Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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Background & Study Purpose

Covid-19 Covid-19 is an ongoing contagious disease with a high reproductive rate, affecting hundreds of millions of people globally. On March 11, 2020, the World Health Organization (WHO) declared that the Covid-19 outbreak has exceeded the limit of epidemic and become a global pandemic. This suggests that the basic reproductive rate R0 is far larger than 1, so urgent public health action on R0 reduction needs to be taken.

Vaccination vaccination is one of the most effective ways to lower the number of susceptible contacts k, thus lowering the basic reproductive rate R0. It is crucial to examine the efficacy of the vaccine, since it is directly related to the degree to which R0 is controlled. The safety of the vaccine is critical since it is related to the potential for the mass area vaccination.

The recent New York vaccine mandate policy has brought a significant amount of debate and protest. In fact, ever since the introduction of COVID-19 vaccine, anti-vaccination groups have been actively challenging the validity of the vaccines. The reasonings of the anti-vaccination movement include but are not limited to: death due to the vaccine; the mRNA vaccine altering gene expression; obtaining infection after vaccination (ROUQUETTE, 2021). As such, it is urgent to prove the efficacy of COVID-19 vaccine with reliable evidence.

Covid-19, Vaccination, and Epidemiology The pandemic caused devastating medical, economic and social consequences. In order to restore the medical, economic and social normality of the whole world, the need for a safe and efficient vaccine is urgent. This is especially true for those with the highest risk of infections.

The researchers chose to do this analysis since they have previously reported another study proving the phase 1 safety and immunogenicity of the BNT162b2 vaccine candidate from clinical trials. Furthermore, findings from studies conducted in the United States and Germany showed that two doses of BNT162b2 had tremendous efficacy, and minor safety issues. As a result, the vaccine candidate BNT162b2 has progressed to the phase 3.

Research Question

The specific research questions addressed in the paper were whether or not the BNT162b2 mRNA COVID-19 vaccine was effective, how effective it was, and whether or not it was safe for public use and distribution.

This study was not designed to investigate the single dose regimen, but they have found the vaccine efficacy against Covid-19 was 52% during the interval between the two doses. They also intend to assess the BNT162b2 in pregnant women, children younger than 12 years, and those in special risk groups. Moreover, the stability studies and formulation optimization designed for mitigating the cold storage and shipping method of the BNT162B2 vaccine is in progress.

The BNT162b2 vaccine is the intervention that is being tested throughout the study. The goal of this study is to test the safety and efficacy of the BNT162b2 vaccine, so participants are divided into two groups with each group receiving either the placebo or the vaccine. This method allows the researchers to compare the adverse outcomes of both groups and to analyze the effectiveness of BNT162b2 vaccine.

Study Population

The population in which the study is conducted is composed of people sixteen years of age and older. It focuses on people with the highest risk of Covid-19 and its complications, including older adults, people with certain coexisting conditions, front-line workers, as well as younger adults, who recently had an increasing rate of severe Covid-19 infection. Participants should not have conditions that may affect the result of the study. Immunocompromised individuals had different reaction mechanisms to vaccines or the virus, which is why only people who were healthy or had stable health conditions may participate.

The study population was sampled from a source population. The participants were drawn from an interactive web-based system, where anyone who were interested in the study had access. The source population of the study was the people at risk of Covid who sought vaccines. The study population was randomly sampled from 152 spots in six countries, using a stratified sampling of three age groups: 12 to 15 years, 16 to 55 years or older than 55 years. However, the spots chosen were not representative, with most of the spots being in the United States. A total of 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide. The individuals are randomly assigned in a 1:1 ratio to receive two doses of either the placebo or the BNT162b2 vaccine candidate.

