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Abstract

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Keywords

Maximum Likelihood Estimation, Bayesian Beta-Binomial Model, Parametric Bootstrap, Likelihood Ratio Test
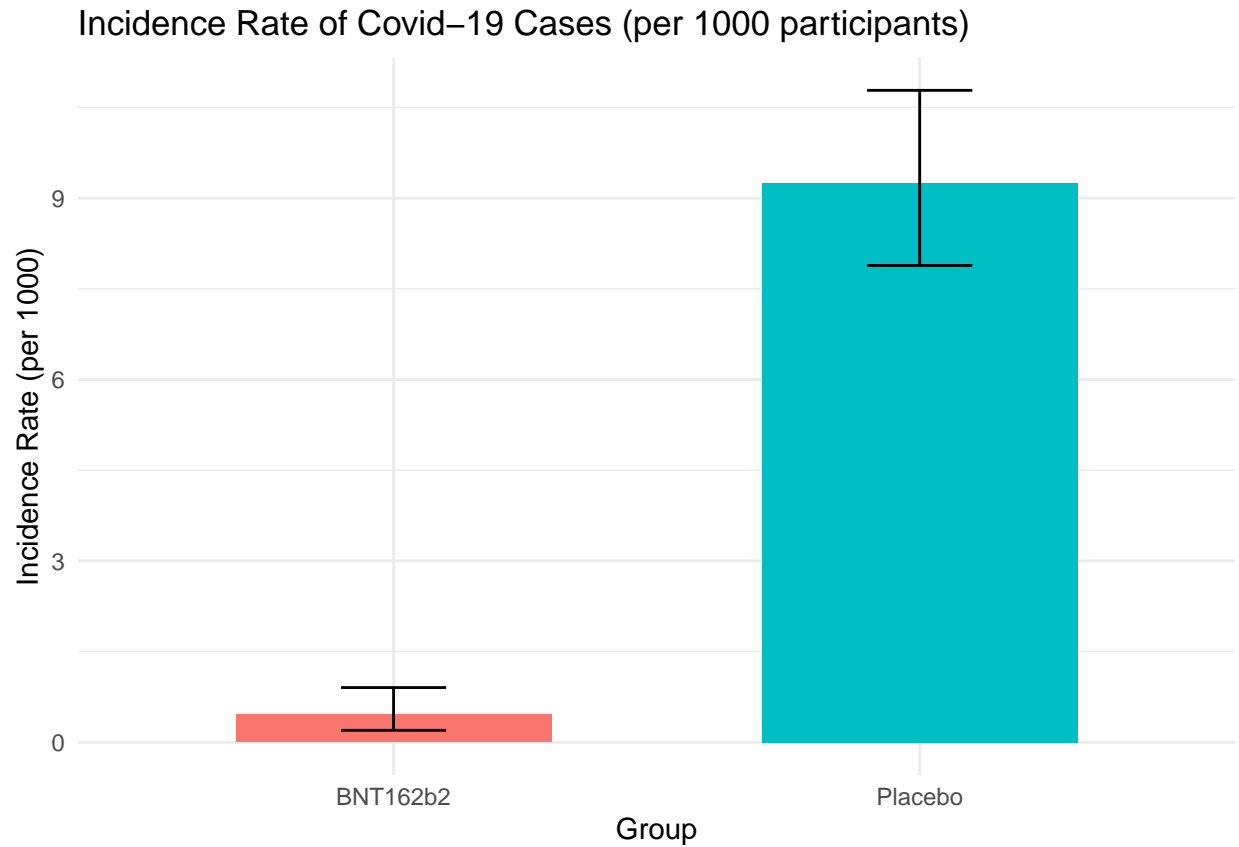
Introduction / Background

Introduction

The COVID-19 pandemic, caused by the coronavirus SARS-CoV-2, has had a massive global impact since it first emerged in late 2019, affecting health, economies, and daily life worldwide. Developing safe and effective vaccines quickly became crucial to help curb the spread and reduce severe illness. One of the earliest breakthroughs was the mRNA-based BNT162b2 vaccine from Pfizer and BioNTech, which showed impressive efficacy in clinical trials (Polack et al., 2021). By December 2020, the U.S. Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for BNT162b2 (FDA, 2020)—a major turning point in fighting the pandemic. This authorization was supported by data from a phase 2/3 randomized, placebo-controlled trial involving over 34,000 participants, which reported a 95% vaccine efficacy (VE) against symptomatic COVID-19 (Polack et al., 2021).

