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Warpspeed vaccine vindication and an homage -- Part 3

Nov 10, 2020 *14 mins read*

Yahoo (not the service provider), yippee, and all those other cries of joy. After my last couple of posts what appears this morning…

> *Earlier on Monday, pharmaceutical giant Pfizer and its partner BioNTech said their experimental vaccine was 90% effective in preventing COVID-19. It is the first of the vaccine attempts to reach the clinical milestone. … That news comes from an interim analysis of a study involving 43,538 volunteers, 42% of whom had "diverse backgrounds." … The vaccine proved to be more than 90% effective in the first 94 subjects who were infected by the new coronavirus and developed at least one symptom, the companies said Monday. … While promising, this analysis alone does not provide enough information about the vaccine for Pfizer to ask the FDA for permission to distribute it. … The agency has informed manufacturers that it wants a minimum of two months of follow-up data from at least half of the volunteers. The FDA says the reason for that requirement is that most dangerous side effects from a vaccine occur within two months of getting the final injection. Pfizer says that data won't be available until the third week in November.*

NPR (https://www.npr.org/sections/health-shots/2020/11/09/933006651/pfizer-says-experimental-covid-19-vaccine-is-more-than-90-effective)

I've spent the last two posts exploring vaccine effectiveness **(N.B. I have no data on safety this is just about effectiveness)**, and what should appear this morning but more data (always a good thing). Leaving aside the good news for humanity it means my timing is great and I get to have more fun as well as following through on my plan to show a little respect for a great book.

In my last two posts I did some basic statistical analysis of how confident we should feel about the effectiveness of a vaccine for COVID-19 (Operation Warpspeed). A reminder I'm not an epidemiologist, I don't have any data for safety, and we're still quite early in the Phase III trials – just past the point at which they can take a first "peek" at the data (which is doubleblind). You'll be best served if you've already read the previous post.

You can also read the full study design and justification online although it runs to 136 pages before references.

That's where we'll pick up in this post. First let's load some essential libraries.

```
library(dplyr)
library(ggplot2)
library(kableExtra)
theme_set(theme_bw())
```

Last time

Last time we used a variety of bayesian tools and techniques to model our potential results. At the time we were looking at Moderna possibilities, as it turns out Pfizer got there first (the more successful candidates the better as far as I'm concerned).

Since each of the trials is slightly different in terms of numbers let's replicate the little table from the first post about effectiveness. That gave us estimates for the rate of infection for both those who received the placebo and those who received the actual vaccine.

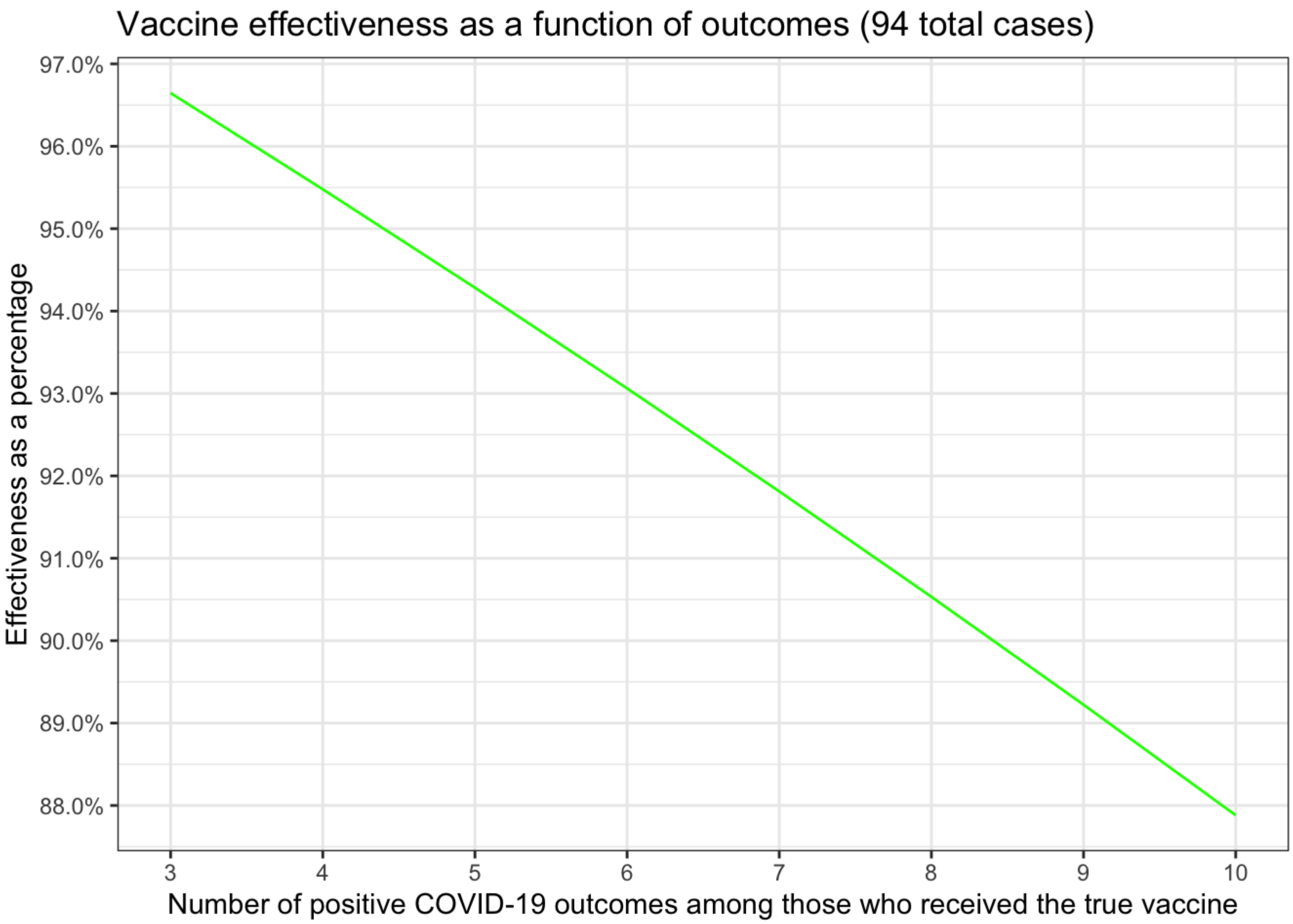
$$\frac{placebo\ infection\ rate - vaccinated\ infection\ rate}{placebo\ infection\ rate} \times 100$$

This gives us what we really want to investigate which is the percentage difference in infection rates. We're looking for (since we multiplied by 100) a number that is above 90. Here's the little table and chart we made in the first post updated for the Pfizer data.