The inclusive criteria for the eligibility requirements in the study is composed of being either male or female participants ages 16 or older, being willing and able to comply with all study

procedures, and being healthy or having stable chronic medical conditions including but not limited to HIV, hepatitis B virus or hepatitis C infection. Alternatively, exclusion criteria includes having a medical history of Covid-19, a history of severe reaction associate with any vaccine or allergic reaction to any component of the vaccine, a receipt of medications that prevent Covid-19, treatment with immunosuppressive therapy, a diagnosis with an immunocompromising condition, or being a woman who is pregnant or breastfeeding. The inclusive criteria is reasonable because it emphasizes populations who had the highest risk of Covid-19 infections, such as older adults, and people with medical conditions that cause a weak immune system. It is important to evaluate the safety and efficacy of the vaccine on people with stable chronic medical conditions. The researchers can observe if there are any safety and efficacy differences between the healthy people, and the people with stable chronic medical conditions to conduct further studies. These exclusive criteria are also reasonable because people with a medical history of Covid-19 may have greater resistance to the virus and impact the result and rationality of the study; moreover, it is reasonable to exclude people with problems in immune function not only due to the possibility of them affecting the study result but also due to the potential risk for them to encounter safety issues, which is unethical.

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Hispanic or Latinx	5,266 (27.9)	5,277 (28.0)	10,543 (28.0)
Country — no. (%)			
Argentina	2,883 (15.3)	2,881 (15.3)	5,764 (15.3)
Brazil	1,145 (6.1)	1,139 (6.0)	2,284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
United States	14,460 (76.7)	14,454 (76.7)	28,914 (76.7)
Age group — no. (%)			
16–55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Age at vaccination — yr			
Median	52.0	52.0	52.0
Range	16–89	16–91	16–91
Body-mass index‡			
≥30.0: obese	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)

Table 1. Demographic Characteristics of the Participants in the Main Safety Population.

Study Design and Evidence Quality

Study Design This study is a randomized controlled trial, which randomly assigned participants in 1 to 1 ratio to receive two doses, 21 days apart, of BNT162b2 vaccine injection or the saline placebo (Polack et al., 2020). Randomization clinical trial is the gold standard study design for causal inference since it maximizes the comparability of known and unknown causes of outcomes other than the exposure of interest between groups. According to *Table 1*, it is clear that some known variables, sex, race, country and age, are evenly distributed in vaccine and placebo groups after randomization. Moreover, investigators and participants were unknown about the assigned groups. The use of double blinding preserved the comparability between groups by preventing the biased subjective assessments of investigators and biased behaviors of participants and helped reduce the non-compliance and loss to follow-up rate.

Data Collection The study endpoints were Covid-19 cases occurring at least seven days after the second dose of injection and the adverse reaction within two months of the second dose. Investigators collected the number of cases and surveillance time to analyze the vaccine efficacy. These data were collected by observations, laboratory tests and self-reports. Each type of measurement has its strengths and limitations. The laboratory test reduces the subjective biases with other diseases that have similar symptoms, while some adverse effects could not be measured through objective assessments, so self-reports and observations were necessary to fill this blank.

Exposure The study's exposure is the BNT162b2 vaccine and it was measured by participants who received the BNT162b2 vaccine versus the placebo.

Confirmed Covid-19 The Covid-19 case was confirmed by the presence of at least one respiratory symptom with a positive test by laboratory. The respiratory symptoms included fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, the new loss of taste or smell, sore throat, diarrhea, or vomiting (Polack et al., 2020).

Adverse Events The adverse events were assessed by the scheduled safety clinical assessment and the electronic-diary recorded by participants using an application installed on a provision device or the participant's personal device. The participants were asked to monitor and report local reactions, systemic events and antipyretic medication usages for seven days after each dose through e-diary; If there were any adverse reactions or events that happened beyond this period following the injection, the participants were also requested to report that information to investigators (Polack et al., 2020). Participants received a thermometer with instructions on how to measure oral temperature at home to record information regarding fever and temperature was collected daily through the e-diary during evening (Polack et al., 2020).

Some precautions were regulated to ensure data accuracy. The combinations of laboratory tests and observations complemented one another to minimize misclassification of outcomes. A clinical assessment, including medical history, was performed at the first visit for each participant to establish a baseline medical condition (Polack et al., 2020). The laboratory tests used to confirm Covid-19 infection had to be done at the central laboratory or local testing facility and "investigator is responsible for verifying that data entries are accurate and resolving any discrepancy between study data and participants' medical records" (Polack et al., 2020). Precautions were also taken to ensure the safety of this study, specifically a stopping rule that would be triggered when adverse events are out of proportion.

Temporality The key exclusion criteria of enrollment was the medical history of COVID-19, while a clinical assessment was performed before the injection of the vaccine to establish a baseline of physical conditions. These procedures ensured that exposure, getting BNT162b2 vaccine or placebo, preceded the development of outcomes, infected with COVID-19 and adverse events. Then the temporality of the association was granted.

