Placebo-Controlled Efficacy Analysis of the COVID-19 Vaccine

Spring 2024

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Abstract

Keywords

Efficacy, Likelihood, COVID-19, Bootstrap, Estimators

Introduction

The Coronavirus disease (COVID-19) affected millions worldwide. It was imperative to global health that a safe and effective vaccine was developed. In late 2020, a multinational, placebo-controlled, observer-blinded study for the efficacy of the Pfizer-BioNTech BNT16b2 COVID-19 mRNA vaccine was conducted where people ages 16 and older in a 1:1 gender ratio were given two doses of either a placebo or the BNT162b2 vaccine. The efficacy of the vaccine is extremely important, because the goal of vaccination efforts are to save lives. The FDA requires at least 30% efficacy for a new vaccine to be approved, but a much higher percentage is desirable. If the vaccine is not sufficiently effective, than the work put into to developing it would be inefficient, and that work should then be focused on the development of a different vaccine. If the vaccine is sufficiently effective, we can recommend that it be widely used. Our hypothesis is that the BNT162B2 vaccine efficacy is 95%, which we will test using different statistical methods discussed, based on another research effort using Bayesian methods (Polack et al. 2020).

Statistical Methods

The data for positive and negative tests between the placebo and vaccine groups is taken from the previous research on the vaccine efficacy (Polack et al. 2020):

Test	Positive	Negative	Total
Vaccine	8	17403	17411
Placebo	162	17349	17511
Total	170	34752	34922

We denote the random variable T as the number of vaccinated individuals from the 170 COVID cases.

$$T \sim Binom(n = 170, \pi)$$

We can define $\pi = \text{P(Vaccine|COVID)} = \frac{\pi_1}{\pi_1+\pi_2}$, given that the sample sizes for the vaccine and placebo groups are approximately equal. Here, π_1 is the proportion of vaccinated individuals who got COVID and π_2 is the proportion of unvaccinated individuals who got COVID. Moreover, we define the vaccine efficacy as $\psi = \frac{1-2\pi}{1-\pi}$ (Senn 2021). We can then formulate the following hypothesis test:

$$H_0 : \psi_0 = 0.95$$
$$H_1 : \psi_0 \neq 0.95$$

We will use a maximum likelihood estimator to conduct a likelihood ratio test as well as bootstrapped confidence intervals to test our hypothesis.

Maximum Likelihood Estimator

One statistical method that we can use to test our hypothesis is the maximum likelihood estimator (MLE) for our efficacy parameter ψ, which we can call $\hat{\psi}_0^{mle}$ given $t_{obs} = 8$ for our positive tests in the vaccine group. In order to calculate this estimator, we can first write the likelihood function of π based on the PDF of T:

$$L(\pi) = \binom{n}{t}\pi^t(1-\pi)^{n-t}$$

Then we write π in the form $\pi = g(\psi)$, given that $\psi = \frac{1-2\pi}{1-\pi}$. We thus have that $\psi - \psi\pi = 1 - 2\pi$, which becomes $2\pi - \psi\pi = 1 - \psi$, which becomes:

$$\pi = \frac{1-\psi}{2-\psi}$$

Because ψ is the parameter we want to make our estimator,we can rewrite our likelihood function in terms of ψ, still based on the PDF of T for $t_{obs} = 8$:

$$L(\psi) = L(g(\psi)) = L\left(\frac{1-\psi}{2-\psi}\right) = \binom{n}{t}\left(\frac{1-\psi}{2-\psi}\right)^t\left(1-\left(\frac{1-\psi}{2-\psi}\right)\right)^{n-t} = \binom{n}{t}\left(\frac{1-\psi}{2-\psi}\right)^t\left(\frac{1}{2-\psi}\right)^{n-t}$$

Mathematically, it is difficult to do much with just this function, so we can log-transform it to convert it from a product to a sum. We can calculate the log-likelihood function for ψ as shown here:

$$\ell(\psi) = \ln(L(\psi) = \ln\left(\binom{n}{t}\right) + t\ln(1-\psi) - t\ln(2-\psi) - (n-t)\ln(2-\psi) = \ln\left(\binom{n}{t}\right) + t\ln(1-\psi) - n\ln(2-\psi)$$