Table 1: Effectiveness as a function of positive COVID cases

Covid Cases (94)		Infection Rate		% difference in rate
vaccinated	placebo	placeborate	vaccinatedrate	effectiveness
3	91	0.0042	0.00014	96.65
4	90	0.0041	0.00019	95.48
5	89	0.0041	0.00023	94.28

Covid Cases (94)		Infection Rate		% difference in rate
vaccinated	placebo	placeborate	vaccinatedrate	effectiveness
6	88	0.0040	0.00028	93.06
7	87	0.0040	0.00033	91.81
8	86	0.0039	0.00037	90.53
9	85	0.0039	0.00042	89.22
10	84	0.0038	0.00046	87.88



Okay now that you're caught up let's push our bayesian skills even farther.

Last post we used several different tools to explore our confidence and the credibility of the data. We used `bayesAB`, `ggdist`, `bayestestR`, `brms`, `tidybayes` and `STAN` to name more than a few. They all produced comparable results which echoed our initial homespun foray from the first post.

Today we're going to use the new Pfizer data and take one more look while paying homage to *Doing Bayesian Data Analysis* by Dr. John K. Kruschke. Hereafter, simply **DBDA**. It's a classic and was my first academic foray into the topic. As opposed to just using tools in R. There are newer books and newer tools but it really does stand the test of time. Having been effusive in my praise which is well deserved I must confess that from the perspective of R code and tools it feels a bit quaint. It was written to make sure that it worked well on a variety of platforms in a much earlier time for beginners. A spectacular feat. But I want to explore the topic with less code and more modern tools.

In chapter 8 (*8.4 – EXAMPLE: DIFFERENCE OF BIASES*) Kruschke explores an example of the differences between two coins using `R`. Actually, he starts the example in 7.4 with an eerily on point example of a drug trial! In today's post we're going to simply adapt the code and modrnize it a bit with some more current R tools to use on our warpspeed trials.

The original DBDA code envisions our Pfizer data as a long dataframe with two columns. One column has information about whether or not the participant tested positive for COVID-19 the other column has information about whether they received the "true" vaccine or a placebo. It's 43,538 rows, 21,999 of whom received the "true" vaccine stored in column `s`, column `y` has Yes or No as a character vector for whether they tested positive for COVID-19. This is where our split is 8 & 86 for the 94 cases. We'll take a `glimpse` and build a quick `table` to make sure we got it right.

```
pfizer_data <-
   data.frame(
      y = c(rep("No", 21999 - 8),
            rep("Yes", 8),
            rep("No", 21539 - 86),
            rep("Yes", 86)),
      s = c(rep("vaccinated", 21999),
            rep("placebo", 21539))
      )

glimpse(pfizer_data)
```

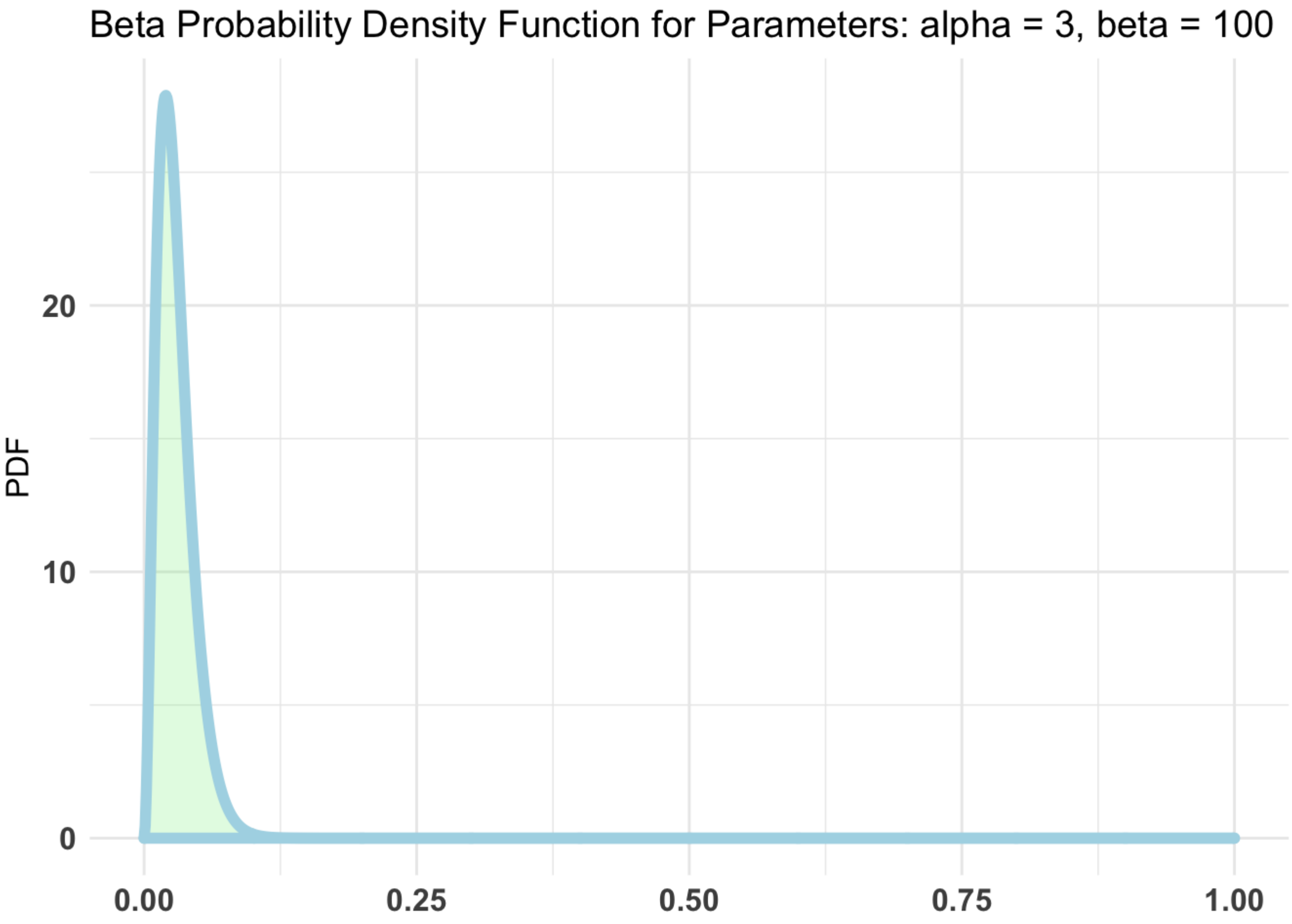
```
## Rows: 43,538
## Columns: 2
## $ y <chr> "No", "No", "No", "No", "No", "No", "No", "No", "No", "No", "No", "…
## $ s <chr> "vaccinated", "vaccinated", "vaccinated", "vaccinated", "vaccinated…
```

```
table(pfizer_data$s, pfizer_data$y)
```

```
##
##                  No   Yes
##   placebo    21453    86
##   vaccinated 21991     8
```

