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The Efficacy of the COVID-19 Vaccine in Mississippi

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THE EFFICACY OF THE COVID-19 VACCINE IN MISSISSIPPI

by

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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

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Approved By

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DEDICATION

This thesis is dedicated to my friends and family who encouraged and supported me throughout the entirety of my thesis journey and throughout the entirety of my college career.

More specifically, I dedicate this thesis to my dad, Dr. Paul Levy. It is his unconditional love, support, and encouragement that pushed me to do my very best work on this thesis (not just my usual bare minimum). He has been my biggest cheerleader every step of the way, sacrificing his time and energy to do so. Dad, thank you. I love you so much.

ACKNOWLEDGEMENTS

I would like to thank everyone who has helped and guided me throughout this process. First, I would like to thank Dr. Xin Dang for her constant support and guidance over the past year. This thesis would not be possible without her. I would also like to thank Dr. Hailin Sang and Dr. Eva Tatum for being a part of my committee. Lastly, I would like to thank Dr. Paul Byers and Theresa Kittle, along with the Mississippi State Epidemiology Department, for providing me their time and data.

ABSTRACT

ILYSE MIRIAM LEVY: THE EFFICACY OF THE COVID-19 VACCINE IN MISSISSIPPI

(Under the direction of Dr. Xin Dang)

By tracking and analyzing fifty-three weeks of COVID-19 data, this thesis analyzes the efficacy of the COVID-19 vaccine within the State of Mississippi. Over the course of these fifty-three weeks, I have also been able to calculate the confidence intervals for vaccination efficacy and the risk reduction due to vaccination by using data regarding the correlations between deaths and vaccination status, provided to me by the Mississippi Office of Epidemiology. My analysis demonstrates that the COVID-19 vaccine is effective not only in Mississippi but also across the globe.

PREFACE

This project has been my greatest accomplishment to date. I look forward to seeing the impact that this thesis may have in the future.

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LIST OF ABBREVIATIONS

COVID-19	SARS-CoV-2 / Coronavirus
WHO	World Health Organization
mRNA	messenger RNA
J&J	Johnson & Johnson
APC	Dendritic cells
FDA	Food and Drug Administration
Pfizer	BNT162b2 mRNA COVID-19 Vaccine
RR	Risk Ratio
C.I.	Confidence Interval
VE	Vaccine Efficacy
S	Survival Probability
PPV	Proportion Population Vaccinated
PVC	People Among Cases
IRR	Incidence Rate Ratio
CDC	Centers for Disease Control and Prevention
R_0	basic reproductive number
k	comparable dispersion parameter

"Facts are stubborn things; and whatever may be our wishes, our inclinations, or the dictates of our passion, they cannot alter the state of facts and evidence".

- John Adams

Introduction

In December of 2019, the COVID-19 virus made its first appearance in Wuhan, China. Approximately one month after, in late January 2020, COVID-19 entered the United States. The COVID-19 virus rapidly began infecting large numbers of people across the United States as well as across the rest of the world. On March 11, 2020, the World Health Organization ("WHO") deemed this virus a pandemic, thus aligning it with previous detrimental pandemics, such as the 2009 H1N1 Influenza and the 1918 Spanish Influenza. Just one day after the WHO categorized this virus as a serious pandemic, COVID-19 emerged in the state of Mississippi on March 12, 2020.

The rapid spread of this virus took the world by surprise, creating shortages of hospital beds, personal protective gear, and morgues. This virus and its severity soon became life-altering for people all around the world, which put pressure on companies to quickly create an effective vaccine against the virus. Most vaccines contain a weakened or inactivated virus, which requires adequate time to properly perform safety testing. Inactivated vaccines only induce antibody mediated immunity. Subunit vaccines, on the other hand, only contain a portion of the virus, usually a spike protein. Subunit vaccines cannot cause diseases; however, they may be less

effective because the immune system will not see the vaccine as a threat. Thus, this requires some aggivents to be added to stimulate the antigen producing cells to pick up the vaccine. Since vaccines containing inactivated viruses require extensive safety testing and subunit vaccines are less effective, scientists and companies were pushed by the COVID-19 outbreak to find a different, more effective vaccine form that could be produced and distributed quickly in attempt to curb the pandemic. This need for a new vaccine led to the creation and distribution of three COVID-19 vaccines: Moderna, Pfizer, and Johnson & Johnson.

Both Moderna and Pfizer are messenger RNA ("mRNA") vaccines, which trigger an immune response within the body by guiding human cells to make protein. The virus attaches itself to human cells using its spikes. Messenger RNA vaccines introduce mRNA that contain information for making the viral protein. These molecules are delivered in a lipid covering that eventually fuse with the cell membrane. Then, inside the cytoplasm, the mRNA is translated into viral antigen, which is then displayed on the surface of the cell. Although this form of vaccine is more fragile and must be stored in a cold place, mRNA vaccines are extremely unlikely to integrate into the human genome, which is not the case with DNA vaccines.

DNA vaccines, which help combat viruses within both animals and humans, introduce viral DNA into the nucleus of the cell, where it is transcribed into mRNA, which is then translated into viral spike protein in the cytoplasm and displayed on the cell's surface. These vaccines require a special delivery method to reach the nucleus of the cell, such as utilizing a harmless unrelated adenovirus as a vehicle to deliver the DNA. This means the vaccine is also

known as a viral vector vaccine. The viral vector vaccine cannot replicate or cause disease, but it can deliver the DNA. However, the chosen viral vector cannot include anything that someone is already immune to because it will blunt the effectiveness of the vaccine, so a non-human adenovirus is chosen instead. DNA vaccines have raised concerns about the possibility of viral DNA integration into the human genome; however, animal models have shown that integration frequency is well below the frequency of natural spontaneous gene mutations.

Ultimately, mRNA vaccines were more effective with respect to COVID-19 because they release viral antigens to trigger immune response without actually causing the disease. This type of vaccine introduces mRNA that contains information for making the viral protein. These molecules are delivered in a lipid covering that will eventually fuse with the cell membrane. Then, inside the cytoplasm, the mRNA is translated into viral antigen, which is then displayed on the surface of the cell. It then uses the host cell's machinery to replicate, which allows it to produce more viral proteins and genetic material. This genetic material and viral protein release more viral material that go on to infect more cells. These newly infected cells produce symptoms. Infected cells alert the immune system by displaying viral proteins on their surface. This presents the viral antigen to immune cells, such as Cytotoxic T-cells. The debris of dead viral cells are picked up by antigen presenting cells, of which dendritic cells are most effective. Dendritic cells (“APC”) patrol body tissues and sample their environment for intruders. The cells then grab the antigen and go towards the nearest lymph node where they give the antigen to the Helper T-cells, while also helping activate B- cells in lymph nodes.

Although the process takes a few weeks after receiving the mRNA vaccine, the immune cells created from the vaccine work together to form two types of immunity: cell mediated immunity and antibody mediated immunity. The immunity process in response to a vaccine can be similar to that of a mild infection, even though there is none. The lymph nodes can become tender and swollen from antibodies forming in response to the vaccine; however, this is expected because these are signs that the vaccine is working and preventing severe illness due to COVID-19 [1].

Section 1

Prior to gaining FDA approval for distribution of the COVID-19 vaccine, many case studies had to be done to prove the overall safety and efficacy of the COVID-19 vaccines created by different companies. The three companies that had successful case studies and were able to eventually gain FDA approval are Pfizer, Moderna, and Johnson & Johnson.

In December 2020, Pfizer did a case study on the BNT162b2 mRNA COVID-19 Vaccine. This was done through a multinational, placebo-controlled, observer-blinded randomized trial in which the vaccine was evaluated based on its efficacy and safety [2]. There was a 1:1 randomization of patients 16 and older who were not immunocompromised to receive two doses of either a placebo or the actual vaccine. These doses were given 21 days apart, and each dose was tested on its safety side effects and overall efficacy against COVID-19. There were a total of 43,548 participants that underwent randomization. Out of the 43,448 people that received injections, 21,720 received the BNT162b2 (Pfizer) and the other 21,728 received the placebo. Both population groups had very similar demographics, each containing around 50.5% male, 49.5% female, and 57.7% of the participants were between 16 and 55 years old [2].

Ultimately, Pfizer's case study revealed that the BNT162b2 vaccine was 95% effective in preventing COVID-19. Throughout the trial, there were only 8 COVID-19 cases with BNT162b2 and 162 COVID-19 cases with the placebo. A two-dose regimen of BNT162b2 proved to provide 95% protection against COVID-19 in persons 16 years of age or older. The safety of the

vaccine over a median of 2 months was comparable to that of other viral vaccines, such as side effects including headache, nausea, and injection site soreness. The vaccine efficacy along with the probability of approval were calculated by using the Bayesian beta-binomial model [2]. The Bayesian beta-binomial model uses the underlying proportion of success as its only parameter, making it easy to visualize in a trial similar to the Pfizer case study [3]. Thus, according to this model, there was a "success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%" [2].

A few months later in February 2021, Johnson & Johnson was given FDA approval for Emergency use of its single-dose COVID-19 vaccine for the prevention of COVID-19 in patients 18 years and older. This decision was made by the FDA due to the vaccine trial carried out by J&J.

The Johnson & Johnson ("J&J") single-dose COVID-19 vaccine trial was a Phase 3 ENSEMBLE study, which is a double-blind, placebo-controlled trial consisting of patients 18 years and older [4]. This case study analyzed the vaccine's protection against moderate to severe COVID-19 disease while also tracking its efficacy at the 14 day and 28-day mark after the vaccine was administered. This trial was conducted across eight countries and three continents. There was a total of 43,783 trial participants, with 14,672 participants 60 years or older. Out of the total number of participants, 55% were male and 41% were immunocompromised or had comorbidities.

The trial showed that the J&J single-dose COVID-19 vaccine was 66% effective in preventing moderate to severe COVID-19. The level of protection after 28 days was 72% in the USA, 66% in Latin America, and 57% in South Africa. Overall, this vaccine was 85% effective in preventing hospitalization and death across all regions, which deemed it effective [4].