Our estimator is defined as where the log-likelihood function is maximized by the parameter ψ, and we can find this by computing $\arg\max_{\psi} \ell(\psi|t)$, or in other words, by taking the derivative of this function and setting it equal to 0. So we can calculate $\ell'(\psi) = 0$ here:

$$\frac{d}{d\psi}\ell(\psi) = \frac{d}{d\psi}\ln\left(\binom{n}{t}\right) + \frac{d}{d\psi}t\ln(1-\psi) - \frac{d}{d\psi}n\ln(2-\psi) = \frac{n}{2-\psi} - \frac{t}{1-\psi} = 0$$

We can then solve $\frac{n}{2-\psi} = \frac{t}{1-\psi}$. We get that $n - n\psi = 2t - t\psi$, which becomes $t\psi - n\psi = 2t - n$. Assuming that this critical point is a maximum, we have that our estimator estimator is $\widehat{\psi}_0^{mle} = \frac{2t-n}{t-n}$. We cannot use the estimator on its own to make much inference about our hypothesis. However, e can use our MLE to perform a likelihood ratio test, defined as $W = 2\left(\ell\left(\hat{\psi}_0^{mle}\right) - \ell\left(\psi_0^{null}\right)\right)$. A small W corresponds with statistical significance for rejecting the null hypothesis, and vice versa. For a sufficiently sized n, which we have as $n = 170$, the distribution $W \sim \chi_1^2$ holds, letting us compute a P-value for our hypothesis. We can compute this value of W here as:

$$W = 2\left(\left(\ln\left(\binom{n}{t}\right) + t\ln\left(1-\widehat{\psi}_0^{mle}\right) - n\ln\left(2-\widehat{\psi}_0^{mle}\right)\right) - \left(\ln\left(\binom{n}{t}\right) + t\ln\left(1-\psi_0^{null}\right) - n\ln\left(2-\psi_0^{null}\right)\right)\right)$$

This becomes:

$$W = 2t\ln\left(1-\widehat{\psi}_0^{mle}\right) - 2n\ln\left(2-\widehat{\psi}_0^{mle}\right) - 2t\ln\left(1-\psi_0^{null}\right) + 2n\ln\left(2-\psi_0^{null}\right)$$

Bootstrap

The bootstrap approach involves repeatedly resampling the observed data with replacement to create numerous simulated datasets. For each simulated dataset, we compute the proportions of COVID-19 cases in both groups, and subsequently, the efficacy parameter ψ. This process provides a distribution of the efficacy estimates from which we can derive confidence intervals.

Step-wise we begin by creating two subsets of the data: one for the vaccine group and one for the placebo group. This step ensures that we can accurately calculate the number of subjects and the proportions of COVID-19 cases within each group.

Once the proportions are calculated, we compute the observed efficacy parameter π and subsequently ψ. The parameter π is defined as the proportion of COVID-19 cases in the vaccine group divided by the sum of the proportions in both the vaccine and placebo groups. The efficacy parameter ψ is then calculated using the formula $\psi = \frac{1-2\pi}{1-\pi}$. These parameters provide a basis for comparing the vaccine's efficacy against COVID-19.

To assess the variability of the efficacy estimate, we perform a bootstrap simulation with 10,000 iterations. In each iteration, resample the data with replacement to generate new datasets for both the vaccine and placebo groups. For each bootstrap sample, we recalculate the proportions of COVID-19 cases and subsequently the efficacy parameter ψ. This process generates a distribution of ψ values, which can be used to estimate the confidence interval.

We calculate the 95% confidence interval for the efficacy parameter ψ using the quantiles of the bootstrap distribution. This interval provides a range within which the true efficacy is likely to lie, based on the variability observed in the bootstrap samples.

Results

For our MLE, we can plug in $t_{obs} = 8$ and $n = 170$ to $\widehat{\psi}_0^{mle} = \frac{2t-n}{t-n}$, we get $\widehat{\psi}_0^{mle} = \frac{16-170}{8-170} = \frac{77}{81} = 0.9506$. We can also use the Newton Raphson method to estimate ψ to get the same value, shown in the appendix.