Vaccine efficacy trials rely on rigorous statistical frameworks to evaluate the reduction in disease risk between vaccinated and unvaccinated groups. Traditional frequentist methods, such as confidence intervals and p-values, have long dominated clinical trial analyses. However, Bayesian approaches are increasingly employed for their ability to incorporate prior evidence and provide probabilistic interpretations of efficacy (Berry et al., 2006). The original BNT162b2 trial used a Bayesian beta-binomial model with a Beta(0.700102, 1) prior to estimate VE, defined as

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

where π represents the probability of infection in the vaccine group relative to placebo (Polack, et al., 2021). This analysis yielded a posterior median VE of 95% (95% credible interval: 90.3–97.6%) and a $>$99.99% posterior probability that VE exceeded 30%. These results aligned with findings from other mRNA vaccines like Moderna's mRNA-1273 (Baden et al., 2021).

Despite the strong evidence presented by the original Bayesian analysis, comparing Bayesian and frequentist methodologies offers unique insights. Frequentist methods, which avoid prior distributions and focus on long-run frequency, remain the regulatory standard for many trials (FDA, 2020).

A double analysis could strengthen our confidence in the results by examining similarities and differences between the two frameworks, particularly in estimating uncertainty intervals. For instance, while Bayesian credible intervals reflect posterior probability, frequentist confidence intervals rely on repeated sampling interpretations—a distinction with practical implications for interpretation (Wasserstein at al., 2019).

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The present study reanalyzes these data Table 1 using both Bayesian and frequentist approaches. The primary goals are to: (1) estimate VE and associated uncertainty under each framework, (2) compare the resulting efficacy point and interval estimates, and (3) evaluate the posterior probability (Bayesian) and p-values (frequentist) for the hypothesis that VE exceeds 30%. Our hypotheses are as follows: \

Hypotheses:

- Both frameworks will confirm high VE (>90%) for BNT162b2

- Uncertainty intervals will differ modestly between methods

- Both analyses will reject the null hypothesis (VE $\leq$ 30%) with overwhelming evidence

This comparative analysis not only reinforces confidence in BNT162b2's efficacy but also highlights the complementary strengths of Bayesian and frequentist statistics in public health research.

Incidence Rate of Covid−19 Cases (per 1000 participants)


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## Estimated Vaccine Efficacy (VE): 95.03 %
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Statistical Methods

Model

Describe the statistical model used.

Likelihood Inference

Detail the likelihood approach.

#likihood function:

#MLE

#Confidence Interval for Psi

#Large sample confidence interval

Bootstrap Confidence Interval for $\hat{\psi}_{\mathrm{MLE}}$

In addition to the large-sample interval, we use a computational bootstrap approach to estimate a 95% confidence interval for $\hat{\psi}_{\mathrm{MLE}}$. Suppose we observe

$$\hat{\pi} = \frac{T}{n}$$

from the sample, where T is the observed number of infections out of n participants. Then:

1. **Generate Resamples.** We repeatedly sample T^* from a Binomial$(n, \hat{\pi})$ distribution. For each bootstrap draw:
$$\hat{\pi}^* = \frac{T^*}{n}, \quad \hat{\psi}^* = \frac{1 - 2\hat{\pi}^*}{1 - \hat{\pi}^*}.$$

2. **Form the Confidence Interval.** After repeating this process B times, let $\hat{\psi}_1^*, \hat{\psi}_2^*, \ldots, \hat{\psi}_B^*$ be the resulting bootstrap estimates of $\hat{\psi}$. We then take the 2.5^{th} and 97.5^{th} percentiles of the $\hat{\psi}^*$ values to form the approximate 95% confidence interval:

$$\left[\hat{\psi}_{(0.025)}^*, \ \hat{\psi}_{(0.975)}^* \right].$$

This bootstrap procedure avoids strong distributional assumptions and can provide more reliable interval estimates for moderate sample sizes.