Using the given raw data from the Pfizer case study, I did my own calculations to mimic how both Pfizer and J&J got their trial results.

Vaccine Efficacy:

Risk of COVID-19 among vaccinated: $\frac{8}{21720} = .00036 = .036\%$

Risk of COVID-19 among unvaccinated: $\frac{162}{21728} = .0075 = .75\%$

Risk Ratio: $\frac{.00036}{.0075} = .048$

Vaccine Efficacy: $\frac{(.75-.036)}{.75} = .952 = 95.2\%$ effective

Confidence Interval of Vaccine Efficacy:

Cases (X, Y) = (8,162)

Participants = 43540

Efficacy = 95.2%

Risk Ratio: $RR = .048$

95% Confidence Interval = $1 - RR^{\left(\pm 1.96\sqrt{\left(\frac{1}{x}+\frac{1}{y}\right)}\right)}$

I calculated the 95% Confidence Interval as follows: $1 - RR^{\left(1.96\sqrt{\left(\frac{1}{x}+\frac{1}{y}\right)}\right)} = 1 - .048^{\left(\sqrt{\left(\frac{1}{8}+\frac{1}{162}\right)}\right)}$

$= 1 - .048^{(.70987)}$

$= .90238$

$1 - RR^{\left(-1.96\sqrt{\left(\frac{1}{x}+\frac{1}{y}\right)}\right)} = 1 - .048^{\left(-1.96\sqrt{\left(\frac{1}{8}+\frac{1}{162}\right)}\right)}$

$= 1 - .048^{(-.70907)}$

$= .9764$

Thus, the 95% Confidence Interval = (0.902,0.976)

Therefore, this is accurate because 95.2% lies within this interval.

To do these calculations accurately, I calculated the variance of the log of the risk ratio log (RR), and constructed a 95% Confidence Interval based on a Poisson distribution assumption. The Risk Ratio can be determined by a ratio of the disease rates of the vaccinated group to the control group (unvaccinated group). This means, the smaller the rate among the vaccinated relative to the unvaccinated, the higher the vaccine efficacy. For the Confidence Interval, both the vaccinated group (X) and control group (Y) follow a Poisson Distribution. Confidence Intervals are sometimes also calculated by using Binomial distribution, however for this kind of study, the Poisson distribution allows for a more realistic interval. Since COVID-19 exposure has to be taken into account, the individuals recruited over time could possibly have

had different exposures. This makes Binomial distribution less accurate because we cannot assume equal distribution [5].

Overall, my calculations using the raw data from the Pfizer trial match up with the statistics that Pfizer stated in their case study.

Based on the case studies, trials, and efficacy calculations of the Moderna, Pfizer, and Johnson & Johnson vaccines, each vaccine was deemed effective in preventing severe COVID-19 related illness. Thus, each vaccine was given FDA approval. However, the data shows that J&J has a greater variability than both Modern and Pfizer since, by early 2021, it was the only vaccination that had been tested against other variants [6]. The J&J vaccine was also found to be far less effective than Moderna and Pfizer. This efficacy difference is due to the fact that the studies were done at different times in different environments against a background of different strains. Consequently, the J&J vaccine is hard to compare to Pfizer and Moderna. Although the efficacy of Moderna and Pfizer is significantly higher than Johnson & Johnson, all three vaccines have a 100% efficacy against hospitalization and death, which is the most important aspect of the vaccine trials to gain FDA approval [7].

Although the J&J, Moderna, and Pfizer vaccine ultimately gained FDA approval for its efficacy against severe COVID-19 illness, it is crucial to further delve into the similarities and differences of these vaccines and analyze case studies with data similar to the results of the initial successful trials.

By February 2021, the J&J vaccine could be given to people 18 and older, the Pfizer vaccine was able to be given to people ages 16 and older, and Moderna was actively doing case studies on administering the vaccine in people ages 12 - 17 years old. This case study was the beginning to many other trials that would eventually allow the vaccines to be given to people younger than 18 years old. Other than age restrictions early on in the vaccination roll-out phase, the main difference between the Moderna, Pfizer, and J&J vaccines is that J&J is a Viral Vectored Vaccine, whereas Pfizer and Moderna are made using mRNA. Thus, each vaccine requires different storage procedures. Since Moderna and Pfizer are mRNA vaccines, they are required to be stored at cold temperatures, which creates accessibility problems. However, since J&J is a Viral Vectored Vaccine, it requires no special storage procedure, and therefore will be able to be administered in more places than the Pfizer or Moderna vaccine.

Along with different storage procedures, each vaccine also has a different timeline of efficacy. This timeline of efficacy is initially dictated by the fact that J&J is a single dose vaccine, whereas Moderna and Pfizer are two-dose vaccines, as of February 2021, before third doses were necessary and available. The intervals between doses are as follows: Moderna - 28 days; Pfizer- 21 days; J&J – single dose.

The common side-effects after each vaccine dose also vary between each vaccine type. Most side-effects occur after the second dose of Moderna/Pfizer is administered, which cannot be compared to the J&J single dose vaccine. Anaphylaxis has been another side effect for some

people receiving Moderna or Pfizer, but there is only one case of anaphylaxis associated with the J&J vaccine as of February 2021 [6]. Other COVID-19 vaccine related side-effects that have been observed include injection site soreness, nausea, headache, and fever.

Shortly after the FDA approval of Moderna, J&J, and Pfizer vaccines in the United States and across the globe, Canada gained FDA approval for a fourth vaccine created by AstraZeneca. The AstraZeneca trial used a meningococcal vaccine rather than a placebo for the control group. This caused some younger participants to experience reactions from both the COVID-19 vaccine and the meningococcal vaccine. The expected side effects seem to be worse after the second dose of Moderna and Pfizer, while they are worse after the first dose of AstraZeneca. Otherwise, the side effects remained very similar in all four vaccines. These side effects are extremely similar to those due to vaccines such as the shingles vaccine, but worse than the side effects from the flu vaccine. This trial also showed that the efficacy of the AstraZeneca vaccine was much closer to that of J&J, than to the efficacy of Moderna and Pfizer. More specifically, J&J and AstraZeneca both had around a 60-70% efficacy, while both Moderna and Pfizer had an efficacy of ~95% [8]. An explanation of the lower efficacy in the AstraZeneca and J&J vaccines could be from a greater number of infections from variants of concern; however, it is difficult to compare the efficacy of these vaccines due to the differing amounts of doses needed and timing of said dose(s). Alison Thompson, an associate professor who studies public health policy and ethics at the University of Toronto, also pointed out that the difference in efficacy between these vaccines might change over time and close the gap between the efficacy of these four vaccines. She said, “As we get more data about the kind of efficacy that they have over the longer term, we may see

those [efficacy] numbers come down significantly for the mRNA [Pfizer and Moderna] vaccines" [8].

Some similarities amongst all four vaccines include: they seem to equally protect different age groups, sexes, and races, when combating more severe cases and hospitalizations, and they satisfy Health Canada's 50% efficacy standard. However, these vaccines also have many differences. The main difference between Moderna, Pfizer, J&J, and AstraZeneca is that Moderna and Pfizer trick the immune system by using mRNA to provoke a response, while J&J and AstraZeneca use adenovirus (another respiratory virus) to provoke a response from the immune system. The storage of these vaccines is also different. Moderna and Pfizer have to be stored in freezers, while J&J and AstraZeneca can be stored in refrigerators.

Following the approval and authorization of the Moderna and J&J vaccines for ages 18+, and the authorization of the Pfizer vaccine for ages 16+ and Pfizer, case studies and trials were carried out by both Moderna and Pfizer to lower the age limit of the COVID-19 vaccine. In January of 2021, Pfizer conducted a trial with 2,200 young adults aged 12–15. Shortly after in February of 2021, Moderna conducted a trial with 3,000 young adults aged 12–17 [8]. Since these trials were successful and deemed the vaccine effective and safe for children ages 12 and older, Moderna started testing their vaccine in babies and children 6 months - 11 years old in mid-March of 2021.

For this trial, which included 6,750 infants and children between 6 months and 11 years old, Moderna began testing different doses on the participants. Some participants only received one-quarter of the dose that was currently being administered to adults, while others were given one-half the dose or an equal dose to that of an adult. Through this trial technique, Moderna was able to determine the correct doses for infants and children. Then, Moderna followed up this trial with a trial comparing the correct dosage for young children against a placebo injection. Stephen Spector, a professor of pediatrics at the University of California San Diego School of Medicine, who led a trial of the Moderna vaccine measured the efficacy of the vaccine in young children by measuring "the levels of neutralizing antibodies, which prevent SARS-CoV-2 from infecting cells" [9].

Although it is more difficult to prove that the vaccine is effective in children because children are less likely to show COVID-19 symptoms than compared to adults, it is imperative that young children get vaccinated to gain herd immunity. Since the age group of Unites States citizens 18 years and younger make up about 23% of the United States population, thus making it nearly impossible to gain herd immunity without the vaccination of this demographic.

According to the United States Centers for Disease Control and Prevention, as of March 17, 2021, 226 people under 18 died with COVID-19 in the United States, compared with more than 417,000 deaths of people ages 65 and older and more than 517,000 deaths overall [9]. Thus, although officials predicted that a vaccine for children may take months or even a year to authorize, Spector, along with the chair of the Committee on Infectious Disease for the

American Academy of Pediatrics, Dr. Yvonne Maldonado, believe that the vaccine is crucial for the health and safety of young children and those in contact with them. Dr. Maldonado, who was working on the Pfizer trial for young children, said, “I - by training, I'm a vaccinologist. And I do believe that - we know that vaccines have prevented 75% of deaths in children around the world in the last 20 years” [10].