In my earlier posts I have been using a flat uninformed prior. That's not "bad" since in bayesian inference an abundance of data, as we have, will overcome (correct/update) the priors even if they are off, that's the point. But just to be a little more accurate let's pick priors that are more like our beliefs. **Remember** that these priors are not about our belief in how effective the vaccine is, rather they are about our prior knowledge of how likely it is to get COVID-19 in either condition $\theta[1]$ and $\theta[2]$. We could express different values for each but we won't. We just want a prior that expresses our knowledge that for both of them infection rates are very low – whether they received the placebo or the true vaccine the likelihood of contracting COVID-19 appears to be less than 1%. Using `bayesAB::plotBeta(3, 100)` to plot it something like this.

```
bayesAB::plotBeta(3, 100)
```



We’re treating COVID-19 outcomes as simple binomial equations (a coin flip if you will). But **both** of our coins are unlikely to have equal numbers of positive versus negative cases. That leads us to expressing our model in the JAGS language before we feed it to `run.jags`. To simply quote from **DBDA**

> *In the above code, notice that the index i goes through the total number of data values, which is the total number of rows in the data file. So you can also think of i as the row number. The important novelty of this model specification is the use of “nested indexing” for theta[s[i]] in the dbern distribution. For example, consider when the for loop gets to i = 12. Notice from the data file that s[12] is 2. Therefore, the statement y[i] ~ dbern(theta[s[i]]) becomes y[12] ~ dbern(theta[s[12]]) which becomes y[12] ~ dbern(theta[2]). Thus, the data values for subject s are modeled by the appropriate corresponding θs.*

```
# THE MODEL.
modelString <- "
  model {
    for ( i in 1:Ntotal ) {
      y[i] ~ dbern( theta[s[i]] )
    }
    for ( sIdx in 1:Nsubj ) {
      theta[sIdx] ~ dbeta(3 , 100)
    }
  }
  " # close quote for modelString
```

So we have a dataframe with our Pfizer data, priors, and a model. What we need to do now is make sure the data is in a format `run.jags` can understand and express any preferences we have for starting values for our chains. The data is pretty straight-forward and hopefully a little clearer than the way **DBDA** approaches it. Our model tells us we need 4 data elements, `y`, `s`, `Ntotal`, and `Nsubj`. Let's get these right from `pfizer_data` on the fly. We know that `pfizer_data$y` is either `character` or `factor` so a simple `ifelse` gets us to the 0/1 format we need. `s` also needs to be numeric but an integer starting at 1 for however many categories there are so we'll force to factor and then integer. `Ntotal` is simply the total number of particpants `nrow` and `Nsubj` the number of categories for `s`. Voila.

```
# Specify the data in a list, for later shipment to JAGS:
dataList = list(
   y = ifelse(pfizer_data$y == "No", 0, 1),
   s = as.integer(factor(pfizer_data$s)),
   Ntotal = nrow(pfizer_data) ,
   Nsubj = nlevels(factor(pfizer_data$s))
)
```

`runjags::run.jags` is actually very good about setting initial values but for the practice we'll develop our own little function. The doco says "or a function with either 1 argument representing the chain or no arguments." Since we plan on running it in parallel we'll make use of the `chain` parameter. The doco states "The special variables '.RNG.seed', '.RNG.name', and '.RNG.state' are allowed for explicit control over random number generators in JAGS." Again, the default behavior is perfectly fine but while we're playing we may as well. So for our random number generation we'll use `base::Super-Duper`. To generate reasonable distinct initial $\theta[1]$ and $\theta[2]$ values for each parallel process we'll use a small for loop and `sample` the actual data. The `0.001 + 0.998 * sum(resampledy) / length(resampledy)` code is an idea from **DBDA** to keep us from accidentally going to zero. We test it against a notional chain = 3.

```
initsfunctionX <- function(chain) {
   .RNG.seed <- c(1:chain)[chain]
   .RNG.name <- rep("base::Super-Duper", chain)[chain]
   theta <- rep(sum(dataList$y) / length(dataList$y), dataList$Nsubj)
   for (i in min(dataList$s):max(dataList$s)) {
      resampledy <- sample(dataList$y[dataList$s == i], replace=TRUE )
      theta[i] <- 0.001 + 0.998 * sum(resampledy) / length(resampledy)
   }

   return(list(.RNG.seed = .RNG.seed,
               .RNG.name = .RNG.name,
               theta = theta))
}

initsfunctionX(3)
```

```
## $.RNG.seed
## [1] 3
##
## $.RNG.name
## [1] "base::Super-Duper"
##
## $theta
## [1] 0.005262779 0.001226828
```

Okay now we have all the requisite pieces let's roll. 4 chains in parallel each sampling 15,000 with the default burnin = 4000. The chains converge nicely. No problems with auto-correlation or cross correlation.

```
pfizer_chains <-
   runjags::run.jags(modelString,
                     sample = 15000,
                     n.chains = 4,
                     method = "parallel",
                     monitor = "theta",
                     data = dataList,
                     inits = initsfunctionX)
```