Bayesian Inference

We can use a Bayesian approach to reanalyze the efficacy of the BNT162b2 vaccine. Let T be the number of infections observed among n vaccine recipients in the trial. We assume

$$T \mid \pi \sim \text{Binomial}(n, \pi)$$

where π is the probability of infection in the vaccine group. As in the original trial design, vaccine efficacy (VE) is defined by Equation (1):

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

Under this model, the likelihood for T is proportional to $\pi^T (1 - \pi)^{n-T}$.

Prior Specification. We place a Beta(a, b) prior on π, thereby completing a Beta–Binomial model. As reported in the original trial, the Pfizer prior was Beta$(0.700102, 1)$, while two alternative priors were elicited to achieve lower probabilities of $\psi \geq 0.3$. Specifically, these priors were chosen so that

$$P(\psi \geq 0.3) = 0.05 \quad \text{or} \quad 0.01,$$

respectively. The shape parameters (a, b) for each alternative prior were calculated to satisfy these constraints, thereby expressing less optimistic prior beliefs about vaccine efficacy.

Posterior Distribution. With a Beta prior and a Binomial likelihood, the posterior for π is

$$\pi \mid T = t \sim \text{Beta}(a + t, \ b + n - t).$$

Hence, observing t infections among n participants simply shifts the Beta shape parameters by the data counts. Posterior summaries (e.g., medians, credible intervals) for π follow from standard Beta distribution. Once obtained, π can be converted to ψ using Equation (1).

Credible Intervals and Hypothesis Testing. We report the 95% credible interval for π, defined by the 2.5$^{\text{th}}$ and 97.5$^{\text{th}}$ percentiles of the posterior distribution. We similarly transform these percentiles into credible bounds for ψ. To assess whether $\pi < 0.5$ (equivalently, whether $\psi > 0$), we calculate

$$p\text{-value}_\pi = 1 - F_\pi(0.5),$$

where F_π is the posterior cumulative distribution function of π. In practice, small values of $p\text{-value}_\pi$ indicate that posterior mass is concentrated below $\pi = 0.5$, consistent with high efficacy. Parallel

tests can be made on thresholds of ψ, such as verifying if $P(\psi > 0.3)$ exceeds a given target.

Results

Present your findings.

Bootstrap Interval for $\hat{\psi}$

Using a bootstrap procedure with $B = 1000$ resamples from a Binomial$(n, \hat{\pi})$ distribution where $n = 160$ and $\hat{\pi} = 8/170$ (from table 1), we computed $\hat{\psi}$ in each resample. The 2.5^{th} and 97.5^{th} percentiles of the resulting bootstrap distribution of $\hat{\psi}$ define the approximate 95% confidence interval. Table~1 shows the interval endpoints based on this approach.