Before the first dose of injection, the researchers also collected the participants' sex, race or ethnic group, country, age, age at vaccination, and body-mass index, which could be utilized for the analysis of the generalizability of the study results.

Results

Efficacy

The analysis of results was based on the original randomized assignment group, also known as intend-to-treat analysis. For the efficacy outcome, the measure of effect utilized was vaccine efficacy, which could be calculated by 1- incidence risk ratio (Polack et al., 2020). The resulting 99.9% confidence interval of the vaccine efficacy does not include 30% and greatly above 30%, which implies higher efficacy than the original hypothesis that the 98.6% confidence interval of the vaccine efficacy above 30%. 30% is the threshold efficacy for a vaccine to be authorized by FDA, so it should be the null value of the analysis. The resulting efficacy showed that BNT162b2 was effective in preventing Covid-19 disease.

The results were performed in two populations: participants who had no evidence of existing or prior SARS-CoV-2 infection, and participants with and those without evidence of prior SARS CoV-2 infection.

The following 2x2 table shows the Covid-19 cases at least seven days after the second dose among participants who had no evidence of existing or prior SARS-CoV-2 infection:

	Covid-19 Case	Uninfected	Total Participants	Total person-years
BNT162b2	8	18190	18198	2214
Placebo	162	18163	18325	2222
Total	170	36353	36523	4436

Among participants without evidence of prior infection, the number of diseased cases in the vaccine group is 8, with 2214 person-years; the number of diseased in the placebo group is 162, with 2222 person-years.

Incidence Rate Ratio = (8/2214) / (162/2222) = 0.050

Participants without evidence of infection who were vaccinated with BNT162b2, after at least 7 days of the second dose, had a 95% lower rate of Covid-19 infection compared to participants without evidence of infection who were injected with placebo.

The efficacy of BNT162b2 among participants without evidence of prior infection is 95% with a 95% confidence interval of 90.3%-97.6% (Polack et al., 2020).

The table for participants with and those without evidence of prior SARS CoV-2 infection is shown here:

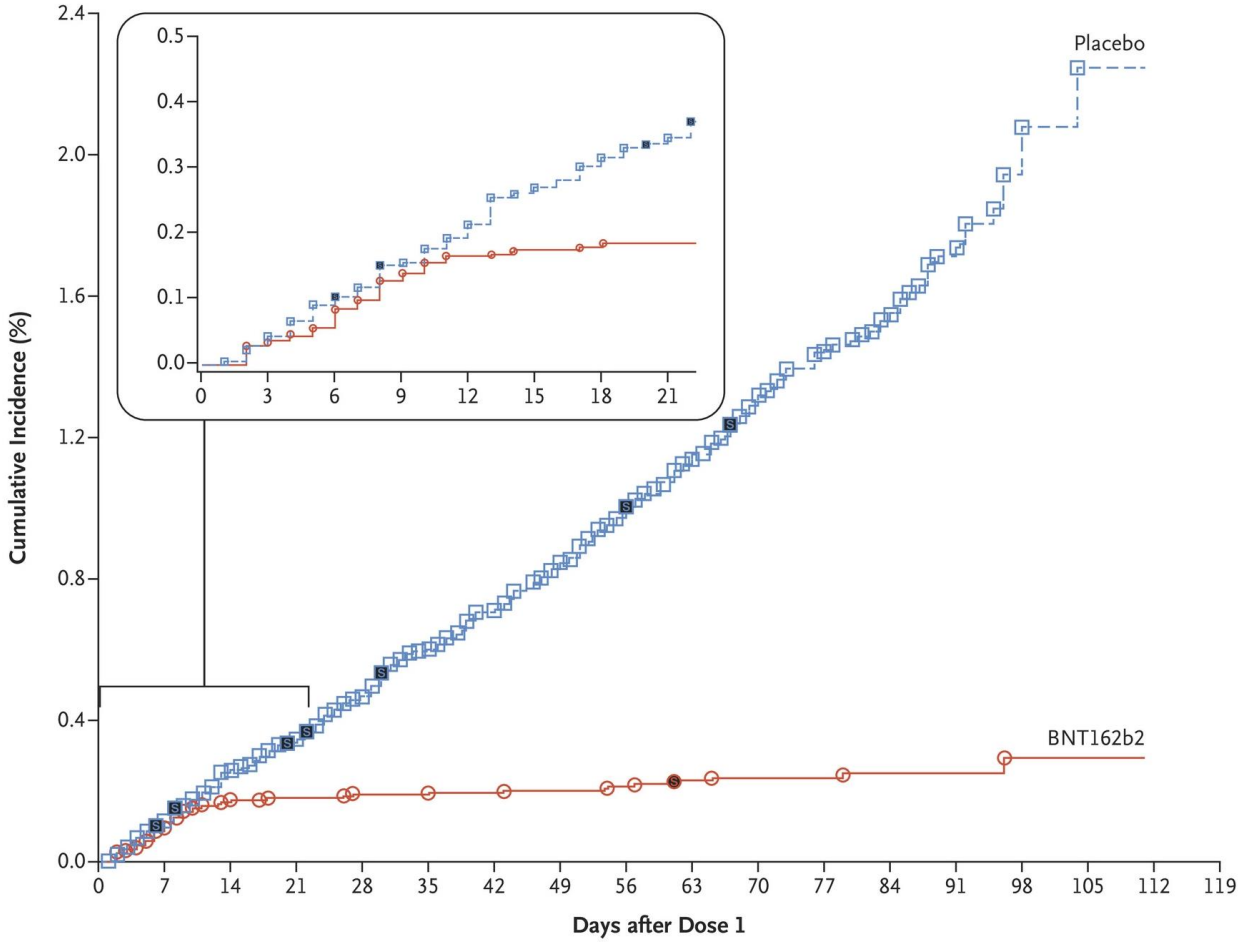
	Covid-19 Case	Uninfected	Total Participants	Total person-years
BNT162b2	9	19956	19965	2332
Placebo	169	20003	20172	2345
Total	178	39968	40137	4677