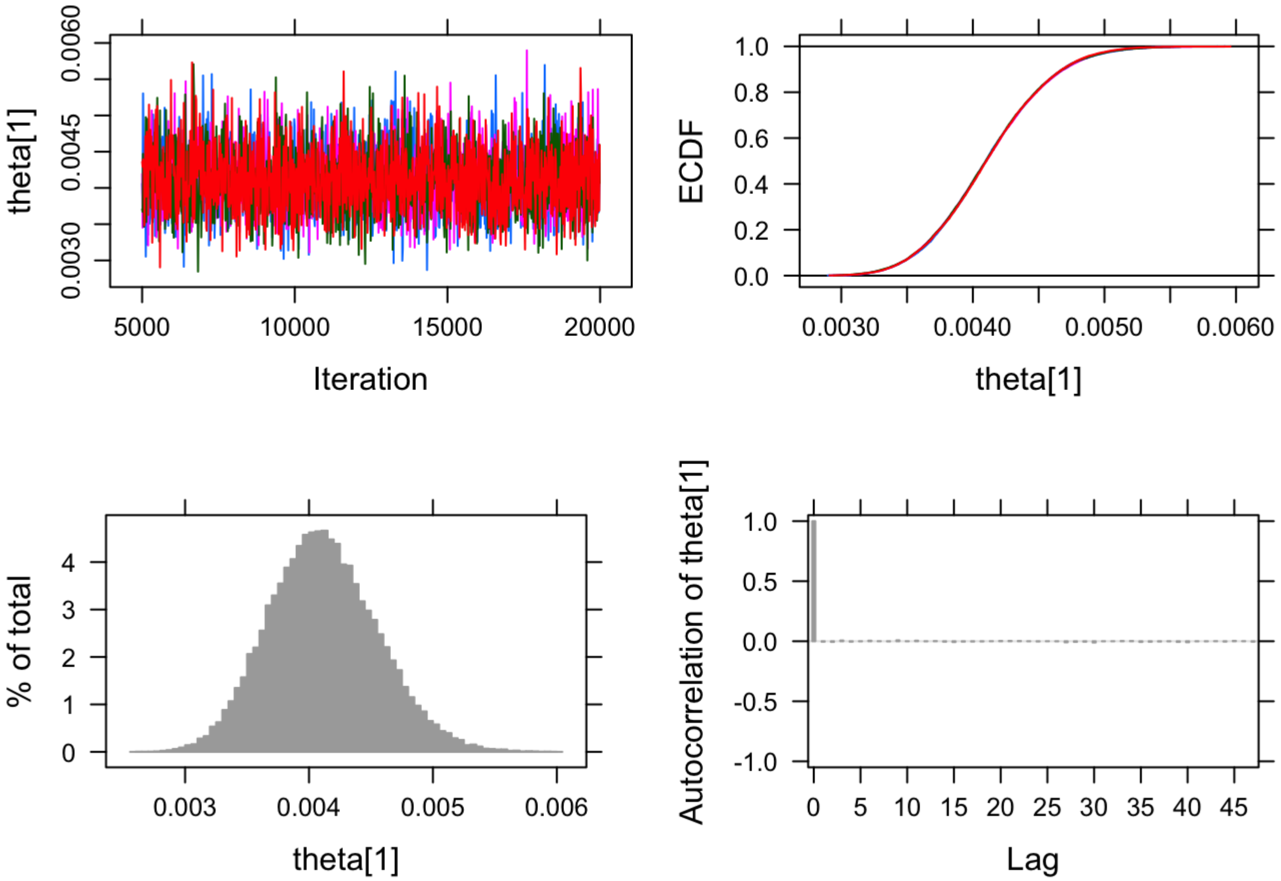
```
## Calling 4 simulations using the parallel method...
## Following the progress of chain 1 (the program will wait for all chains
## to finish before continuing):
## Welcome to JAGS 4.3.0 on Tue Nov 10 15:24:57 2020
## JAGS is free software and comes with ABSOLUTELY NO WARRANTY
## Loading module: basemod: ok
## Loading module: bugs: ok
## . . Reading data file data.txt
## . Compiling model graph
##    Resolving undeclared variables
##    Allocating nodes
## Graph information:
##    Observed stochastic nodes: 43538
##    Unobserved stochastic nodes: 2
##    Total graph size: 87082
## . Reading parameter file inits1.txt
## . Initializing model
## . Adaptation skipped: model is not in adaptive mode.
## . Updating 4000
## -------------------------------------------------| 4000
## ************************************************** 100%
## . . Updating 15000
## -------------------------------------------------| 15000
## ************************************************** 100%
## . . . . Updating 0
## . Deleting model
## All chains have finished
## Note: the model did not require adaptation
## Simulation complete.  Reading coda files...
## Coda files loaded successfully
## Calculating summary statistics...
## Calculating the Gelman-Rubin statistic for 2 variables....
## Finished running the simulation
```

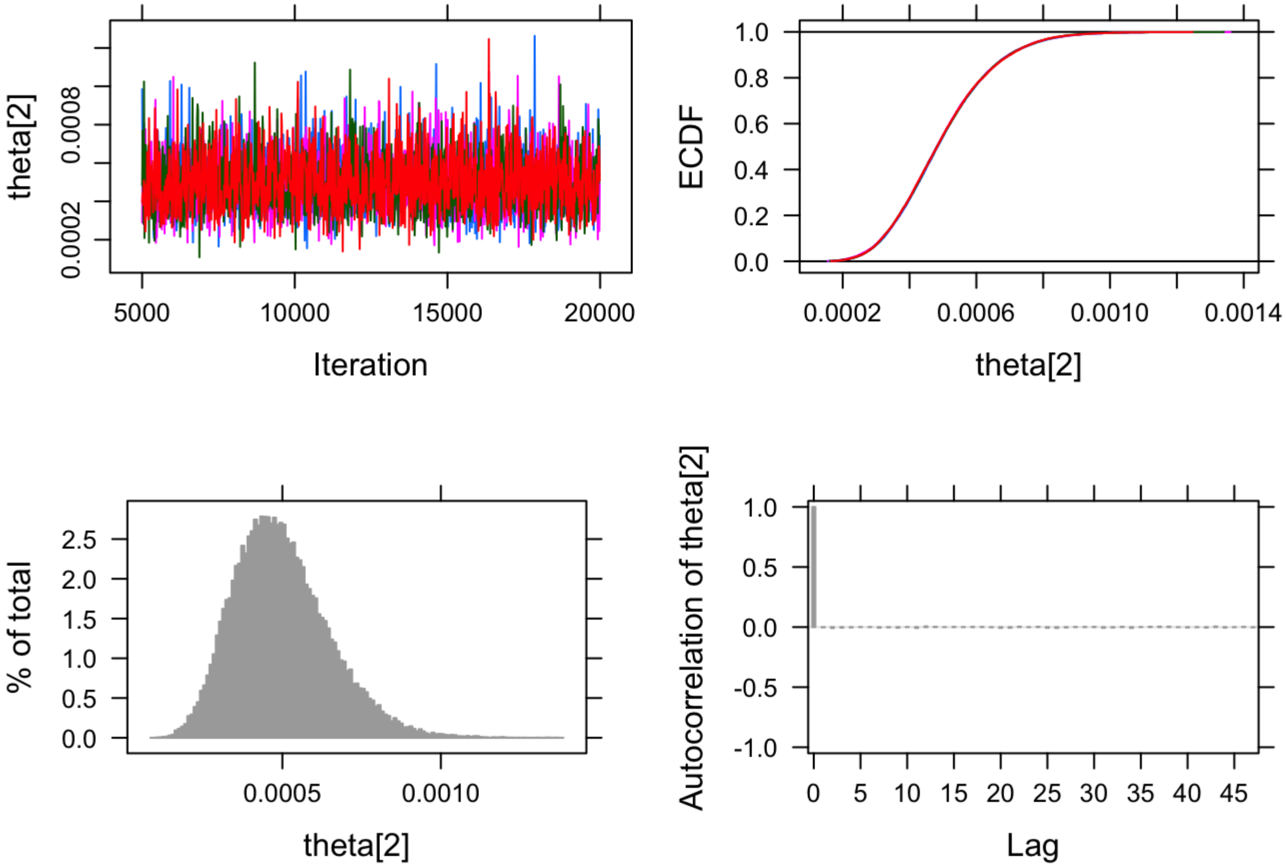
```
summary(pfizer_chains)
```

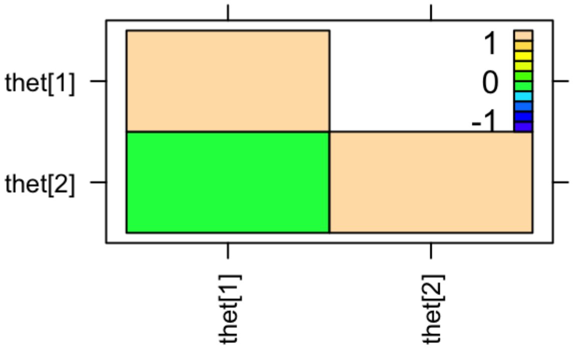
```
##              Lower95       Median     Upper95         Mean           SD Mode
## theta[1] 0.003266840 0.0041005650 0.004955990 0.0041170315 0.0004329743   NA
## theta[2] 0.000227758 0.0004830805 0.000801565 0.0004981343 0.0001504770   NA
##                 MCerr MC%ofSD SSeff         AC.10     psrf
## theta[1] 2.168746e-06     0.5 39857 -0.0001435265 1.000007
## theta[2] 7.432855e-07     0.5 40985  0.0006641947 1.000047
```

```
plot(pfizer_chains)
```

```
## Generating plots...
```