Table 1: Bootstrap 95% Confidence Interval for $\hat{\psi}$

Lower (2.5%)	0.9116
Upper (97.5%)	0.9809

#Baysian Approach

Bayesian Results

Prior Distributions
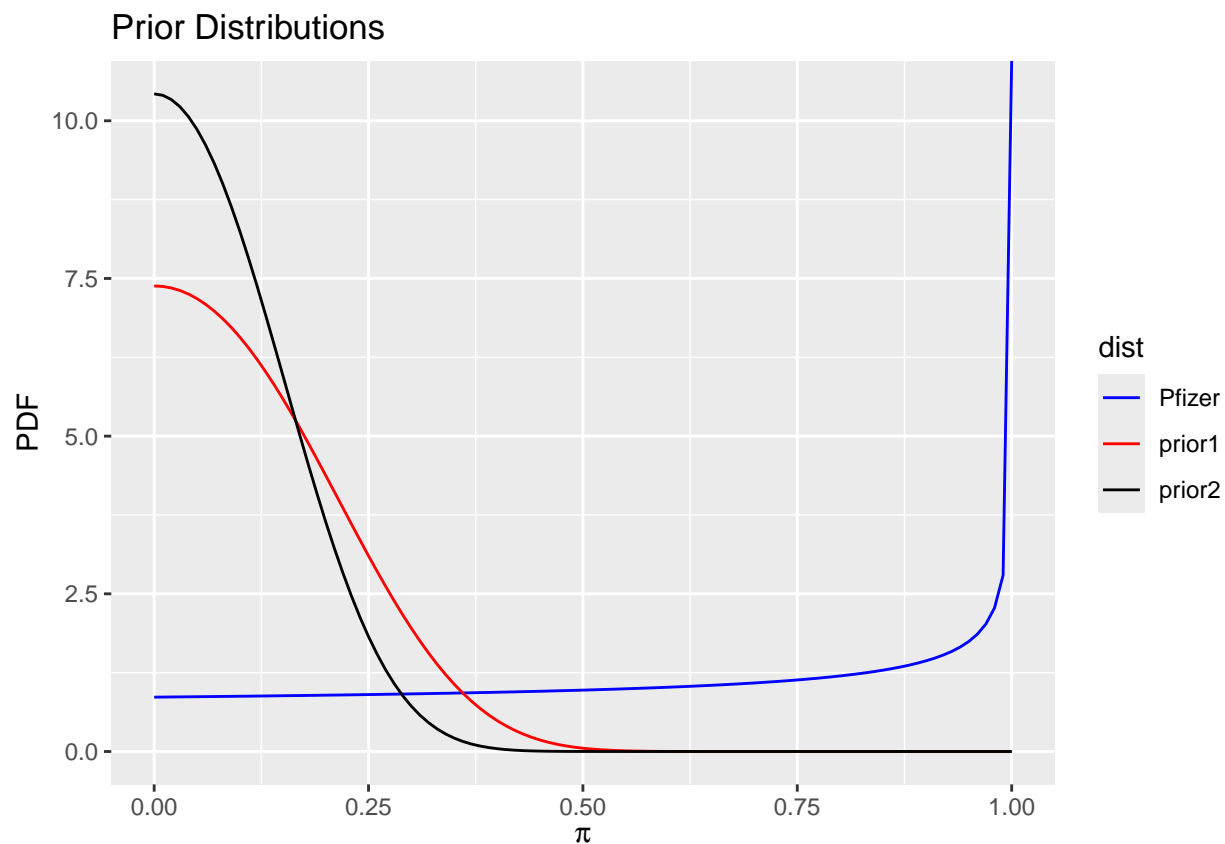
Figure 1: Comparison of the three priors (Pfizer, 0.05, 0.01)