For the likelihood ratio test, we can plug in our values $\widehat{\psi}_0^{mle} = 0.9506$, $\psi_0^{null} = 0.95$, $t = 8$, and $n = 170$ to our W to get:

$$W = 2(8)\ln(1 - 0.9506) - 2(170)\ln(2 - 0.9506) - 2(8)\ln(1 - 0.95) + 2(170)\ln(2 - 0.95) = 0.0012$$

As stated prior, our sample size is large enough to where $W \sim \chi_1^2$, so we can calculate P-value for our hypothesis as $P(W \geq 0.0012) = 0.9726$. This P-value is very large, so we fail to reject the null hypothesis under our likelihood ratio test that the COVID-19 vaccine efficacy is 95%.

For our bootstrap, the analysis was performed with 10000 iterations to ensure a stable estimate of the vaccine efficacy. The observed efficacy, calculated from the original data, was consistent with the findings of Polack et al. (2020). The histogram of the bootstrap ψ values revealed a right-skewed distribution, indicating that most of the bootstrap samples support a high efficacy of the vaccine. The 95% confidence interval for ψ derived from the bootstrap distribution, ranged from 0.91 to 0.98, closely aligning with the Bayesian credible interval reported in the original study.

(Histogram)

(Segmented line graph)

Conclusion

References

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Polack, Fernando P., Stephen J. Thomas, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart, John L. Perez, et al. 2020. "Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine." *New England Journal of Medicine* 383 (27): 2603–15. https://doi.org/10.1056/NEJMoa2034577.

Senn, Stephen. 2021. "S. Senn: 'Beta Testing': The Pfizer/BioNTech Statistical Analysis of Their Covid-19 Vaccine Trial (Guest Post)." *Error Statistics Philosophy.* https://errorstatistics.com/2021/01/17/s-senn-beta-testing-the-pfizer-biontech-statistical-analysis-of-their-covid-19-vaccine-trial-guest-post/.

Appendix

Newton Rhapson MLE Approximation

```
loglik <- function(psi, T, n){
  if (psi > 1 | psi < 0)
    return(NA)
  else
    return(log(choose(n, T)) + (T * log(1 - psi)) - (n * log(2 - psi)))
}

estimation <- maxLik2(loglik = loglik, start = 0.55, method = "NR", tol = 1e-4,
                      T = 8, n = 170)

print(estimation)
```

```
## Maximum Likelihood estimation
## Newton-Raphson maximisation, 6 iterations
## Return code 2: successive function values within tolerance limit (tol)
## Log-Likelihood: -1.944994 (1 free parameter(s))
## Estimate(s): 0.9506174
```

Likelihood Ratio Test Calculation

```
W = (2 * 8 * log(1 - (77 / 81))) - (2 * 170 * log(2 - (77 / 81))) -
    (2 * 8 * log(1 - 0.95)) + (2 * 170 * log(2 - 0.95))

p_value <- round(pchisq(q = W, df = 1, lower.tail=F), 4)
```

Here, W is 0.0012 and the corresponding P-value is 0.9726.