Among participants with and those without evidence of prior SARS CoV-2 infection, the number of diseased cases in the vaccine group is 9, with 2332 person-years; the number of diseased in the placebo group is 169, with 2345 person-years.

Incidence Rate Ratio = (9/2332) / (169/2345) = 0.054

Participants who were vaccinated with BNT162b2, after at least 7 days of the second dose, had a 94.6% lower rate of Covid-19 infection compared to participants who were injected with a placebo. The efficacy of BNT162b2 among participants with or without evidence of prior infection is 94.6% with a 95% confidence interval of 89.9%-97.3% (Polack et al., 2020).

The association between COVID-19 infection and the BNT162b2 vaccine is protective since the rate ratio is less than 1. Neither 95% confidence intervals include the null value, 30%, so the resulting efficacy is significant at the 0.05 significance level.



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19.

Dose-Response The efficacy against COVID-19 is higher after the second dose of the BNT162b2 vaccine compared to the first dose. Between the first dose and the second dose, 39 Covid-19 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% after the first dose (Polack et al., 2020). An increase of

vaccine efficacy after the second dose, 95%, demonstrated a dose-response relationship between the vaccine and the disease.

Safety

Polack et al. concluded that the safety of the BNT162b2 vaccine over a median of 2 months was similar to that of other viral vaccines (Polack et al., 2020). According to data collected, BNT162b2 recipients reported more adverse events than placebo recipients.

Adverse Events the most commonly reported adverse events were short-term, mild-to-moderate pain at the injection site, fatigue, and headache (Polack et al., 2020). The 2x2 table for any adverse event is shown below:

	Adverse event	Non Diseased	Total Participants who received at least one dose
BNT162b2	5770	15851	21621
Placebo	2638	18993	21631
Total	8408	34844	43252

The number of any adverse event after the first dose is 5770 among 21621 participants who received at least one dose of BNT162b2, while the number is 2638 among 21631 participants who received at least one dose of placebo.

Risk ratio of any adverse event = (5770/21621) / (2638/21631) = 2.19

BNT162b2 recipients, after the first dose, had 2.19 times the risk of getting any adverse event compared with placebo recipients. The association between adverse events and the vaccine is causal since the risk ratio is greater than 1.