Section 2

Throughout the entirety of the COVID-19 Pandemic, the Mississippi State Department of Health has provided updated data regarding COVID-19 and the COVID-19 vaccine. By tracking this data for a full year, I have been able to put together and analyze graphs in order to demonstrate and prove the efficacy of the COVID-19 vaccine. The COVID-19 vaccination data that I have tracked and graphed includes the data for Moderna, Pfizer, and J&J vaccines combined rather than separate data for each vaccine type. Also, the term "fully vaccinated" refers to a person who has received two doses of Moderna or Pfizer and a single dose of the J&J vaccine and onset is 14 days after the last dose was received. Thus, individuals who have only received one dose of Moderna or Pfizer are counted in the "unvaccinated" or "not vaccinated" category.

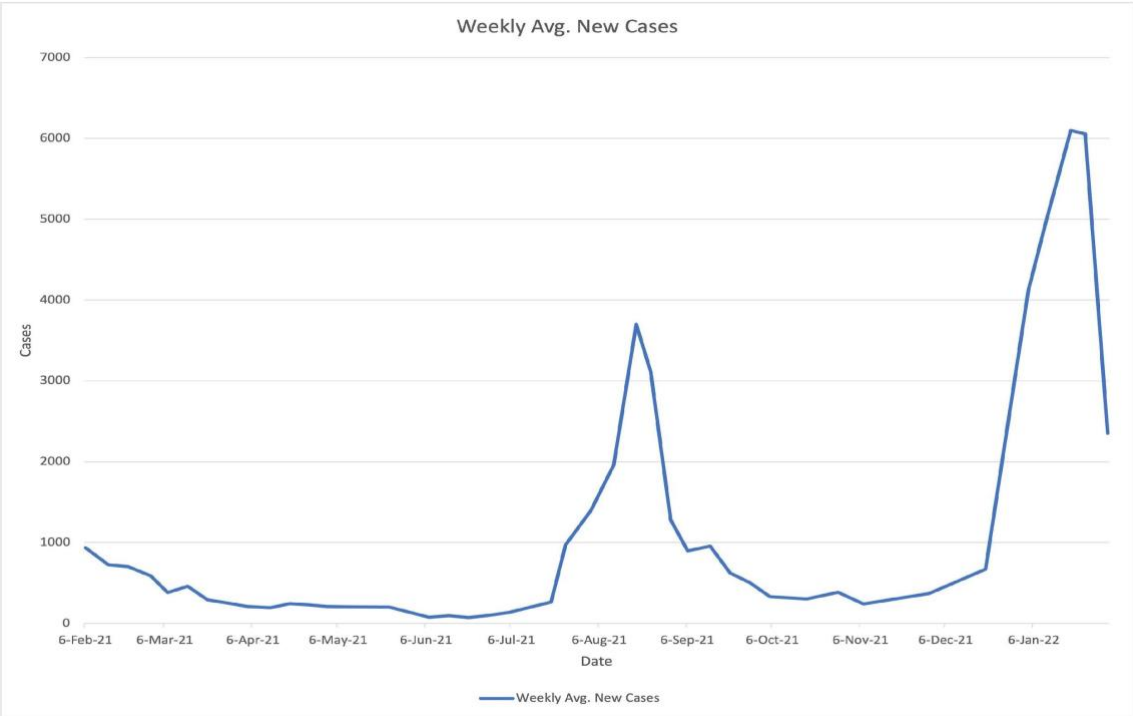


Figure 1.1

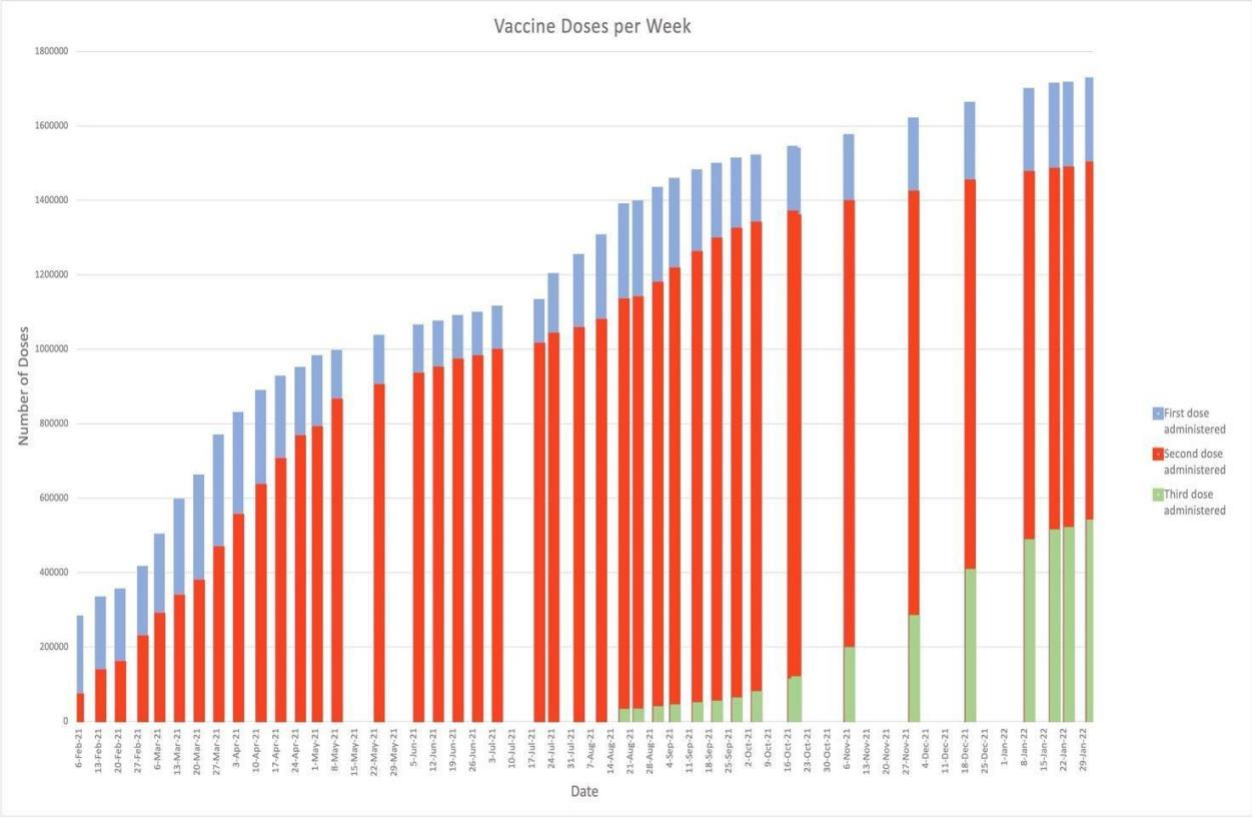


Figure 1.2

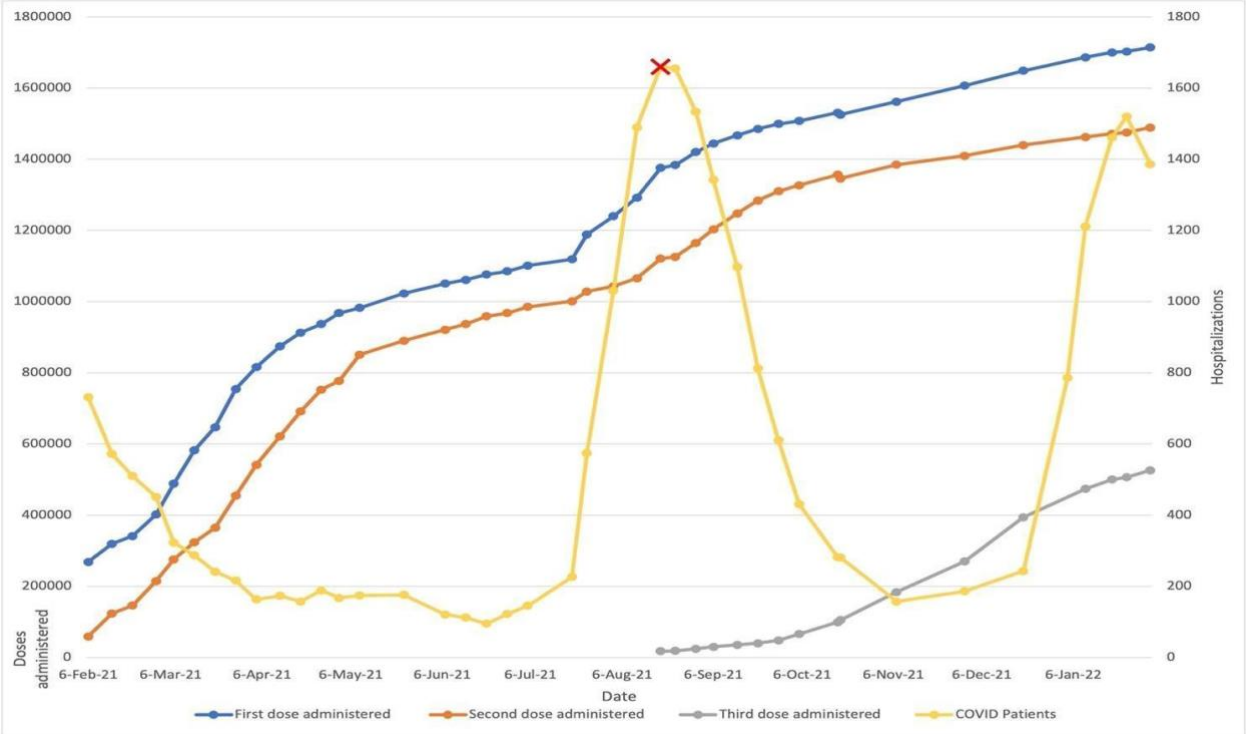


Figure 1.3

As shown in Figure 1.1 and Figure 1.3 above, as more first and second dosages were administered in the State of Mississippi starting in February 2021, the number of hospitalizations due to the Alpha variant of COVID-19 began to decrease. However, in early July 2021, there is a clear spike in COVID-19 hospitalizations despite the increasing numbers of people receiving the COVID-19 vaccine, as seen in Figure 1.2. This spike was due to a new COVID-19 variant hitting Mississippi, this variant being known as the Delta variant.