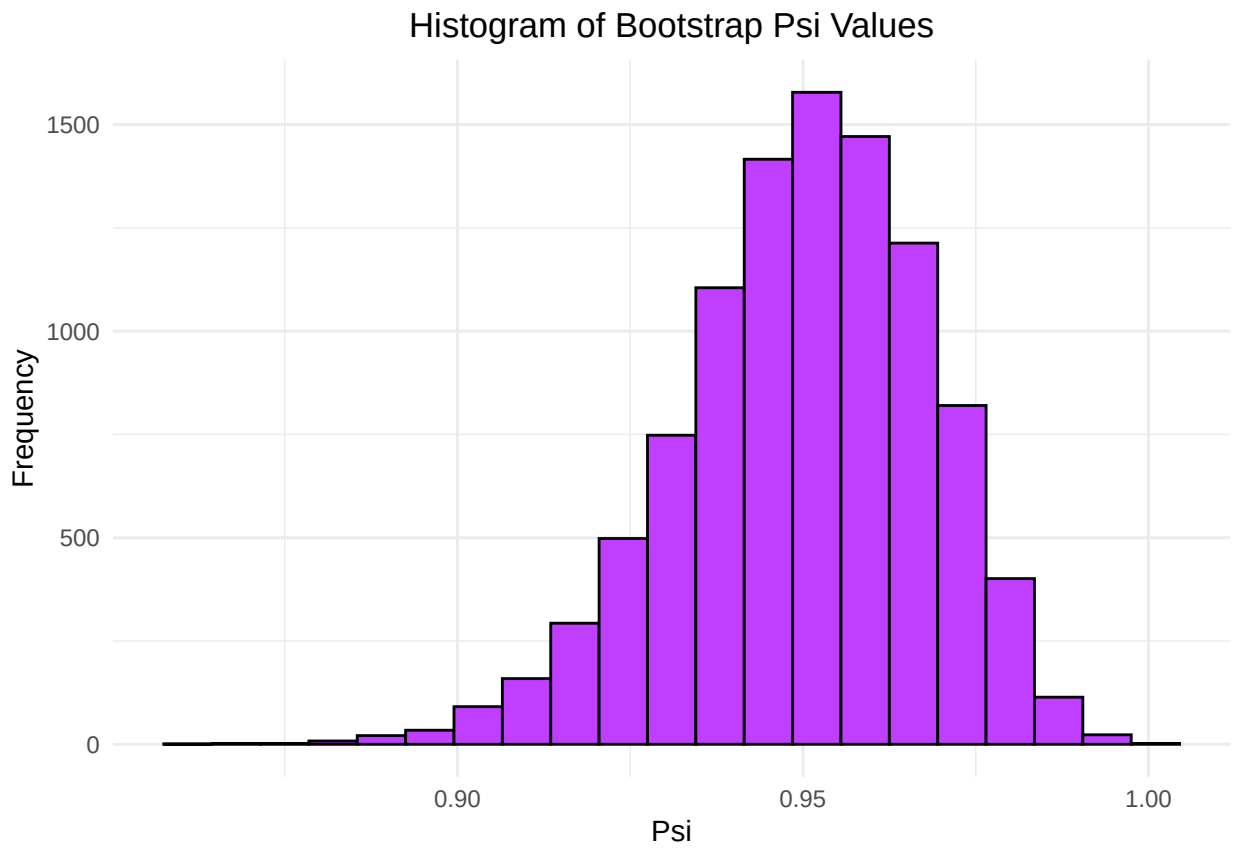
Bootstrap

```
data <- read.csv("data.csv")

vaccine <- data %>%
  filter(Test == "Vaccine")

placebo <- data %>%
  filter(Test == "Placebo")

n_vaccine <- vaccine$COVID + vaccine$No_COVID
```

```r
n_placebo <- placebo$COVID + placebo$No_COVID

prop_vaccine <- vaccine$COVID[1] / n_vaccine
prop_placebo <- placebo$COVID[1] / n_placebo

observed_pi <- prop_vaccine/(prop_vaccine + prop_placebo)

observed_psi <- (1 - 2*observed_pi)/(1 - observed_pi)
```

```r
n_bootstrap <- 10000
bootstrap_psis <- numeric(n_bootstrap)
set.seed(123)

for (i in 1:n_bootstrap) {
  vaccine_sample <- sample(c(0, 1), size = n_vaccine, replace = TRUE,
                           prob = c(1 - prop_vaccine, prop_vaccine))
  placebo_sample <- sample(c(0, 1), size = n_placebo, replace = TRUE,
                           prob = c(1 - prop_placebo, prop_placebo))

  prop_vaccine_boot <- mean(vaccine_sample)
  prop_placebo_boot <- mean(placebo_sample)

  bootstrap_pi <- prop_vaccine_boot / (prop_vaccine_boot + prop_placebo_boot)

  bootstrap_psis[i] <- (1 - 2 * bootstrap_pi) / (1 - bootstrap_pi)
}
```

```r
bootstrap_df <- data.frame(psi = bootstrap_psis)

ggplot(bootstrap_df, aes(x = psi)) +
  geom_histogram(binwidth = 0.007, fill = "darkorchid1", color = "black") +
  labs(title = "Histogram of Bootstrap Psi Values", x = "Psi", y = "Frequency") +
  theme_minimal() +
  theme(plot.title = element_text(hjust = 0.5))
```