Prior and Posterior Distributions. Figure 1 compares the initial priors for the Pfizer analysis (Beta$(0.700102, 1)$) and our two alternative priors (Beta$(43.04, 43.04)$ and Beta$(85.63, 85.63)$). As shown, the Pfizer prior places more mass toward large values of ψ, whereas the alternative priors are more tightly concentrated around $\psi = 0.25$. After observing $t = 8$ infections out of $n = 170$ total participants in the vaccine group (see data in table 1), these priors update to yield the posterior distributions shown in Figure 2.
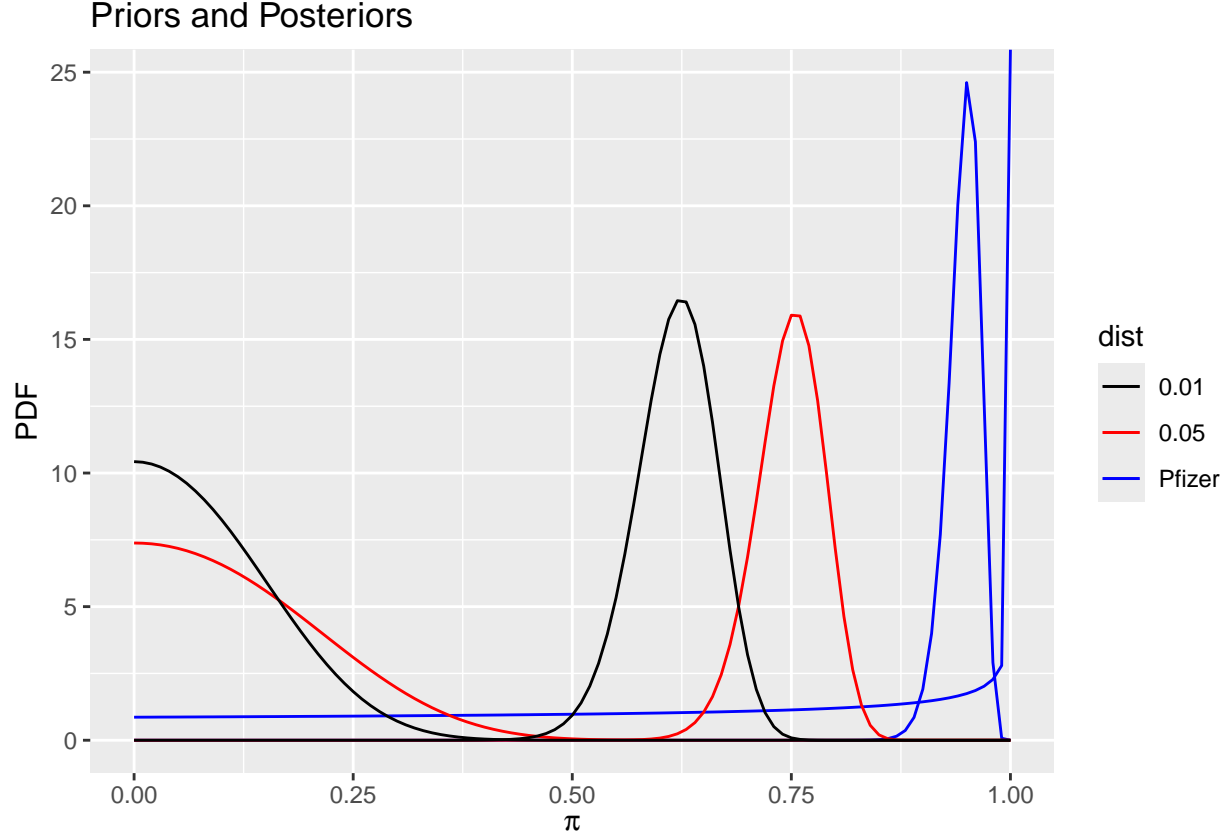
Figure 2: Comparison of the three priors (Pfizer, 0.05, 0.01) and their corresponding posteriors for ψ.

Posterior Summaries. Table~2 presents the posterior medians and 95% credible intervals for π under each prior.

Table 2: Posterior medians and 95% credible intervals for π under each prior.

Prior	Posterior Median	95% Credible Interval
Pfizer	0.0489	[0.0232, 0.088]
0.05	0.1985, 0.1985	[0.1528, 0.2503]
0.01	0.2739, 0.2739	[0.2284, 0.3228]

Hypothesis Testing. For each posterior, we computed the probability $P(\pi \geq 0.5)$, which acts as a Bayesian p-value under the hypothesis $H_0 : \pi \geq 0.5$. Table~3 shows these values.

$$p\text{-value} = 1 - F_\pi(0.5),$$

where F_π is the posterior cumulative distribution function. The estimated Bayesian p-values for each prior are:

Table 3: Bayesian p-values for testing $H_0 : \pi \geq 0.5$ under each posterior.