theta[1]
0.0030
0.0045
0.0060
5000
10000
15000
20000
Iteration
ECDF
1.0
0.8
0.6
0.4
0.2
0.0
0.0030
0.0040
0.0050
0.0060
theta[1]
% of total
4
3
2
1
0
0.003
0.004
0.005
0.006
theta[1]
Autocorrelation of theta[1]
1.0
0.5
0.0
-0.5
-1.0
0
5
10
15
20
25
30
35
40
45
Lag

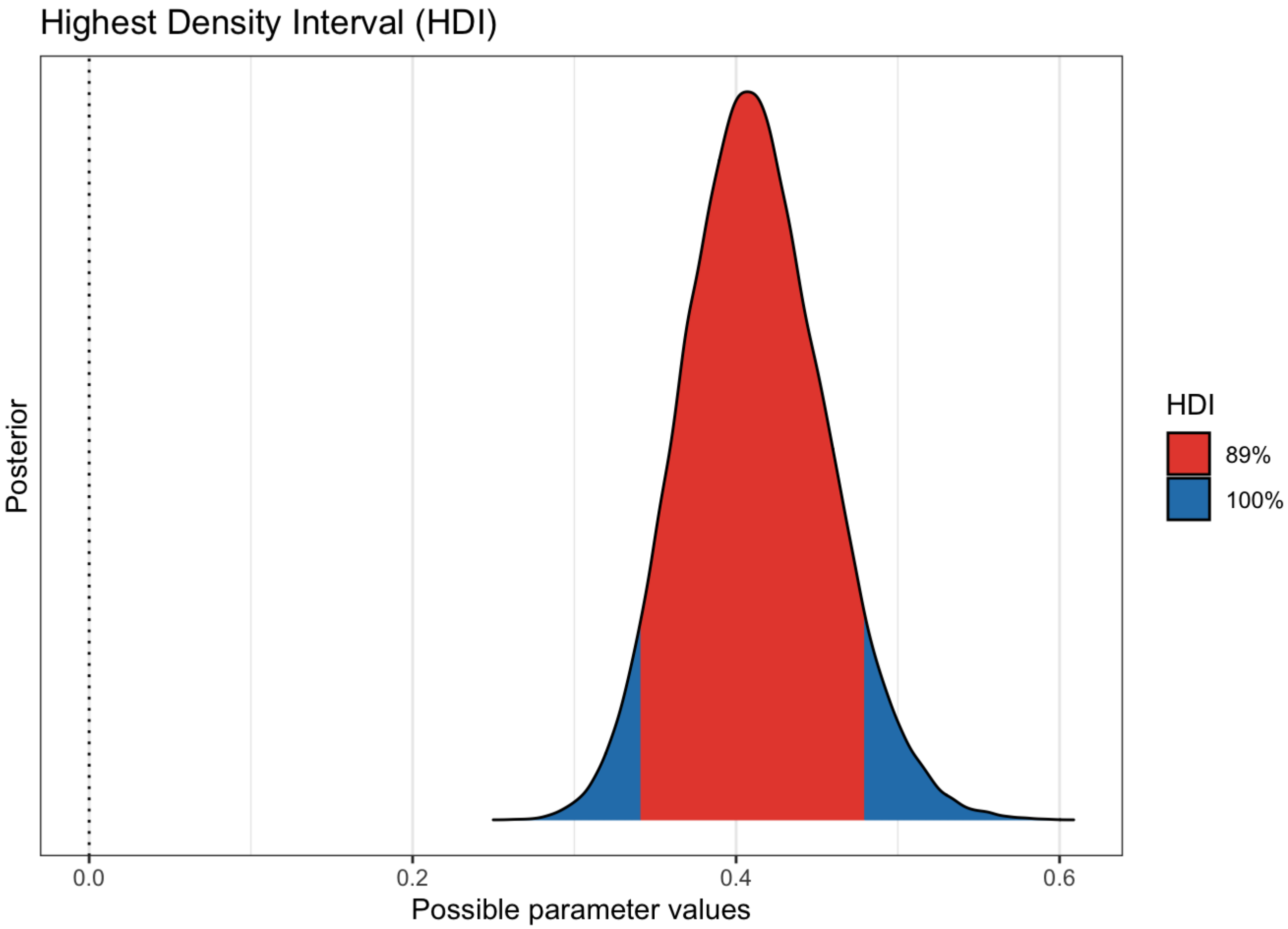

theta[2]
0.0002
0.0008
5000
10000
15000
20000
Iteration
ECDF
1.0
0.8
0.6
0.4
0.2
0.0
0.0002
0.0006
0.0010
0.0014
theta[2]
% of total
2.5
2.0
1.5
1.0
0.5
0.0
0.0005
0.0010
theta[2]
Autocorrelation of theta[2]
1.0
0.5
0.0
-0.5
-1.0
0
5
10
15
20
25
30
35
40
45
Lag