In late July 2021, a case study was done regarding the efficacy of the COVID-19 vaccine against the Delta variant. This trial had a test-negative case control design which compared the vaccination status of a symptomatic COVID-19 patient versus the vaccination status of a symptomatic patient with a negative COVID-19 test. This method tests the difference between the efficacy of the vaccine against Delta compared to the efficacy of the vaccine against Alpha in patients 16 years of age and older. It should be noted that this trial considered a vaccinated person to have received either one dose or two doses, with symptoms occurring 21 or more days after the first dose was administered and 14 or more days after the second dose was administered.

To differentiate the patients with the Delta variant rather than the Alpha variant, whole-genome sequencing was used. Along with sequencing, PCR testing on the spike (“S”) gene target status was used to identify the Delta variant amongst the positive COVID-19 samples being analyzed. The S Target was helpful in this identification because it was discovered in April 2021 that approximately 98% to 100% of the Alpha variant COVID-19 cases tested negative for the S

Target, while *72.2%* of the Delta variant COVID-19 cases tested positive for the S Target. This result increased in May 2021 when it was discovered that *93%* of the samples that were deemed cases of the Delta variant contained a positive S Target.

The results of this trial showed that among the *19,109* sequenced sample tests that were used in this trial, vaccination status was linked to approximately *92%* of these samples. By the end of the trial, the Alpha variant was detected in *14,837* of the samples and the Delta variant was detected in *4272* of the samples. Thus, by analyzing these results, it was found that the efficacy of a single dose of the vaccine was significantly lower against the Delta Variant than against the Alpha variant. More specifically, one dose of the COVID-19 vaccine was *30.7%* effective against the Delta variant with a *95%* Confidence Interval of (*25.2,35.7*). This can be compared to the *48.7%* efficacy of one dose against the Alpha variant, with a *95%* Confidence Interval of (*45.5,51.7*).

It is apparent that the difference between the efficacy of a single vaccine dose against the Alpha variant and the Delta variant is fairly significant; however, the results of the efficacy of two doses of the vaccine had a much smaller difference. The data shows that being fully vaccinated is 93.7% effective against the Alpha variant and 88.0% effective against the Delta variant, with 95% Confidence Intervals of (91.6,95.3) and (85.3,90.1) respectively [11].

Although the results of this case study seemed hopeful for the efficacy of the vaccine against the Delta variant, over time as the numbers of vaccinations increased, the number of

severe COVID-19 cases increased as well [Fig. 1.3]. Thus, the Delta variant introduced a problem that needed to be solved quickly and effectively. Unlike the Alpha variant, which mainly targeted the elderly and immunocompromised, the Delta variant targeted the younger unvaccinated population.

The third dose, or booster shot, of the vaccine was highly encouraged and available to people 50 years of age and older by August 2021. Around this time, the Israeli Minister of Health Nitzan Horowitz received his third dose and encouraged the Israeli citizens, along with the rest of the world, to follow suit. He cautioned, "Now is a critical time... We're in a race against the pandemic" [12]. By August 2021, Israel not only had some of the world's highest vaccination rates with 78% of the Israeli population 12 years and older being fully vaccinated, it also had some of the highest infection rates in the world with more than 600 new COVID-19 cases per day per every million people.

Through the course of the Pandemic, Israel was being watched closely by the rest of the world due their early and extensive vaccination of their population. Thus, as the Delta variant became more and more threatening, the world looked to Israel as the model. As of August 2021, research found that people that received their vaccinations in January were 2.26 times more likely to get a breakthrough infection than people who received the vaccine in April. This shed some light on the situation in Israel because most of the Israeli citizens received their vaccination in the time frame from December 2020 to February 2021. Similarly, regarding the spike in cases in the rest of the world, the people that received their vaccinations first were the elderly and

those with the weakest immune systems [12]. Therefore, although the Delta variant targeted the young unvaccinated portion of the population, the vaccinated elderly and immunocompromised portion of the population were also being affected due to the vaccine efficacy decreasing over time.

By August 15, 2021, a total of 514 Israelis were hospitalized due to a severe case of COVID-19. Of these people, 59% were fully vaccinated and 87% of the fully vaccinated patients were 60 years of age or older. However, according to data from the Ministry of Health, people 60 years of age and older who have received a third dose were half as likely to be hospitalized as their fully vaccinated peers. Due to this data and the concerning amount of severe COVID-19 cases rapidly arising in Israel, the country administered third doses of the COVID-19 vaccine to over one million citizens by late August 2021. Luckily, out of 4500 people who got vaccination boosters, 88% said symptoms were no worse than the other doses [12].

Ultimately, as Figure 1.3 shows, the spike of hospitalizations due to the Delta variant did not respond to the increase of vaccinations until the third dose of the vaccine was introduced. After the third dose was administered to more and more Mississippi residents, the spike due to the Delta variant began to decrease and COVID-19 hospitalizations were far less frequent. Therefore, the third dose was effective against severe illness and hospitalizations due to COVID-19. This relationship between the third COVID-19 dose and severe COVID-19 hospitalizations is demonstrated by the red X marked on Figure 1.3 [Fig. 1.3].

Section 3

After the third dose of the vaccine helped to blunt the increasing severe COVID-19 cases due to the Delta variant, another COVID-19 variant was introduced. Beginning in late December 2021, the Omicron variant made its way to Mississippi despite the increasing vaccination status of the state as a whole.

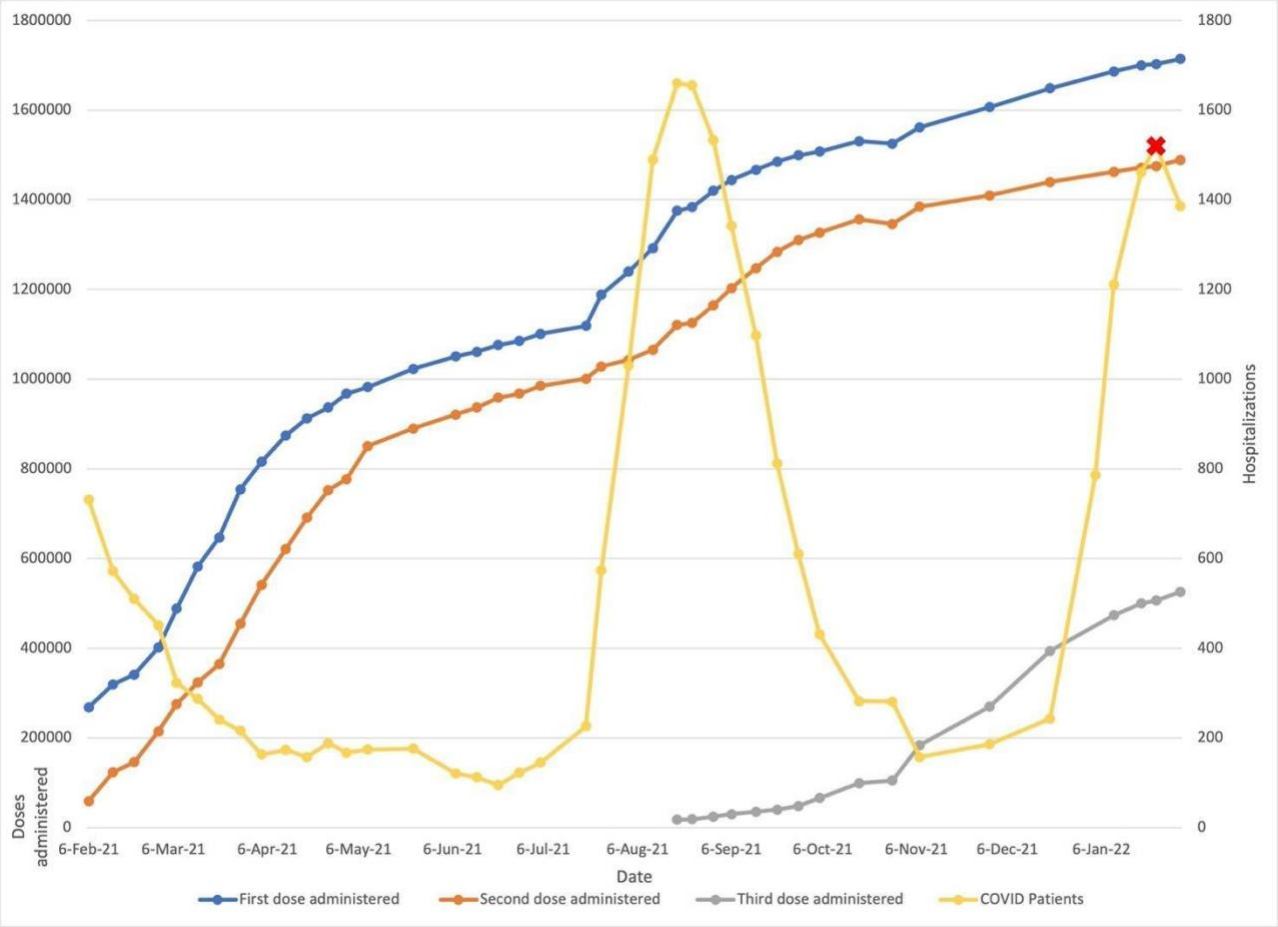


Figure 2.1

The Omicron variant was deemed less severe than the Alpha and Delta variants by many people across the globe; however, was this really the case? An associate professor of epidemiology at Harvard, William Hanage, and an assistant professor at Massachusetts General Hospital and Harvard Medical School, Roby Bhattacharyya, recently published a paper in which they stated that the perception of the Omicron virus to be "milder" was actually due to greater level of population immunity. They hypothesized that being vaccinated against or exposed to any other strain of COVID-19 most likely helped to reduce the severity of a possible Omicron infection. However, they still strongly believe that unvaccinated people need to get vaccinated and vaccinated people need to get boosted to protect themselves and others from severe COVID-19 related illness [13].