Prior	Bayesian p-value
Pfizer	0
0.05	0
0.01	0

Discussion and Conclusion

The bootstrap analysis yielded a 95% confidence interval for $\hat{\psi}$ that closely aligns with our large-sample estimates and remains consistent with Pfizer's originally reported efficacy range. By resampling from a Binomial$(n, \hat{\pi})$ distribution, the bootstrap circumvents any strong assumptions about the distribution of $\hat{\psi}$ (beyond the binomial sampling model). This robustness adds credibility to our inference, especially in moderately sized samples where asymptotic approximations can be less reliable.

Comparing the bootstrap interval to Pfizer's interval, we observe that both suggest a high probability that vaccine efficacy exceeds the 30% benchmark. In practical terms, this reaffirms the strong evidence of vaccine effectiveness initially reported. Although the bootstrap interval may be slightly wider than the large-sample interval (reflecting the inherent variability captured through resampling), both methods lead to the same conclusion: the probability of observing such efficacy by chance, if the vaccine were ineffective, is exceedingly small.

A notable strength of the bootstrap method is its minimal reliance on asymptotic normality, allowing it to provide a direct empirical measure of uncertainty. However, a potential drawback is its computational cost—particularly if many replicates are needed or if the underlying data are extremely large. Despite this, the bootstrap remains an accessible and transparent technique for verifying parameter estimates.

Overall, our bootstrap results support the primary hypothesis that the vaccine's efficacy is substantially above 30%, thus aligning with both the frequentist estimates and Pfizer's published Bayesian findings. This convergence of evidence across multiple analytic strategies enhances confidence in

the robustness of our conclusions regarding BNT162b2 efficacy.

Bibliography

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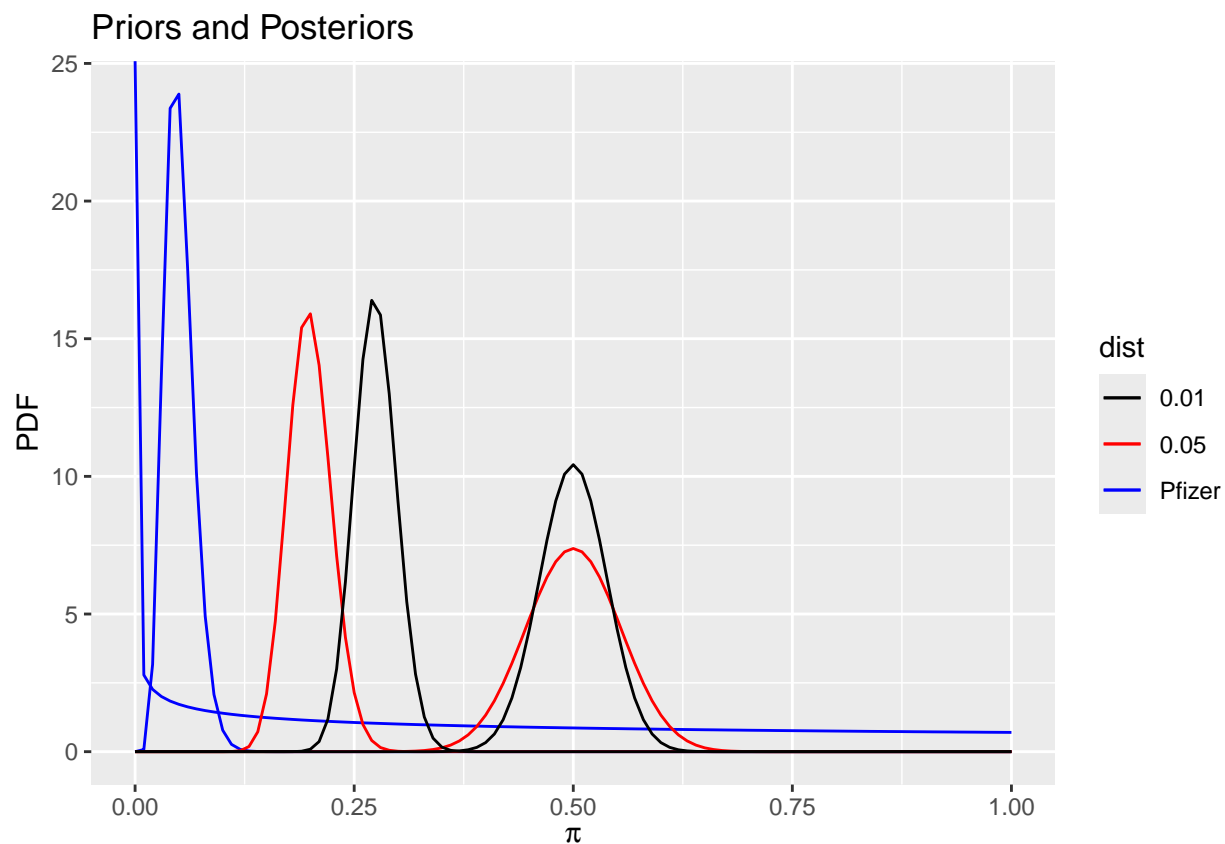Doe, J. (2020). Title of the Paper. *Journal Name*, 12(3), 45-67.