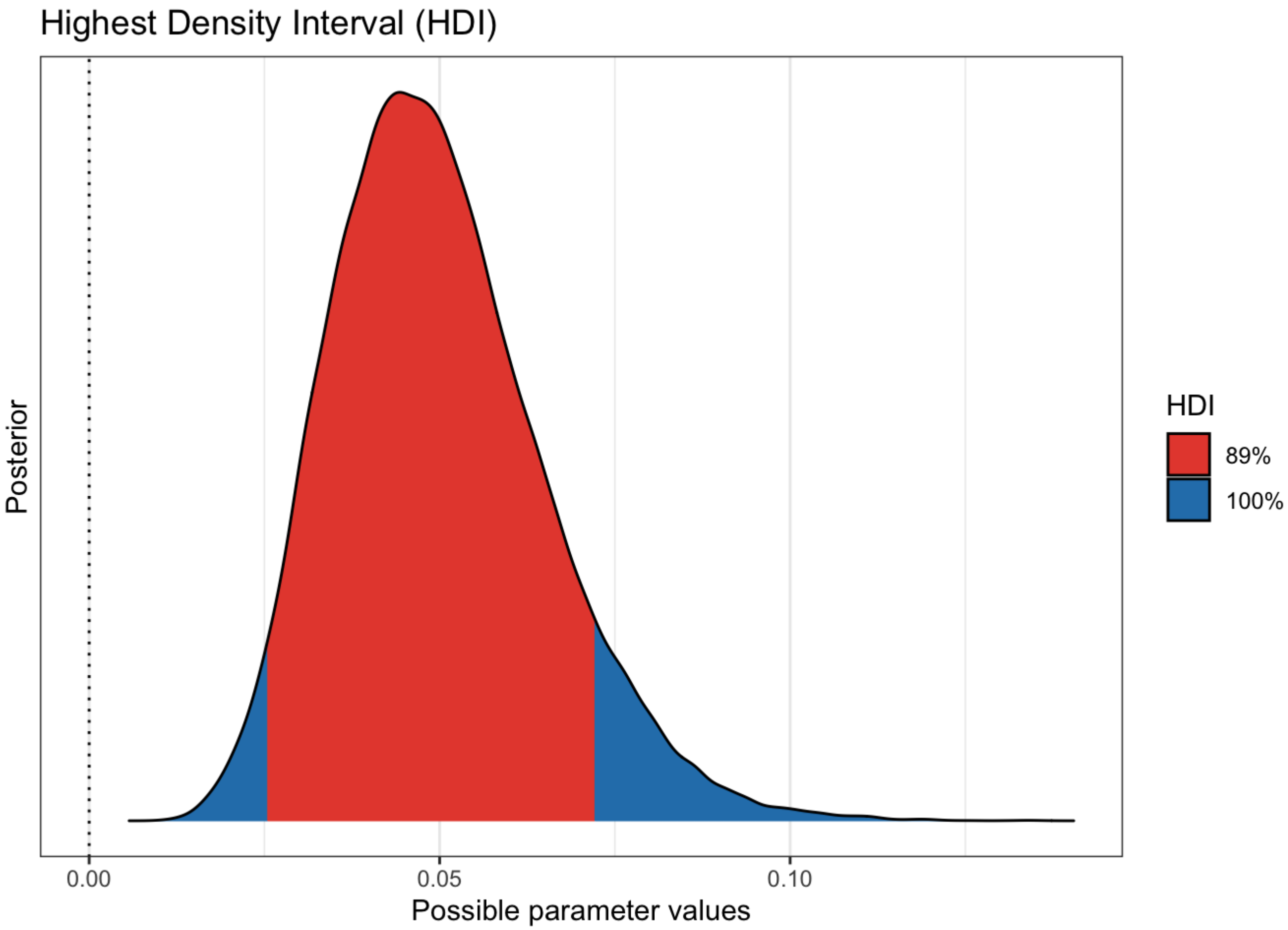
As usual this gives us estimates for the rate of infection for both those who received the placebo and those who received the actual vaccine. We can use `tidybayes::tidy_draws` to extract the chains/draws. We're not really interested in tracking the `.chain`, `.iteration`, and `.draw` information so we'll `select` just the two θs we're interested in. Since Greek letters are sometimes hard to follow we'll rename them back to placebo and vaccinated and multiply by 100 to give us percent as in 8/21999 * 100 = 0.03% infection rate for those that received the true vaccine.

Then we calculate what we really want to investigate which is the percentage difference in infection rates. We're looking for (since we multiplied by 100) a number that is around 90. Which in essence is a 90% effectiveness rating. A series of calls to `bayestestR::hdi` gives us graphical portrayals of what we want to know. We see that more 99% of our draws wind up with a solution greater than 75% effective. That gives us great credibility or confidence that given our data the effectiveness is there.

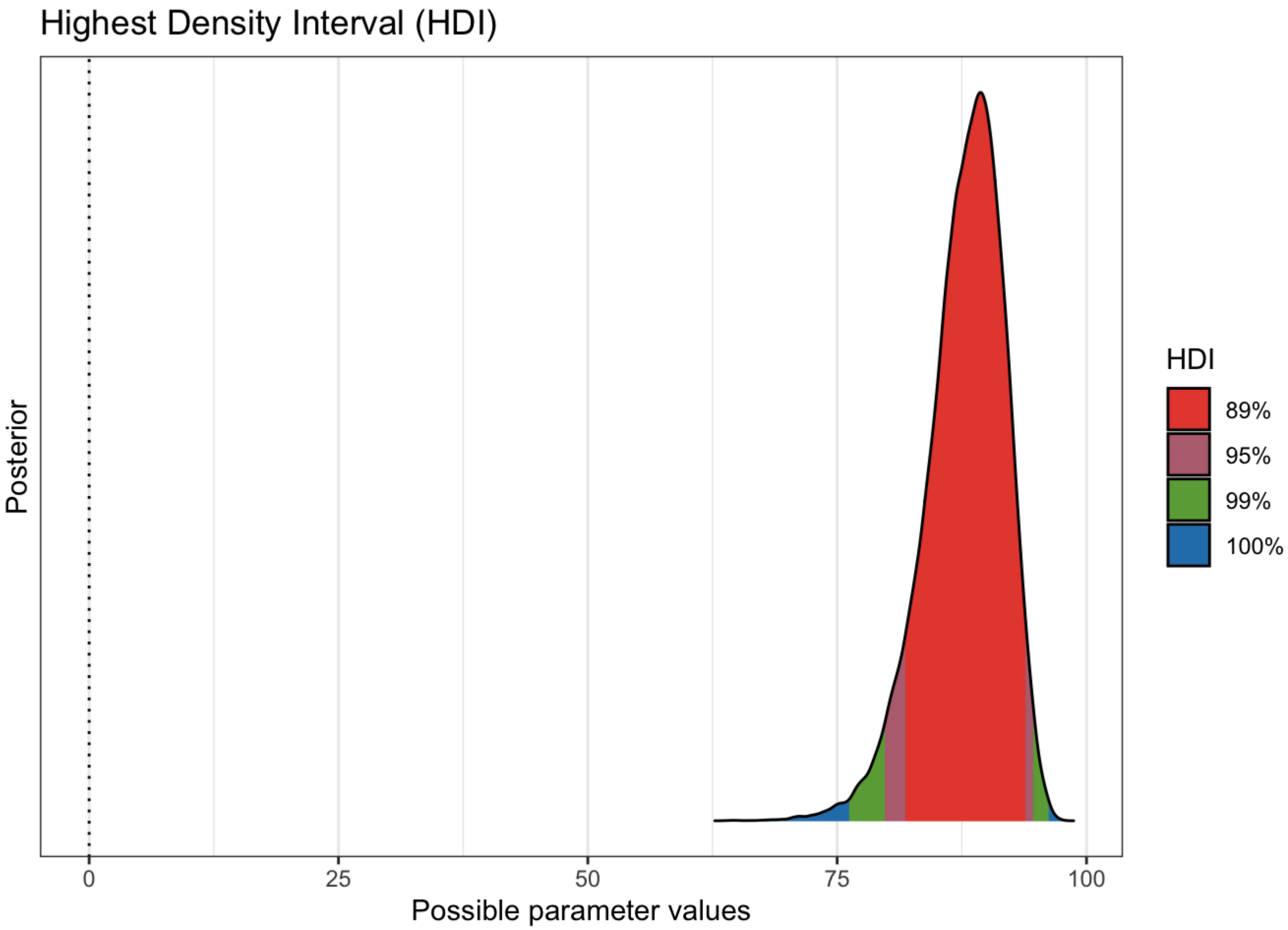
```
library(bayestestR)
pfizer_results <-
   tidybayes::tidy_draws(pfizer_chains) %>%
   select(`theta[1]`:`theta[2]`) %>%
   rename(placebo = `theta[1]`, vaccinated = `theta[2]`) %>%
   mutate(diff_rate = (placebo - vaccinated) / placebo * 100,
          placebo_pct = placebo * 100,
          vaccinated_pct = vaccinated * 100)

plot(bayestestR::hdi(pfizer_results$placebo_pct))
```