A case study regarding the efficacy of the COVID-19 vaccine and booster against the Omicron variant that used a test negative case-control design discovered that the vaccine had limited effect against the Omicron variant. The data showed that two doses of a COVID-19 vaccine was 65.5% effective against the Omicron variant at 2-4 weeks after vaccination, however this efficacy drops below 10% at 25 or more weeks after vaccination. However, the third dose managed to increase the efficacy against Omicron at 2-4 weeks after vaccination to 73.9% , but this efficacy percentage also decreased over time [14].

The Omicron variant is marked on Figure 2.1 with a red X [Fig. 2.1]. It can be seen that the peak of Omicron is lower than that of the Delta variant. Additionally, the duration of the Omicron spike is significantly less than that of the Delta variant as well. Thus, although the vaccine is not nearly as effective against the Omicron variant as it was against the Alpha and

Delta variants, the previous immunity gained through vaccination or exposure to COVID-19 helped to make Omicron a less severe variant.

Section 4

As mentioned in Section 1, early in the COVID-19 pandemic, the vaccine had to go through many trials before it was approved for children under the age of 18. After extensive research, the Centers for Disease Control and Prevention slowly started to lower the age at which someone is able to receive the vaccination(s).

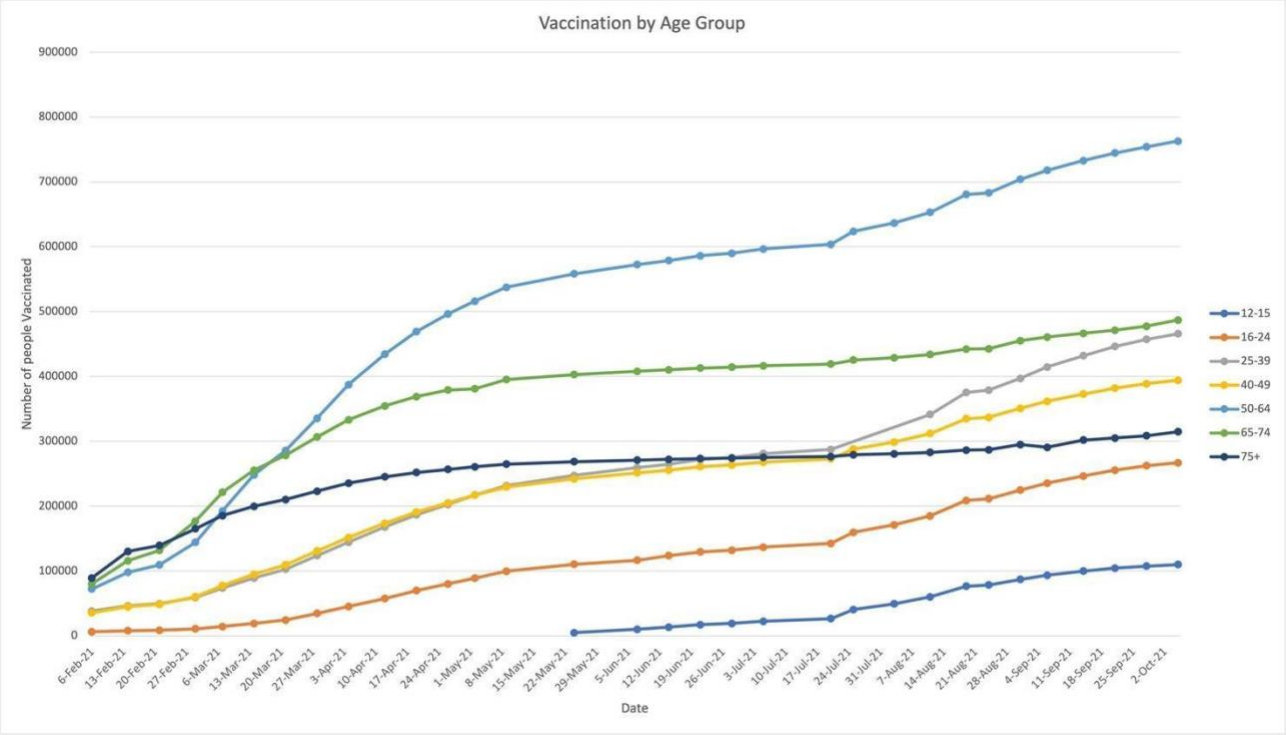


Figure 3.1

As shown in Figure 3.1 above, in February 2021, the age groups containing Mississippians 65 years of age and older were the people with the greatest vaccination rate [Fig 3.1]. This makes sense because around this time, the elderly (65+ years of age) and immunocompromised were the main demographic that were able to get vaccinated. A few

months later in late March of 2021, the data shows that the age group ranged for 50 to 64 years of age surpasses the 65+ age group for vaccination status as a whole. Although the vaccination status of the other age groups increases significantly over time, no age group increases quite as much as the group containing people 50 - 64 years of age.

In May 2021, the age requirement to receive the vaccine was lowered to 12 years of age and older. Thus, as Figure 3.1 demonstrates, data regarding vaccination of the age group containing Mississippians aged 12 –15 years was introduced [Fig. 3.1].

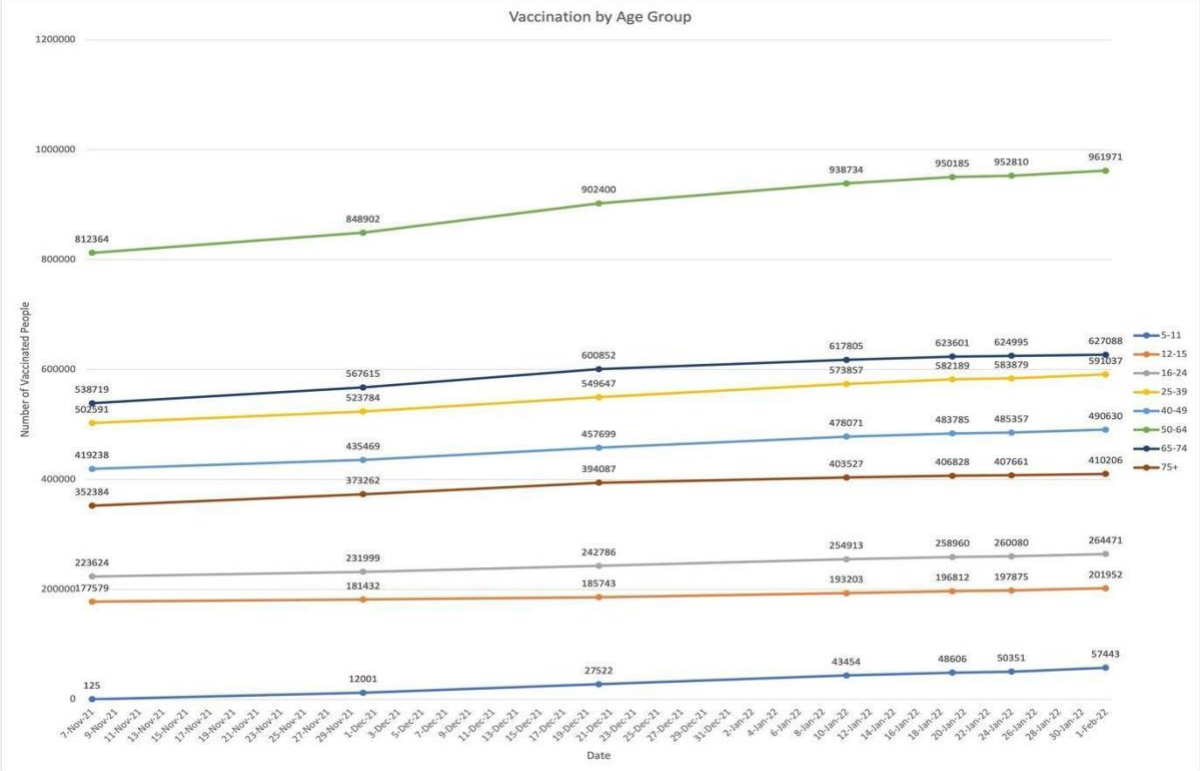


Figure 3.2

Beginning in November of 2021, the CDC approved the COVID-19 vaccine for children ages 5 and older. As Figure 3.2 demonstrates, this age group has been slowly receiving the vaccination since November of 2021, and remains the youngest age group that is approved to receive the COVID-19 vaccine as of January 2022. Overall, each age group that is able to receive the COVID-19 vaccine has had a steady increase in vaccinations over time [Fig. 3.2].

According to the CDC, as of January 2022, Pfizer is the only vaccine FDA approved for individuals 17 years of age and younger. Currently, Moderna and J&J are not FDA approved to be administered in individuals younger than 18 years of age. The CDC also encouraged individuals 12 years of age and older to receive a third dose of the COVID-19 vaccine in order to protect themselves and others against contracting severe COVID-19 cases [15].

Section 5

Ultimately, the efficacy of the COVID-19 vaccine can be best proven by the risk reduction it provided and its overall prevention of COVID-19 related deaths. Early on in the COVID-19 pandemic, specifically the time period from December 2020 to February 2021, newly vaccinated people were matched up in a 1:1 to unvaccinated people that had similar characteristics and demographics. Since the unvaccinated people acted as a control group, a study was able to be conducted on the approximate vaccine efficacy by using the Kaplan-Meier estimator [16].

The Kaplan-Meier Method is a statistical treatment of survival times. It measures the number of subjects who survived or were saved after an intervention over a period of time. Subjects in the study who drop out of a case study due to uncooperativeness or death are labeled as “censored observations” [17]. This method assumes that censored patients have the same survival prospects as patients who continue to participate in the study. This method also assumes that the survival probability for subjects recruited at any point in the case is the same. Lastly, this method assumes that the event happens at the time specified. According to the U.S. National Institutes of Health’s National Library of Medicine, “The Kaplan-Meier survival curve is defined as the probability of surviving in a given length of time while considering time in many small intervals” [17].