Serious adverse events There was no significant difference in the incidence of serious adverse events between the exposed and unexposed groups. The 2x2 table for the serious adverse events is shown below:

	Serious adverse event	Non Diseased	Total Participants who received at least one dose
BNT162b2	126	21495	21621
Placebo	111	21520	21631
Total	237	43015	43252

The number of serious adverse events after the first dose is 126 among BNT162b2 recipients, while the number is 111 among placebo recipients.

Risk ratio of serious adverse event = (126/21621)/(111/21631) = 1.13

BNT162b2 recipients, after the first dose, had 1.13 times the risk of serious adverse events compared with placebo recipients. The risk ratio is close to 1. Thus, Polack et al. concluded that the incidence of serious adverse events was similar in vaccine and placebo groups (Polack et al., 2020).

Types of Biases

Confounders There are several potential confounders that are accounted for in this study such as age, BMI, race, and country. Age is a confounder due to the fact that elders have a higher risk of getting infected by Covid-19 compared to younger age groups, and also have stronger side effects from the infection. Additionally, the older age group is less likely to get vaccinated compared to younger age groups due to the fear of potential negative side effects, and vaccines would not cause aging since age is not on the causal pathway between exposure and disease. This confounder will pull the measure of efficacy away from the null, and the measure of adverse events toward the null. Another confounder that was found through this study was BMI. People with an overweight BMI are more susceptible to Covid-19 because they are less likely to care about their health. Vaccination would not change BMI since BMI is not on the causal pathway between exposure and disease. This confounder will pull the measure of efficacy away from the null. Researchers used random clinical trial to minimize non-comparability in the design phase, and they used stratification to analyze the point estimates of efficacy for subgroups based on age, sex, race, and country in the analysis phase. The efficacy for subgroups of age and gender were close to the overall efficacy, but the efficacy for subgroups such as race and country was different between groups, indicating some covariante effects. Age, gender, race, country and BMI are evenly distributed between the vaccination and placebo groups, so there is a lack of strong evidence regarding non-comparability from confounders in the reported results.

Effect Measure Modifiers The study has some interaction analysis with third variables including gender, race, age, and country. The protective effect towards Covid-19 of the BNT162b2 mRNA vaccine potentially varies between males and females, and among different age groups. Gender difference implies biological genetic variant distinction, which could be the causal partner of the BNT162b2 mRNA on the immunity to the Covid-19 disease and the adverse reactions. Different age groups have significantly different overall underlying physical conditions and lifestyles which could be components of the same causal pie regarding the immunity towards the Covid-19 disease and the adverse reactions with the BNT162b2 mRNA.

The overall rate ratio for the raw data is 0.50.

Males: rate ratio = (3/1124)/(81/1108) = 0.037

Females: rate ratio = (5/1090)/(81/1104) = 0.063

It is found that the rate ratio is significantly different among the male and female groups, so we are able to conclude that gender is an effect measure modification.

Moreover, race and country are variables correlated with many social variables, such as socio-economic status, housing conditions, food security, and medical conditions, which impact the protective effect of the vaccine. The measures of efficacy of the vaccine on Covid-19 are different among gender, race, age, and country groups, so there is evidence regarding effect measure modification of the risk difference scale by gender, age, and country, since the null of efficacy is 0. According to the stratum-specific measure of efficacy, the male group has higher vaccine efficacy compared to the female group. Regarding age, individuals under the age of 55 have higher vaccine efficacy compared to those who are over the age of 55. This evidence implies that the efficacy of the vaccine varies across populations with different distributions of gender and age.

Selection Bias This is a randomized clinical trial, so the potential selection bias is lost to follow up. Procedures that can be used to minimize lost to follow up include the following:

If a participant fails to attend a required study visit, the study site must attempt to contact the participant to reschedule the missed visit as soon as possible. They must also counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant desires to continue the study, and if they should be able to continue in the study.

The investigator must make every effort to regain contact with the participant (3 telephone calls and a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record.

The participants volunteered to enroll in the study, so the participants may have higher risk of Covid-19 exposure compared to non-participants. These individuals include, but are not limited to, public service workers and medical workers. The main reasons for drop-out within this study involved ineligibility and side effects. However, the rate of loss to follow up is similar between exposure groups which emphasizes how there is little potential for selection bias in the study.

