, aes(x = as.factor(Stage.of.Development))) +
  geom_bar()

ggplot(inactived_vaccine_data_factor, aes(x = as.factor(Stage.of.Development))) +
  geom_bar()

ggplot(rna_vaccine_data_factor, aes(x = as.factor(Stage.of.Development))) +
  geom_bar()

ggplot(viralvector_vaccine_data_factor, aes(x = as.factor(Stage.of.Development))) +
  geom_bar()

ggplot(protein_vaccine_data_factor, aes(x = as.factor(Stage.of.Development))) +
  geom_bar()

ggplot(particle_vaccine_data_factor, aes(x = as.factor(Stage.of.Development))) +
  geom_bar()

ggplot(replicating_vaccine_data_factor, aes(x = as.factor(Stage.of.Development))) +
  geom_bar()
```

Results

Table 1. Summary of the Descriptive Statistics such as Mean and Median of the Stage of Development per each Vaccine Type

	Mean	Median	Maximum Stage of Development	Standard Deviation
DNA Based	0.5238	0.0000	3.0000	0.9988088
Inactivated Virus	1.263	1.000	3.0000	1.367437
Non Replicating Viral Vector	0.6667	0.0000	4.0000	1.221103
Protein Subunit	0.3639	0.0000	3.0000	0.7849073
Replicating Viral Vector	0.3478	0.0000	2.0000	0.6388292
RNA based	0.4688	0.0000	4.0000	1.128802
Virus Like Particle	0.1818	0.0000	2.0000	0.6681531

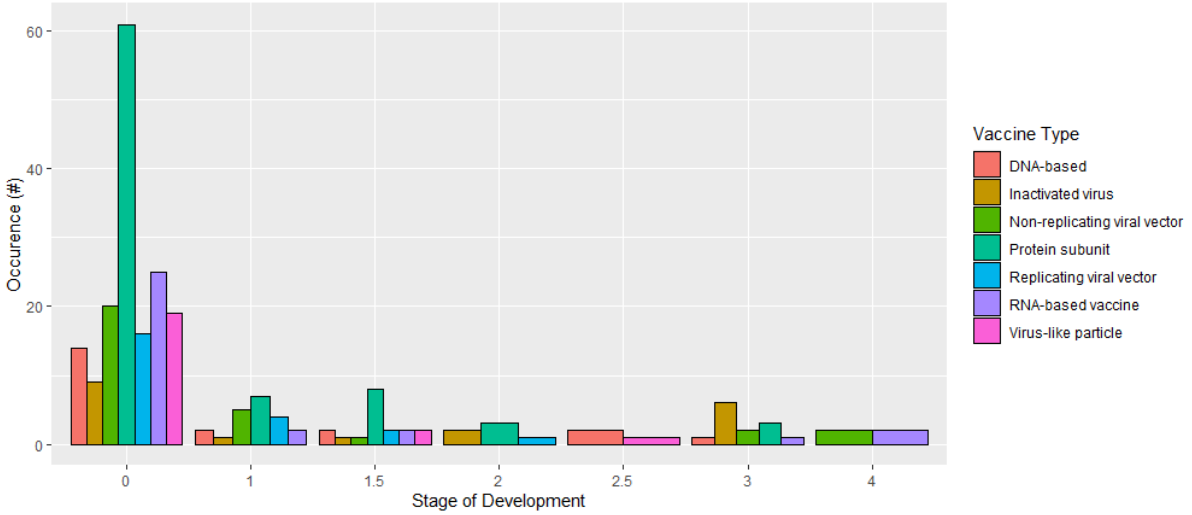


Figure 2a. (Above): Number of Vaccines in Each Stage of Development Per Vaccine Type

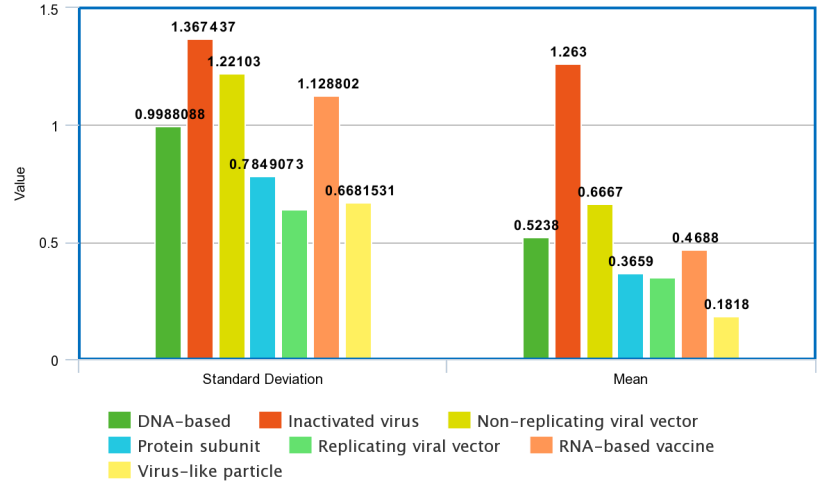


Figure 2b(Above). Standard Deviation and Mean for each Vaccine Type

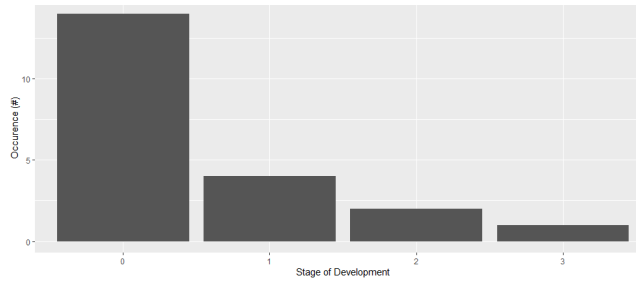


Figure 3. Number of DNA Based Vaccines in Each Stage of Development