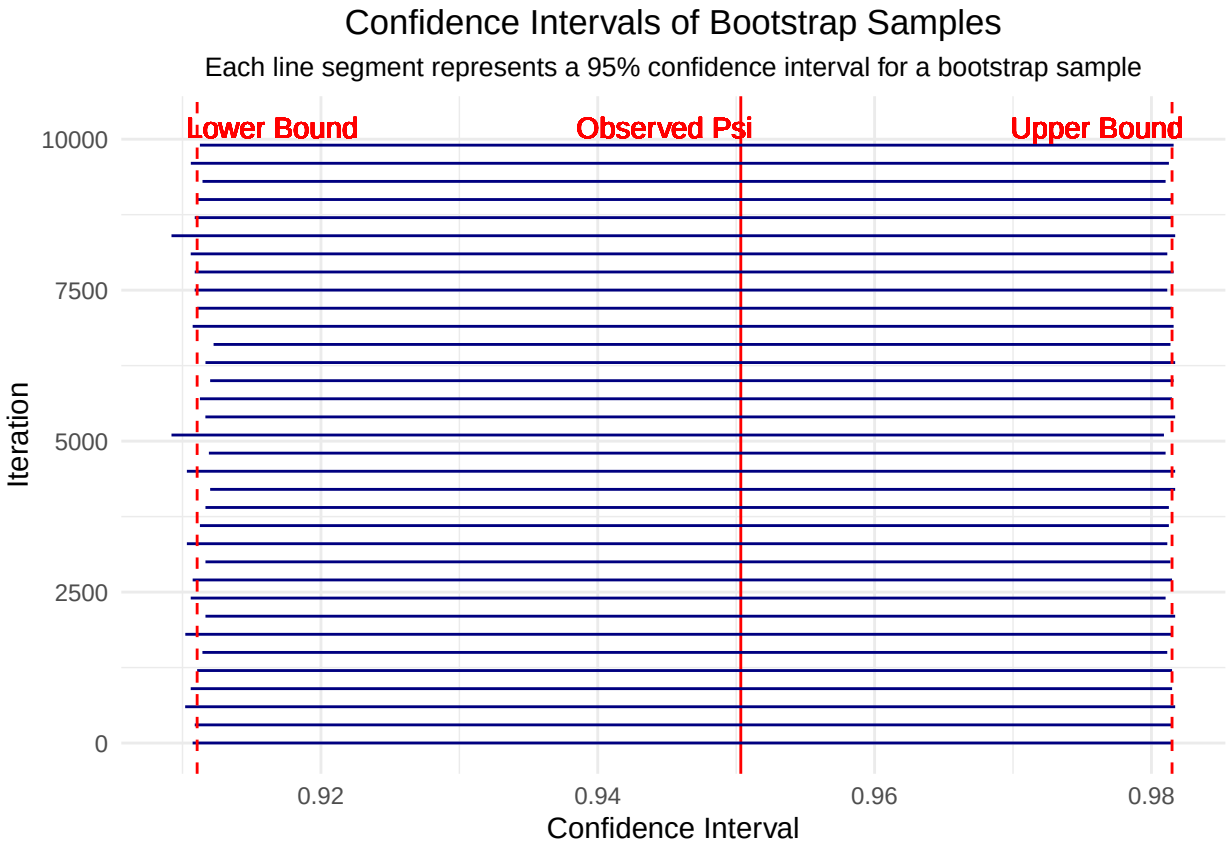



```
overall_ci <- quantile(bootstrap_psis, c(0.025, 0.975))

ci_data <- data.frame(
  Iteration = 1:n_bootstrap,
  Lower = numeric(n_bootstrap),
  Upper = numeric(n_bootstrap)
)

for (i in 1:n_bootstrap) {
  sample_psis <- sample(bootstrap_psis, n_bootstrap, replace = TRUE)
  ci_data$Lower[i] <- quantile(sample_psis, 0.025)
  ci_data$Upper[i] <- quantile(sample_psis, 0.975)
}

print(overall_ci)
```

```
##      2.5%     97.5%
## 0.9110567 0.9814894
```