Regarding efficacy, the Covid-19 infection has to be confirmed by both the presence of at least one symptom of acute respiratory illness, and also a positive laboratory reading. However, due to the fact that there is no regular routine test for Covid-19, the asymptomatic cases would be misclassified as non-infected cases. If vaccines potentially make people more asymptomatic

during infection, this would be a differential misclassification of outcome in the exposed group. The potential bias would pull the measure of effect toward the null. If there is no difference between exposure groups, this would be a non-differential misclassification of outcome. THis means that the potential bias would pull the measure of effect away from the null.

Safety of Outcomes Participants will be asked to assess redness, swelling, and pain at the injection site. Redness and swelling is measured and recorded using a measuring device. Participants are given a thermometer with instructions on how to measure temperature at home. However, participants need to assess symptoms like vomiting, diarrhea, headache, and fatigue chills themselves. These assessments are subjective and could be easily misclassified, which would be a non-differential misclassification of outcome. The potential bias would pull the measure of effect toward the null.

Strength, Limitation, and Generalizability

Strength Randomized control trials with large sample sizes maximize the compatibility of the distribution of variables other than the exposure of interest, low rate of loss to follow-up, measurement using laboratory test to minimize misclassification, stratification analysis of interaction and confounding

Limitation Adverse events that might be triggered by vaccination, such as chronic heart disease and stroke, can not be assessed in this study, since the time period is not long enough for those kinds of chronic diseases to be onset.

Generalizability Key exclusive criteria from this study population include the medical history of Covid-19, the treatment with the immunosuppressive therapy, and the diagnosis with the immunocompromising condition. These medical conditions are potential causal components of the immunity to Covid-19 disease on the same causal pie with the vaccine. Thus, the results cannot be generalized to the population of people with Covid-19 infection history, immunosuppressive therapy, or an immunocompromising condition. There is evidence that age, gender, and country impact the efficacy of the vaccine, so the results of this study can be generalized to populations with similar distributions regarding age, gender and country, and without a medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with immunocompromising condition. The age distribution in the study population is 57.8% 16–55 year olds, and 42.2% >55 year olds. The gender distribution, on the other hand, is 50.6% male, and 49.4% female. The country distribution is 15.3% Argentina, 6.1% Brazil, 2% South Africa, and 76.7% United States. Since the United States takes up 76.7% of the distribution of countries, a large proportion, the results may be generalized to people older than 16 years of age

who lives in the United States and are free of the history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with the immunocompromising condition.

Conclusion and Implication for Public Health

Conclusion This study has furthered the argument for a protective link between exposure and outcome. Specifically, the BNT162b2 mRNA vaccine showed effectiveness in protection against Covid-19. This study contributed to some aspects of Hill's guidelines, such as temporality, because the injection of the vaccine had necessarily occurred prior to the assessment of the health status of that person; it also contributed to specificity since there is no other explanation for the efficacy of the vaccine; it contributed to strength because the efficacy measured is strong enough; it contributed to biological gradient, since the vaccine efficacy for after the second dose is a lot greater than that for after the first dose and before the second dose, and second dose means more exposure; it also contributed to experiment, as this study illustrated well-designed experimental procedures and carefully assessed outcomes. For example, the subjects went through randomization to receive either the BNT162b2 mRNA vaccine or the placebo, which ensured less biased results and supported causation.

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.

Implication for Public Health This study has the potential to influence public health practice. Since it successfully showed that the BNT162b2 mRNA vaccine is effective and safe, the general public would be more willing to accept the vaccine and would likely take the necessary actions to get vaccinated. The health administrators would also likely distribute the vaccines at a greater rate since it is confirmed to be safe and effective. Additionally, follow-up research can assess the long-term effect of this vaccine, and similar research could be inspired to address new variants of the virus such as Delta and Omicron. Researchers can use a greater sample size than

this study utilized and assess individual health statuses and whether they had any adverse events following the vaccination. The follow-up period should be much longer than the follow-up period in this study in order for long-term vaccination effects to be properly assessed.

Works Cited

[1] ROUQUETTE, P. (2021, July 8). *True or false: Countering the claims of COVID-19 vaccine sceptics*. France 24. Retrieved September 29, 2021, from https://www.france24.com/en/europe/20210708-true-or-false-countering-the-claims-of-covid-19-vaccine-sceptics.

[2] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Marc GP, Moreira ED, Zerbini C, Bailey R. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New England Journal of Medicine. New England Journal of Medicine. 2020; 383:2603-2615.