The Survival probability can be calculated as follows:

$$S = \left(\frac{\#\ subjects\ living\ at\ start - \#\ subjects\ died}{\#\ subjects\ living\ at\ start}\right)$$

In this case study, which used the Kaplan-Meier Method, there were 1,163,534 participants, with two groups of 596,618 people all of which being 16 years of age or older. As previously mentioned, the vaccinated participants along with the unvaccinated control participants that were paired up each had similar variables associated with the probability of the vaccination and infection. The covariate balance was evaluated after matching up the vaccinated participants and control / unvaccinated participants. A difference of 0.1 or less was considered to be an acceptable pairing [16]. Based off of the results in Table 1, one can conclude that two doses of the vaccine were much more effective than a single dose of the vaccine, however a single dose of the vaccine was still much more effective than no doses of the vaccine at all [Table 1].

These results of this case study are as follows:

COVID-19 Vaccine Efficacy	14-20 days (After 1st dose)	7+ days (After 2nd dose)
Documented Infection	46%	92%
Symptomatic COVID-19	57%	94%
Hospitalization	74%	87%
Severe Disease	62%	92%
Death	72%	-

Table 1

Although the efficacy of the COVID-19 vaccine against severe illness was calculated and predicted early in the pandemic, the data is not as relevant after the different variants were

introduced. Luckily, there are equations and formulas that allow for the risk reduction that the vaccine provides to be calculated and updated over the course of the pandemic.

According to the CDC, the age-standardized Incidence Rate Ratios ("IRRs") can be successfully calculated by finding the incidence among people who are not fully vaccinated and dividing that by the incidence among fully vaccinated persons. In order to take account of weekly rate variations, 95% Confidence Intervals are calculated for the IRRs. To help demonstrate changes in IRRs, Vaccine Effectiveness ("VE") is estimated as: $\left(1 - \left[\frac{incidence\ in\ vaccinated}{incidence\ in\ unvaccinated}\right]\right)$ [18].

Similarly, the expected percentage of vaccinated People Among Cases ("PVC") was calculated with the following formula:

$$PVC = \frac{[PPV - (PPV * VE)]}{[1 - (PPV * VE)]}$$

*PPV is the proportion of the population vaccinated.

*PVC was calculated using VE estimates of 80%, 90%, and 95%.

By using these calculations, the CDC found that during the time period from April 4, 2021, to July 17, 2021, the IRR decreased by mid-June. They were able to do these calculations based on the data of unvaccinated and fully vaccinated people during this time period. The unvaccinated group consisted of 569,142 (92%) COVID-19 cases, 34,972 (92%) hospitalizations, and 6,132 (91%) COVID-19-associated deaths. On the other hand, the vaccinated group consisted of 46,312 (8%) COVID-19 cases, 2,976 (8%) hospitalizations, and

616 (9%) deaths. However, by June 20, 2021, the vaccinated group consisted of 18% COVID-19 cases, 14% hospitalizations, and 16% deaths.

From this data, the CDC discovered that the IRRs for cases of unvaccinated people versus cases of vaccinated people decreased to 4.6 in late June from a previous 11.1 in early April. The IRRs also decreased over the same time period for hospitalizations and deaths. These IRRs decreased to 10.4 from 13.3 and to 11.3 from 16.6, respectively. From these IRRs, the VE was able to be calculated, and a decrease over time was also discovered in these calculations. The VE against positive cases or infections due to COVID-19 changed from 91% to 78% from April to July, respectively. During this same time period, the VE against hospitalization decreased slightly from 92% to 90% , while the VE against death decreased from 94% to 91% [18].

These results provide both the risk reduction and vaccine efficacy against three different levels of COVID-19 severity. It demonstrated that, although the efficacy and risk reduction decreased over time, the vaccine still provided sufficient protection against all degrees of COVID-19 severity. Since the COVID-19 vaccine prevents and protects people against severe COVID-19 related illness, such as death and hospitalization, it makes sense that these two categories had the highest efficacy and risk reduction compared to the category containing positive cases.

Along with these calculations, the raw COVID-19 data provided to me by the Mississippi State Epidemiologist, Dr. Paul Byers, along with the Mississippi Office of Epidemiology (including Theresa Kittle, Davis Trewolla, and Britney Rust) over the course of the pandemic also proves the overall efficacy of the COVID-19 vaccine against many different levels of COVID-19 severity. By dividing the overall COVID-19 related deaths in Mississippi into unvaccinated and vaccinated groups, it became clear that the vaccine was, in fact, effective against the most severe COVID-19 cases, which may result in death.

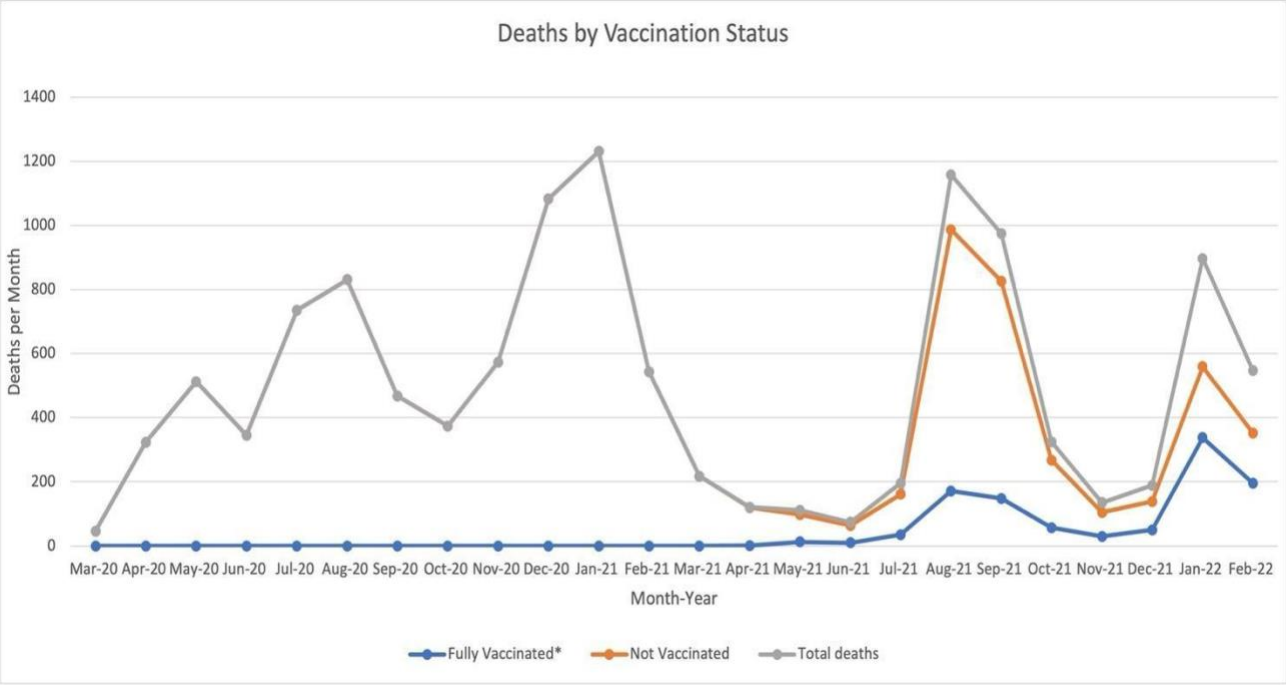


Figure 4.1

By analyzing the raw data, I was able to create a graph that has three categories: fully vaccinated deaths, unvaccinated deaths, and total combined deaths. As Figure 4.1 clearly demonstrates, those who have received two doses of the COVID-19 vaccine were far less likely to succumb to COVID-19 related illness when compared to those who were unvaccinated. As

expected, this data followed the timeline of the vaccine rollout discussed in previous sections. After people were able to receive the vaccination in Mississippi, the number of vaccinated deaths remained significantly lower than unvaccinated deaths throughout the remaining duration of the pandemic. This is demonstrated by the blue line in comparison to the orange line on Figure 4.1 [Fig. 4.1].

The death by vaccine status data also allowed me to manually calculate the approximate COVID-19 vaccine efficacy (VE) against death for each month, as well as an overall efficacy. I did this by using the Vaccine Efficacy formula (previously mentioned in this section) along with the data from Table 2.

COVID-19 Deaths by Vaccination Status (MS)

Month-Year	Fully Vaccinated*	Not Vaccinated	Total deaths
Mar-20	0	46	46
Apr-20	0	323	323
May-20	0	512	512
Jun-20	0	345	345
Jul-20	0	735	735
Aug-20	0	831	831
Sep-20	0	467	467
Oct-20	0	374	374
Nov-20	0	573	573
Dec-20	0	1083	1083
Jan-21	0	1231	1231
Feb-21	0	544	544
Mar-21	0	217	217
Apr-21	1	120	121
May-21	13	98	111
Jun-21	10	64	74
Jul-21	35	161	196
Aug-21	171	987	1158
Sep-21	148	826	974
Oct-21	57	268	325
Nov-21	30	105	135
Dec-21	50	139	189
Jan-22	338	559	897
Feb-22	196	352	548

COURTESY: Mississippi State Department of Health

Table 2

The calculations are as follows:

April 2021: 752,538 fully vaccinated individuals

0.2528 vaccinated, 0.7471 unvaccinated

$$VE = \frac{\left(\frac{120}{0.7471} - \frac{1}{0.2528}\right)}{\left(\frac{120}{0.7471}\right)}$$

$$= 0.9753$$

$$= 97.53\%$$

Thus, the vaccine efficacy against death for April 2021 was 97.53%. I then did this same calculation for every month following until February 2022. The results are show in Table 3.