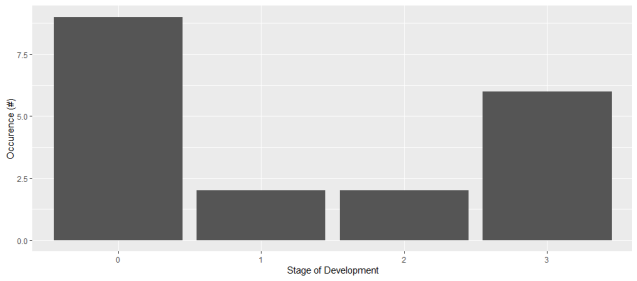


Figure 4. Number of Inactivated Virus Vaccines in Each Stage of Development

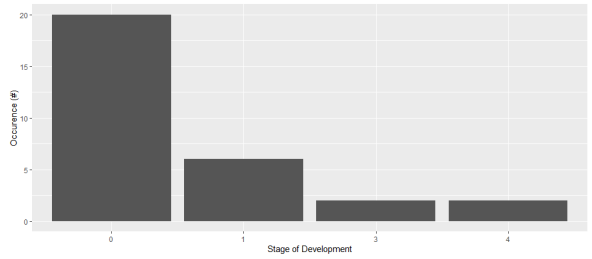


Figure 5. Number of Non-Replicating Viral Vector Vaccines in Each Stage of Development

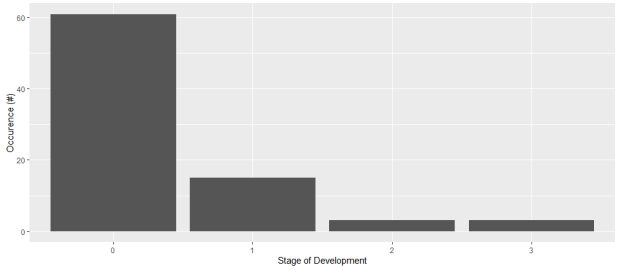


Figure 6. Number of Protein Subunit Vaccines in Each Stage of Development

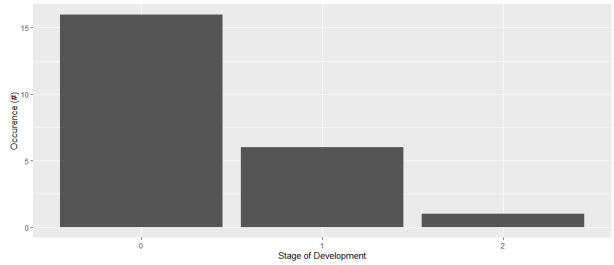


Figure 7. Number of Replicating Viral Vector Vaccines in Each Stage of Development

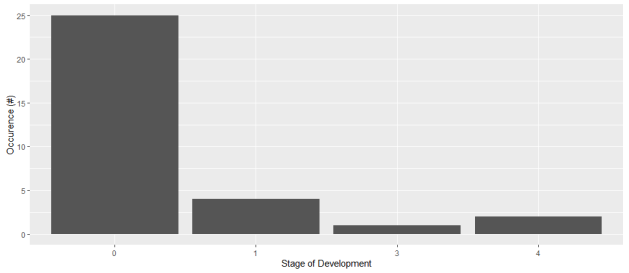


Figure 8. Number of RNA Based Vaccines in Each Stage of Development

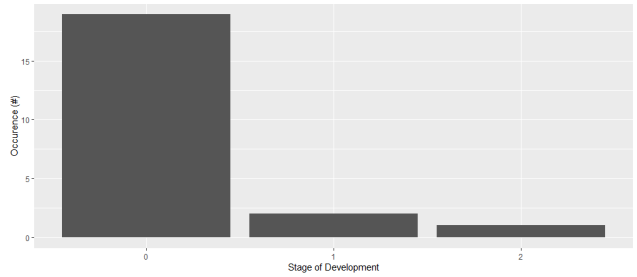


Figure 9. Number of Virus Like Particle Vaccines in Each Stage of Development

Table 2. Results from the Shapiro-Wilks Normality Test and the One way ANOVA (a=0.05)

	p-value
Shapiro Wilks	2.2×10^{-16}
One Way ANOVA	0.014

Table 3. Results from the Tukey Test

	upr	p value
Protein subunit - Inactivated virus	-0.14750653	0.0076229
Replicating viral vector - Inactivated virus	-0.01256393	0.0444046
Virus like particle - Inactivated virus	-0.14480935	0.0114918

Table 4. Chi-Squared Test P-Values when Comparing Viral Vector Vaccines Versus RNA- Based Vaccines per Stage of Development Reached

	Stage 1	Stage 3	Stage 4
P-Value	0.13057	0.255989	0.715001
Number of Non Replicating Viral Vector Vaccines	6	2	2
Number of RNA- Based Vaccines	4	1	2

Discussion

The calculated p-value of the Shapiro Wilks normality test was 2.2×10^{-16}, which was less than the 0.05 p value. This indicates that the mean stage of development amongst all vaccine types significantly deviated from normal distribution. This required the use of a one way ANOVA. The one way ANOVA p value of 0.014, a value less than 0.05, proved there is a statistically significant difference amongst the mean stage of development across the vaccine groupings observed in this investigation and therefore a significant difference in efficacy when passing through clinical trials

As observed in Figure 2a, RNA and Non Replicating viral vector vaccines have progressed the farthest (Stage IV authorization). Using a Chi-Squared test, these two vaccine types showed no significant

statistical difference between each other in progressing to Stage I, III and IV. Therefore, descriptive statistics are needed to further analyse the data. RNA vaccines have a mean stage of development of 0.4688. In comparison, non replicating viral vectors have a mean stage of development of 0.6667. This would suggest that between non replicating viral vector and RNA, non replicating viral vector overall as a vaccine category has more progression through the clinical stages of development. This would suggest non replicating viral vectors are more effective than RNA vaccines. However further factors such as the efficient manufacturing of synthetic mRNA suggest RNA vaccines would most likely progress faster. These factors will be discussed further in our conclusion.