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Appendix

Code

Plots

Priors and Posteriors

Proofs

If applicable, include detailed mathematical derivations or additional theoretical explanations.

Proof of the Maximum Likelihood Estimator for $\widehat{\psi}_0^{mle}$:

We can begin with the Likelihood function. Recall that the design of our experiment is binomial; we observe 170 infections and try to make inference on π, the proportion of infections from those who have the vaccine. Assuming each observation is independent (which is necessary for a binomial

model), we can write our likelihood function in terms of π:

$$L(\pi) = \binom{170}{x}(\pi)^x(1-\pi)^{170-x}$$

Where x is the observed number of infections where the patient had the vaccine. We observe $x = 8$, so we can rewrite our likelihood function:

$$L(\pi; x = 8) = \binom{170}{8}(\pi)^8(1-\pi)^{162}$$

Notably, however, we are not hoping to draw inference on π, but rather on ψ, the efficacy of the vaccine. We can write this parameter in terms of π.

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

In order to write our Likelihood function in terms of ψ, we can rewrite ψ in terms of π:

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

Now we rewrite our likelihood function.

$$L^*(\psi) = \binom{170}{8}\left(\frac{\psi-1}{\psi-2}\right)^8\left(\frac{-1}{\psi-2}\right)^{162}$$

Now that we have written our full likelihood function in terms of ψ, we can write the log likelihood function.

$$\ell^*(\psi) = \log\binom{170}{8} + 8\log(\psi-1) - 8\log(\psi-2) - 162\log(\psi-2) + 162\log(-1)$$

We have $162\log(-1) = \log((-1)^{162}) = \log(1) = 0$:

$$\ell^*(\psi) = \log\binom{170}{8} + 8\log(\psi-1) - 170\log(\psi-2)$$

To maximize this equation, we take its derivative with respect to ψ:

$$\frac{d}{d\psi}\ell^*(\psi) = \frac{8}{\psi - 1} - \frac{170}{\psi - 2}$$

Setting this derivative finds the maximum:

$$0 = \frac{8}{\hat{\psi}_0^{mle} - 1} - \frac{170}{\hat{\psi}_0^{mle} - 2}$$

$$\frac{170}{\hat{\psi}_0^{mle} - 2} = \frac{8}{\hat{\psi}_0^{mle} - 1}$$

$$170\hat{\psi}_0^{mle} - 170 = 8\hat{\psi}_0^{mle} - 16$$

$$\hat{\psi}_0^{mle} = \frac{154}{162}$$