Month- Year	**COVID-19 Vaccine Efficacy against Death**
April- 2021	97.53%
May- 2021	68.91%
June- 2021	67.58%
July- 2021	58.84%
August- 2021	73.07%
September- 2021	77.21%
October- 2021	74.24%
November- 2021	68.25%
December- 2021	61.62%
January- 2022	38.47%
February- 2022	44.38%

Table 3

I then added the data for each month together to calculate the overall COVID-19 vaccine efficacy against death in Mississippi. The results are as follows:

Overall VE: 1488845 fully vaccinated individuals

0.5003 vaccinated, 0.4997 unvaccinated

$$VE = \frac{\left(\frac{10960}{0.4997} - \frac{1049}{0.5003}\right)}{\left(\frac{10960}{0.4997}\right)}$$

$$= 0.90198$$

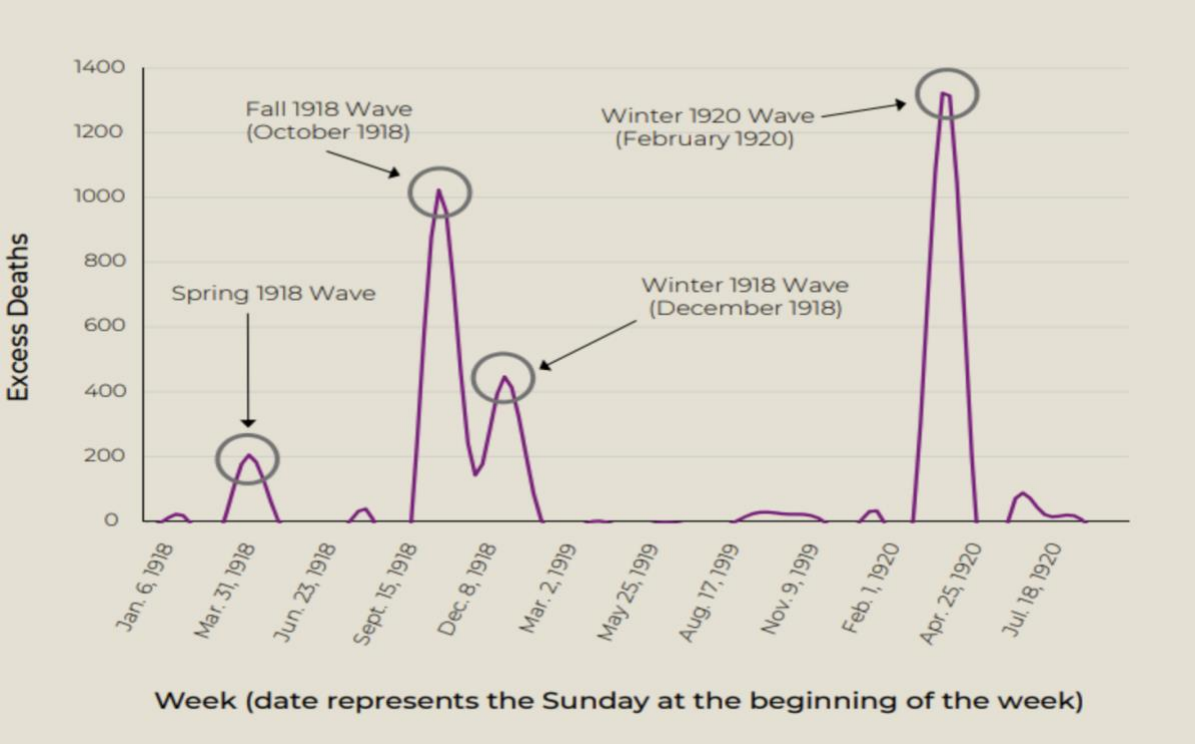
$$\approx 90.2\%$$

Therefore, the overall COVID-19 vaccine efficacy against death in Mississippi is approximately 90.2%. Thus, deeming the COVID-19 vaccine highly effective in preventing death due to COVID-19- related illness.

Section 6

As the pandemic continued to take over the world for months on end, many epidemiologists and researchers across the globe noticed a familiarity of the pattern that COVID-19 and its variants were presenting. This pattern led a professor at the Department of Epidemiology and Biostatistics at Michigan State University to perform a study which compared the trendlines of severe illness due to the COVID-19 pandemic and the 1918 Spanish Influenza pandemic. This professor, Siddharth Chandra, who is also an economics professor, created a graph that depicts the overall pattern of deaths due to the 1918 Spanish Influenza pandemic in Michigan over the entirety of the pandemic from 1918 to 1920 [19].

Spanish 1918 Influenza Deaths per Month in Michigan



COURTESY: Siddharth Chandra Figure 5.1

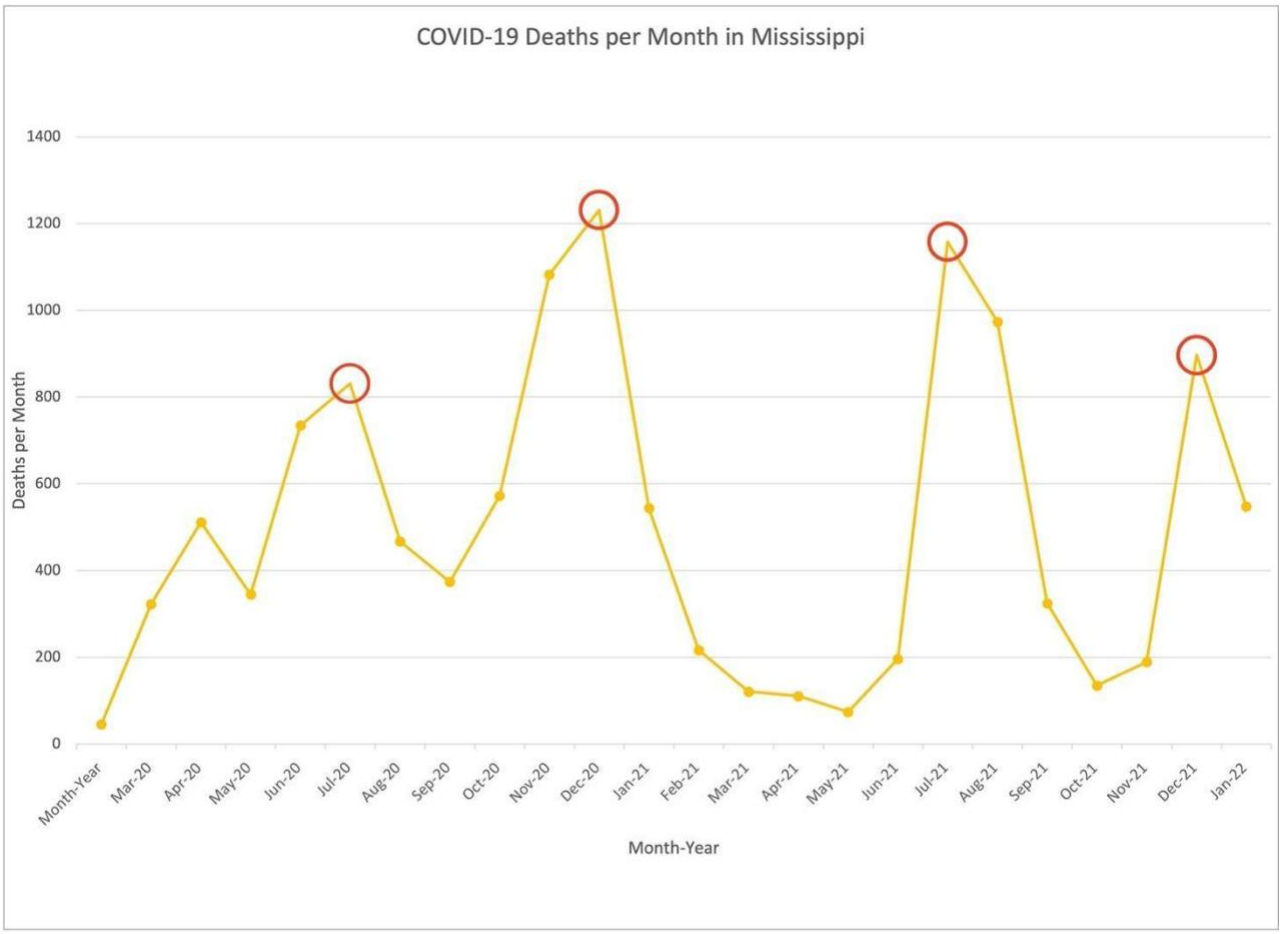


Figure 5.2

With Professor Chandra's graph in mind, I recreated a similar graph using the data of monthly COVID-19 related deaths in Mississippi from 2020 to 2022. As demonstrated in both Figure 5.1 and Figure 5.2, there were four major waves or spikes that are marked on each graph [Fig. 5.1], [Fig. 5.2]. This side-by-side comparison clearly demonstrates the similar trendlines that these two pandemics provided over the course of two years. However, in 1918, there was no vaccine. Thus, epidemiologists and scientists today can analyze the 1918 pandemic and use its data as somewhat of a control group to provide some clues as to what might occur in the current or future pandemics.

In a study conducted comparing the COVID-19 and the 1918 Spanish Influenza Pandemics in the United Kingdom, it was confirmed that the two pandemics have extremely similar waves of infection over the course of the pandemic. The two pandemics share some similarities, such as the basic reproductive number (R_0), which is the average number of infected contacts per infected person according to the textbook *Virus as Populations* [20]. The (R_0) of both the 1918 Pandemic and the current COVID-19 pandemic ranges from 2 to 4. Both pandemics also share the characteristics of high fatality rates and rapid spread.

This study used a comparable dispersion parameter (k), which "controls the variance in distribution of the number of secondary cases caused by a typical primary case" [21]. In this study, it was found that the Spanish 1918 Influenza A/H1N1 had a $k = 0.94$ while the COVID-19 has an approximate $k = 0.80$ [21]. Since a small k-value implies a large contribution by super-spreaders (events with many people) to the total number of infections, both the similar and large k-values represent that both the COVID-19 and 1918 Spanish Influenza infections are challenging to control, and easily sustained within a population. Thus, it is important to focus upon individual COVID-19 cases rather than super-spreader events [22]. The COVID-19 vaccine proved to be beneficial because it focused upon the individual and those around them. Because vaccine technology was not advanced in 1918, the data provided by the 1918 Spanish Influenza pandemic could be useful in predicting and improving the outcome of future pandemics.