In addition, inactivated virus vaccines show potential to progress through clinical stages of development, as they have the highest mean stage of development as seen in Table 1 and Figure 2b. In addition, inactivated virus vaccines have the most vaccines in Stage III development. This suggests a large portion of future inactivated virus vaccines may be approved for use in the near future as a demand for diverse vaccine treatments rises as the COVID-19 pandemic continues to develop. However, both RNA and non replicating viral vector vaccines have reached the highest stage of development and both show relatively larger means compared to the other vaccine types. This difference is seen in the ANOVA test conducted in Table 2 and plotting of the means in Figure 2b.

A limitation of this project is the sample size of the vaccine categories being tested. 7 types of vaccines were tested, and a total dataset of 251 vaccine entries were spread among the aforementioned 7 types. The findings of this paper could be further solidified by conducting an investigation with a larger sample size, with more vaccines for each type. This would ensure the findings of this paper still maintain reputability on a larger scale, as far more vaccine variants are being developed and employed globally as the pandemic continues to evolve. Ideally, to compare vaccine types, all the vaccines from each vaccine type would start development at the same time to determine the speed of vaccine progression through clinical stages. The period at which a vaccine type began development was not controllable as different vaccines of varying vaccine types started development earlier or later than other vaccines. As a result

some vaccines had more background research materials supporting their development and also had more opportunities to be approved for the next developmental stage. Observing vaccine treatments that have had the same opportunities to develop would lead to an investigation that compares the efficacy of vaccine treatments passing through developmental stages purely based on the individual properties of each vaccine treatment rather than a comparative that is influenced by pre-established circumstances such as a longer period of time to be assessed.

Conclusion

The results from the tests have concluded that Non Replicating Viral Vector and RNA Vaccines are most effective in progressing to Stage IV, and are therefore more effective and safe altogether. The graphs of these vaccines indicate they have been most successful at progressing through all the clinical stages, with some even being authorized. In addition to this, because of the ANOVA test performed, it can be concluded that the data is statistically significant. However, this finding indicated that inactivated virus vaccines were the most effective vaccine grouping, which may be due to the data not being normalized. While other vaccines appear to stagnate at certain stages, non replicating Viral Vector and RNA Vaccines are present at every stage, suggesting that they are introduced and progress at a quick rate. Furthermore, Figure 2a and Table 1 prove that RNA and Non replicating Viral Vector treatments on average were the most likely to pass through stage III development. From this statistically significant data, it can be concluded that non replicating Viral Vector and RNA Vaccines are the most effective type of vaccines in general.

When comparing the two vaccines specifically, the Chi-squared test suggests there is no statistical significance between these two vaccine types progression through each specific stage of development. Additionally, they have a similar mean stage of development and similar amounts of vaccines in each clinical stage. This suggests that the two are almost statistically equal. However, due to the efficiency of synthetic mRNA creation, RNA vaccines show more potential to progress rapidly in comparison to non

replicating Viral vector vaccines, as supported by Trafton, 2015[9], Ultimately, RNA vaccines can be more rapidly developed suggesting a large quantity of RNA vaccines can be created faster than non replicating viral vector vaccines. This supports RNA vaccines as the more vaccines available means more vaccines can be distributed. Based on the data collected in this investigation, both RNA and Non Replicating Viral Vector vaccines show significant promise as areas of future focus for emphasized vaccine research and development, as both groups were efficient in passing to stage IV developmental progress. Additionally, investments and further research into inactivated virus vaccines show prevalent merit despite already being an established vaccine type, as they were the most likely out of all treatments to reach stage III development.

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