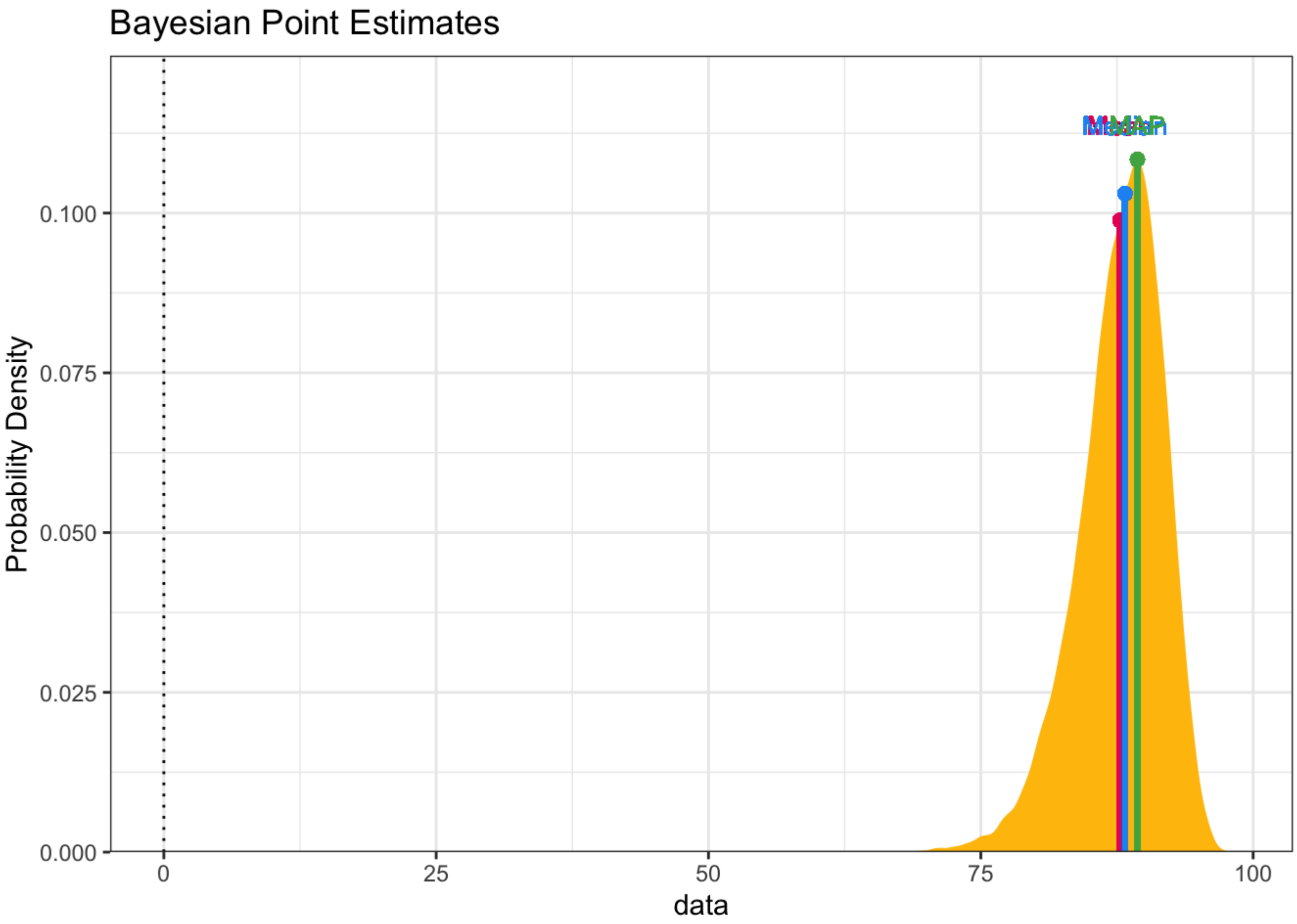
```
plot(bayestestR::hdi(pfizer_results$vaccinated_pct))
```



```
plot(bayestestR::hdi(pfizer_results$diff_rate, ci = c(.89, .95, .99)))
```



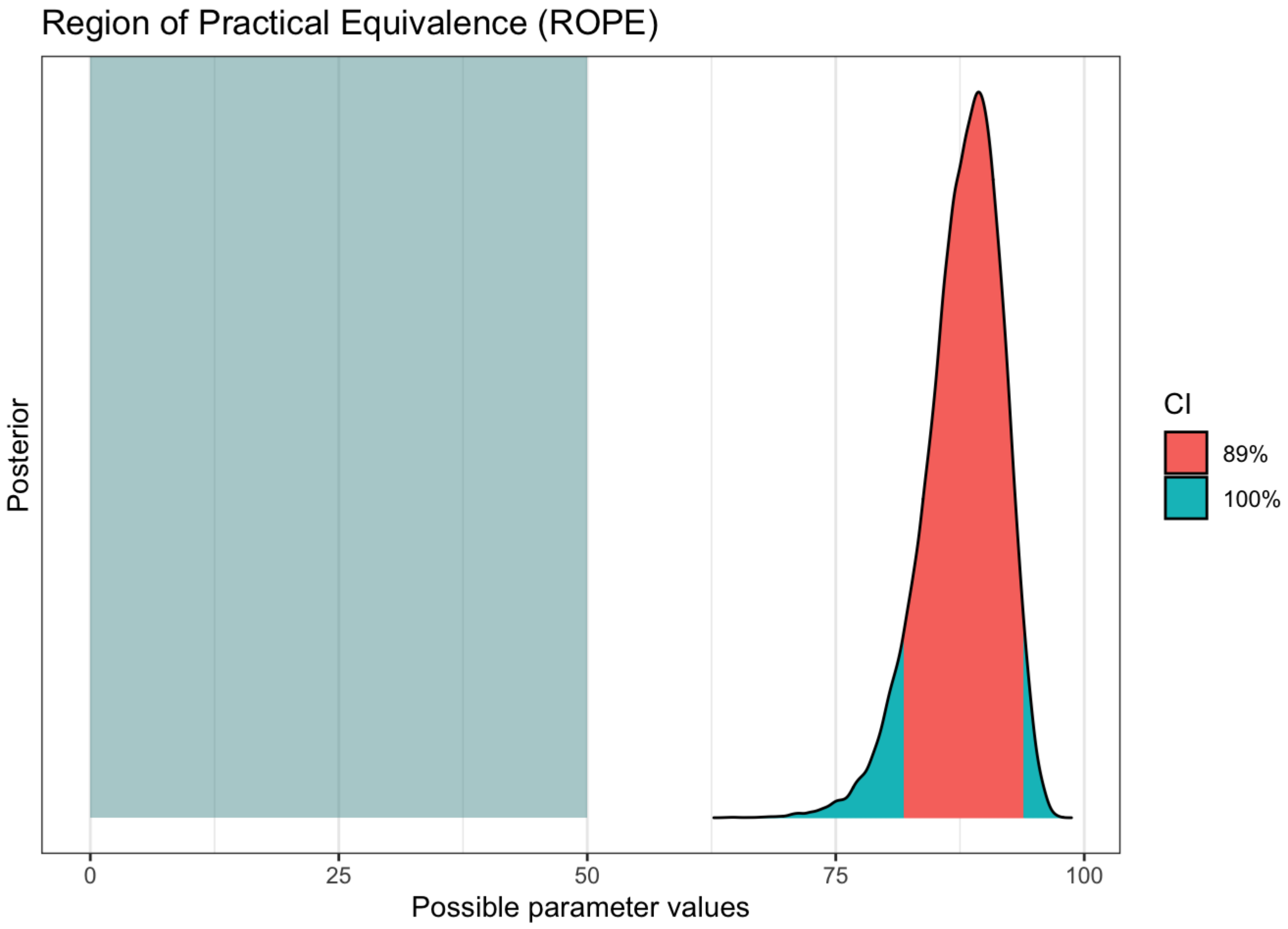
```
plot(bayestestR::point_estimate(pfizer_results$diff_rate))
```