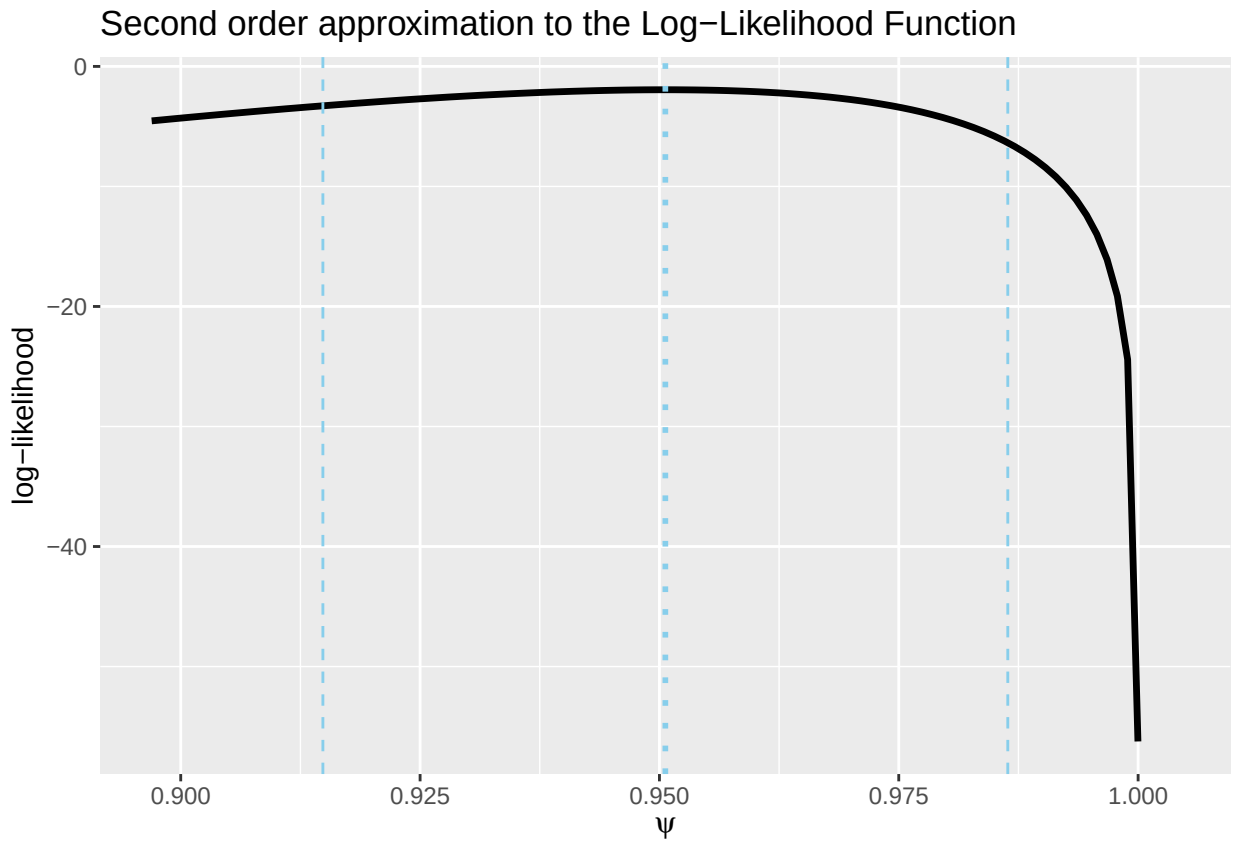
```
plot_data <- ci_data[seq(1, n_bootstrap, by = 300), ]

ggplot(plot_data, aes(y = Iteration)) +
```

```
geom_vline(xintercept = observed_psi, linetype = "solid", color = "red") +
geom_text(aes(x = observed_psi-0.0125,
              y = max(Iteration) + 300, label = "Observed Psi"),
          color = "red", hjust = -0.05) +
geom_segment(aes(yend = Iteration, x = Lower, xend = Upper), color = "navy") +
geom_vline(xintercept = overall_ci[1], linetype = "dashed", color = "red") +
geom_vline(xintercept = overall_ci[2], linetype = "dashed", color = "red") +
geom_text(aes(x = overall_ci[1] + 0.0129,
              y = max(Iteration) + 300, label = "Lower Bound"),
          color = "red", hjust = 1.1) +
geom_text(aes(x = overall_ci[2] - 0.0129, y = max(Iteration) + 300,
              label = "Upper Bound"), color = "red", hjust = -0.1) +
labs(title = "Confidence Intervals of Bootstrap Samples",
     y = "Iteration",
     x = "Confidence Interval",
     subtitle = "Each line segment represents a 95% confidence interval for a bootstrap sampl
theme_minimal() +
theme(plot.title = element_text(hjust = 0.5),
      plot.subtitle = element_text(hjust = 0.5, size = 10),
      axis.text.y = element_text(hjust = 1))
```