In another dispersion-based study conducted regarding the risk reduction provided to an entire family by only a few vaccinated family members, it was discovered that the unvaccinated

family members were at a lower risk due to their vaccinated relatives. These results were found in Sweden (mid-2021) by matching 1:1 a person with immunity, from either the COVID-19 vaccine or a previous COVID-19 infection, to a person without COVID-19 immunity in families containing 2 to 5 members. In this study, there were a total of 1789728 people from 814806 families. The risk reduction of contracting a severe COVID-19-related illness for a non-immune family containing a single immune member was 45% to 61% . This risk reduction increased as the number of family members with immunity also increased. In families contain two immune family members, the risk reduction was 75% to 86% , while families containing 3 or 4 family members had a risk reduction that ranged from 91% to 97% [23].

Applying past lessons to the present, not only can the COVID-19 vaccine provide protection to an individual, but it can also help protect an individual's loved ones. Ultimately, as the data reveals, getting vaccinated is a vital strategy to decrease and hopefully eliminate COVID-19. Therefore, when deciding whether to receive the vaccine, think of the people that would have benefited from a vaccine during the 1918 Spanish Influenza. The COVID-19 vaccine is beneficial for more than just the individual that receives it, it is also beneficial for those in proximity.

Conclusion

The COVID-19 pandemic has clearly been detrimental not only in Mississippi, but also in the entire world. By doing an in-depth analysis of the data provided by the Mississippi State Health Department (approximately two years), the overall efficacy of the COVID-19 vaccines has been proven. Despite the politicization of COVID-19 and its vaccine, the efficacy data remains strong. Thus, by following the wise words of John Adams and eliminating the politics surrounding the vaccine, the facts are clear that the COVID-19 vaccine is effective in preventing severe COVID-19-related illnesses, hospitalizations, and deaths.

REFERENCES

1. Medical Media, A. (2021, January 27). *All types of COVID-19 vaccines, how they work, animation.* YouTube. Retrieved March 9, 2022, from https://www.youtube.com/watch?v=osRo-yz1VQ8%29
2. Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Pérez Marc, G., Moreira, E. D., Zerbini, C., Bailey, R., Swanson, K. A., Roychoudhury, S., Koury, K., Li, P., Kalina, W. V., Cooper, D., Frenck, R. W., Hammitt, L. L., … Gruber, W. C. (2020). Safety and efficacy of the BNT162B2 mrna COVID-19 vaccine. *New England Journal of Medicine*, *383*(27), 2603–2615. https://doi.org/10.1056/nejmoa2034577
3. Bååth, R. (n.d.). *Bayesian Beta-Binomial Model*. Yet another visualization of the Bayesian Beta-Binomial model - Publishable Stuff. Retrieved March 9, 2022, from https://www.sumsar.net/blog/2018/12/visualizing-the-beta-binomial/
4. Johnson & Johnson (NYSE: JNJ) (the Company). (n.d.). *Johnson & Johnson*. Content Lab U.S. Retrieved March 9, 2022, from https://www.jnj.com/johnson-johnson-COVID-19-vaccine-authorized-by-u-s-fda-for-emergency-usefirst-single-shot-vaccine-in-fight-against-global-pandemic
5. Fu, W., Li, J., & Scheet , P. (n.d.). *COVID-19 vaccine efficacy: Accuracy, uncertainty ... - medrxivWenjiang Fu1,2*, Jieni Li3 and Paul Scheet*. medRxiv. Retrieved March 9, 2022, from https://www.medrxiv.org/content/10.1101/2020.12.16.20248359v1.full.pdf
6. 2, H. B. F., Branswell, H., Writer, A. the A. R. H. B. S., Writer, H. B. S., says:, J. A., & says:, L. E. B. (2022, February 17). *Comparing the COVID-19 vaccines developed by Pfizer, Moderna, and Johnson & Johnson*. STAT. Retrieved March 9, 2022, from https://www.statnews.com/2021/02/02/comparing-the-COVID-19-vaccines-developed-by-pfizer-moderna-and-johnson-johnson/
7. Chang, A., & Stoffels, D. P. (2021, January 29). *A look at the latest data on Johnson & Johnson's COVID-19 vaccine*. NPR. Retrieved March 9, 2022, from https://www.npr.org/2021/01/29/962190210/a-look-at-the-latest-data-on-johnson-johnsons-COVID-19-vaccine
8. Chambers, C., Chambers, C., Author, Catharine Chambers Contributor Catharine Chambers is a PhD candidate in epidemiology and Vanier Scholar at the Dalla Lana School of Public Health at the University of Toronto., article, R. this, says:, M. W., says:, I., says:, A. H., says:, T., says:, R., Says:, J., says:, C. F., says:, S. Q., says:, V. M., says:, M. I. C. H. A. E. L. T. H. O. M. A. S., says:, B. W., says:, M., says:, C., says:, P. T. S., … says:, R. S. (2022, January 11). *Comparing vaccines: Efficacy, safety and side effects*. Healthy Debate. Retrieved March 9, 2022, from https://healthydebate.ca/2021/03/topic/comparing-vaccines/
9. Cross, R. (2021, March 18). *COVID-19 Vaccine Trials for Kids Ramp Up*. Cen.acs.org. Retrieved March 9, 2022, from https://cen.acs.org/pharmaceuticals/vaccines/COVID-19-vaccine-trials-kids/99/i10
10. Cornish, A., & Maldonado, D. Y. (2021, March 19). *How the COVID-19 vaccine trials in children are going to work*. NPR. Retrieved March 9, 2022, from https://www.npr.org/2021/03/19/979340096/how-the-COVID-19-trials-in-children-are-going-to-work
11. Lopez Bernal, J., Andrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwall, S., Stowe, J., Tessier, E., Groves, N., Dabrera, G., Myers, R., Campbell, C. N. J., Amirthalingam, G., Edmunds, M., Zambon, M., Brown, K. E., Hopkins, S., Chand, M., &

Ramsay, M. (2021). Effectiveness of COVID-19 vaccines against the B.1.617.2 (delta) variant. *New England Journal of Medicine*, *385*(7), 585–594. https://doi.org/10.1056/nejmoa2108891
12. Wadman, M. (2021, August 16). *A grim warning from Israel: Vaccination blunts, but does not defeat Delta*. Science. Retrieved March 29, 2022, from https://www.science.org/content/article/grim-warning-israel-vaccination-blunts-does-not-defeat-delta
13. Bhattacharyya, R. P., & Hanage, W. P. (2022). Challenges in inferring intrinsic severity of the SARS-COV-2 omicron variant. *New England Journal of Medicine*, *386*(7). https://doi.org/10.1056/nejmp2119682
14. Andrews, N., Stowe, J., Kirsebom, F., Toffa, S., Rickeard, T., Gallagher, E., Gower, C., Kall, M., Groves, N., O'Connell, A.-M., Simons, D., Blomquist, P. B., Zaidi, A., Nash, S., Iwani Binti Abdul Aziz, N., Thelwall, S., Dabrera, G., Myers, R., Amirthalingam, G., … Lopez Bernal, J. (2022). COVID-19 vaccine effectiveness against the Omicron (b.1.1.529) variant. *New England Journal of Medicine*. https://doi.org/10.1056/nejmoa2119451
15. Division of Viral Diseases, & (NCIRD), N. C. for I. and R. D. (2022, January 11). *COVID-19 vaccines for children and teens*. Centers for Disease Control and Prevention. Retrieved March 29, 2022, from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/children-teens.html
16. Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M. A., Hernán, M. A., Lipsitch, M., Reis, B., & Balicer, R. D. (2021). BNT162B2 mrna COVID-19 vaccine in a nationwide mass vaccination setting. *New England Journal of Medicine*, *384*(15), 1412–1423. https://doi.org/10.1056/nejmoa2101765
17. Goel, M. K., Khanna, P., & Kishore, J. (2010, October). *Understanding survival analysis: Kaplan-Meier estimate*. International journal of Ayurveda research. Retrieved March 29, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3059453/
18. CDC, C. for D. C. and P. (2021, September 16). *Monitoring incidence of COVID-19 cases, hospitalizations, and deaths, by vaccination status - 13 U.S. jurisdictions, April 4–July 17, 2021*. Centers for Disease Control and Prevention. Retrieved March 29, 2022, from https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e1.htm?s_cid=mm7037e1_w#suggestedcitation
19. Chandra, S., Christensen, J., Chandra, M., & Paneth, N. (2021). Pandemic reemergence and four waves of excess mortality coinciding with the 1918 influenza pandemic in Michigan: Insights for COVID-19. *American Journal of Public Health*, *111*(3), 430–437. https://doi.org/10.2105/ajph.2020.305969
20. Domingo, E. (2020). Long-term virus evolution in nature. *Virus as Populations*, 225–261. https://doi.org/10.1016/b978-0-12-816331-3.00007-6
21. He, D., Zhao, S., Li, Y., Cao, P., Gao, D., Lou, Y., & Yang, L. (2020). Comparing COVID-19 and the 1918–19 influenza pandemics in the United Kingdom. *International Journal of Infectious Diseases*, *98*, 67–70. https://doi.org/10.1016/j.ijid.2020.06.075
22. He, D., Zhao, S., Xu, X., Lin, Q., Zhuang, Z., Cao, P., Wang, M. H., Lou, Y., Xiao, L., Wu, Y., & Yang, L. (2020, October 16). *Low dispersion in the infectiousness of COVID-19 cases implies difficulty in control - BMC public health*. BioMed Central. Retrieved

March 29, 2022, from https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-020-09624-2

23. Nordström, P., Ballin, M., & Nordström, A. (2021). Association between risk of COVID-19 infection in nonimmune individuals and COVID-19 immunity in their family members. *JAMA Internal Medicine*, *181*(12), 1589. https://doi.org/10.1001/jamainternmed.2021.5814