Visualizations

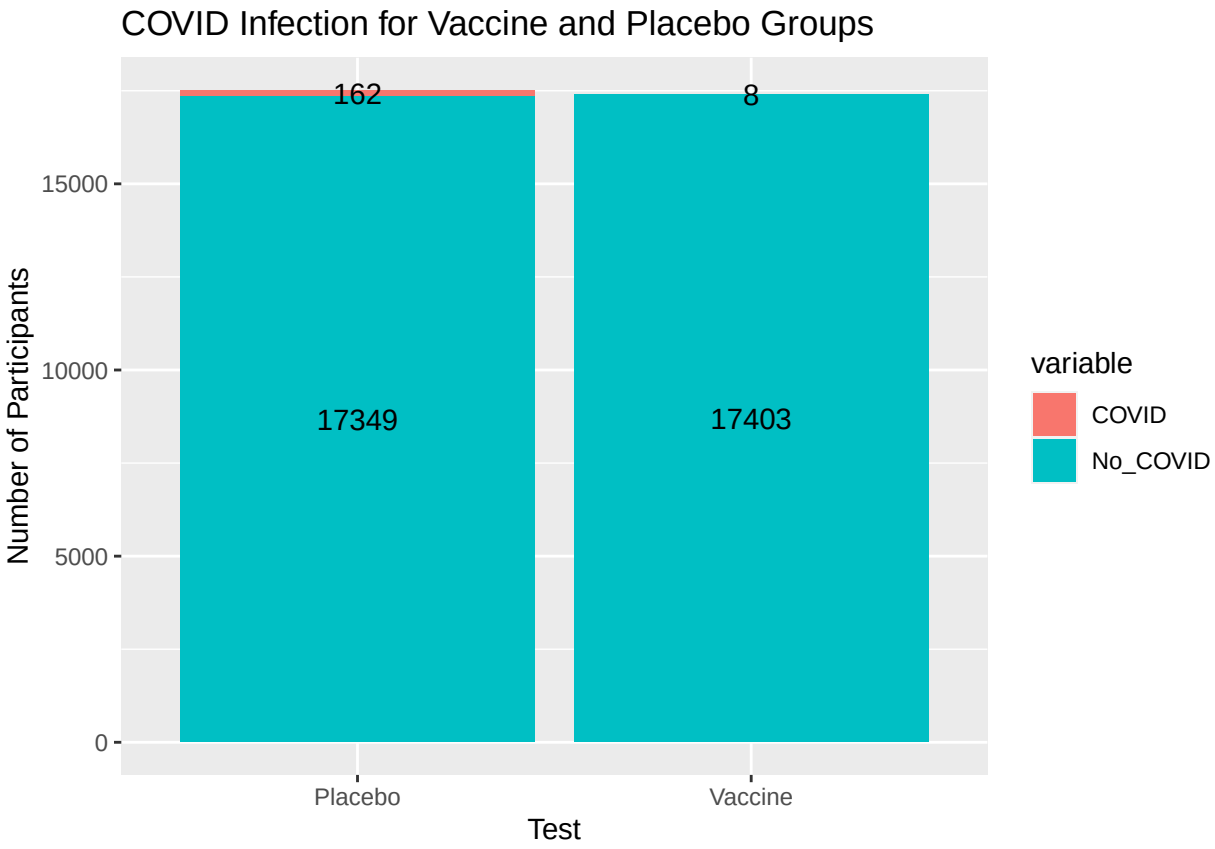
```
plot(estimation) +
    labs(title = "Second order approximation to the Log-Likelihood Function",
         x = expression(psi))
```




```
data_melted <- melt(data, id.vars = "Test")
```

Stacked Barplot

```
ggplot(data_melted, aes(x = Test, y = value, fill = variable)) +
  geom_bar(stat = "identity") +
  geom_text(aes(label = value),
            position = position_stack(vjust = 0.5)) +
  labs(x = "Test", y = "Number of Participants",
       title = "COVID Infection for Vaccine and Placebo Groups")
```


COVID Infection for Vaccine and Placebo Groups
Number of Participants
15000
10000
5000
0
162
8
17349
17403
Placebo
Vaccine
Test
variable
COVID
No_COVID