More credibility for our results

Bayesian don't usually like to talk about significance, but we can show similar concepts with ROPE and practical significance (PS).

```
plot(bayestestR::rope(pfizer_results$diff_rate, range = c(0, 50)))
```



```
bayestestR::p_significance(pfizer_results$diff_rate, threshold = 50)
```

```
## ps [50.00] = 100.00%
```

```
bayestestR::p_significance(pfizer_results$diff_rate, threshold = 75)
```

```
## ps [75.00] = 99.43%
```

```
bayestestR::p_significance(pfizer_results$diff_rate, threshold = 90)
```

```
## ps [90.00] = 31.09%
```

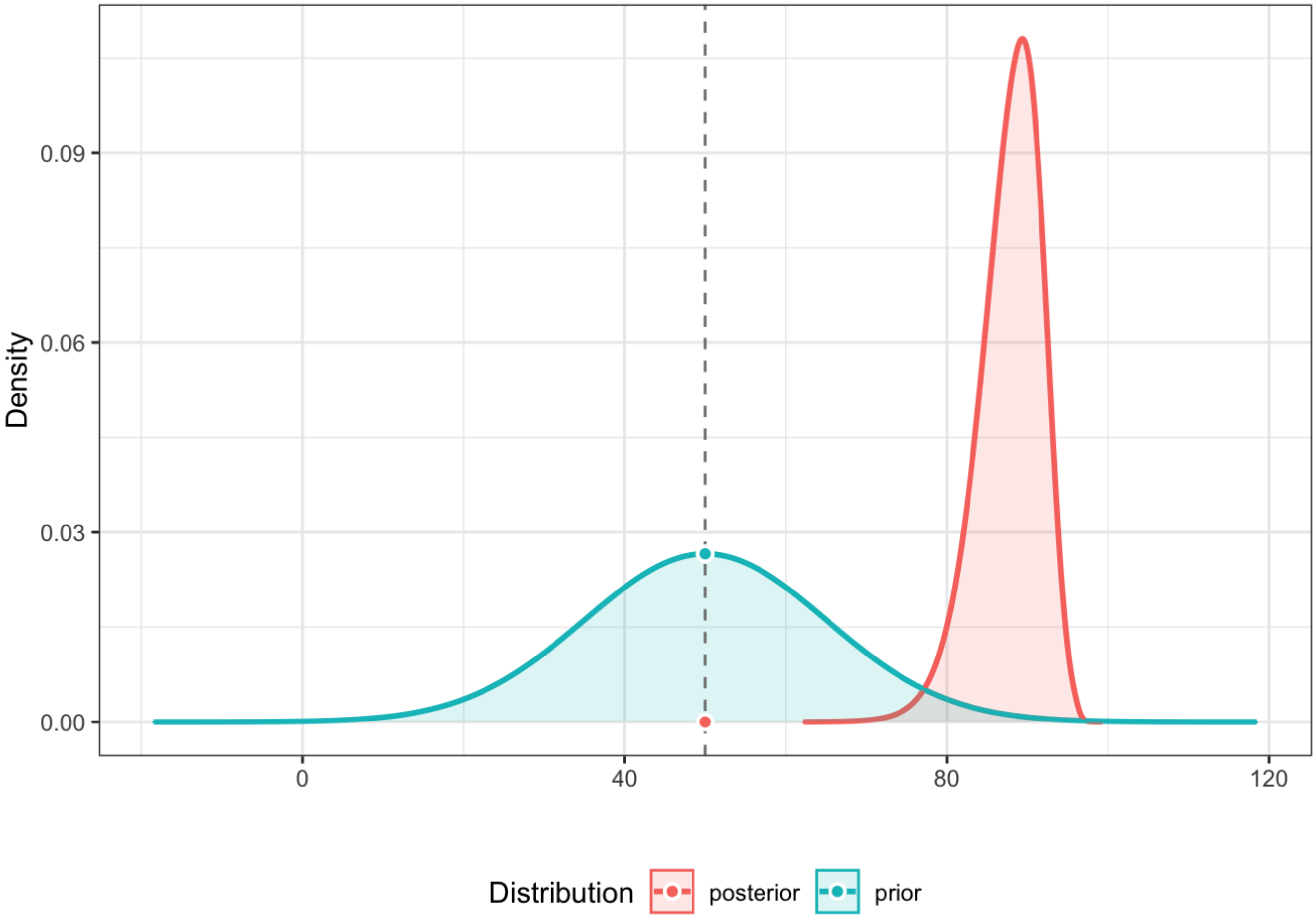
Some bayesians like to work with a Bayes Factor. There's even a fantastic `r` package named `BayesFactor` that focuses on them. A quick example is in order. Suppose that our prior belief before seeing the data was that the Pfizer vaccine would be 50% effective but with a standard deviation of 15% around that 50%. We can operationalize that simply with `prior <- distribution_normal(60000, mean = 50, sd = 15)`. Then we can use `bayesfactor_parameters(pfizer_results$diff_rate, prior, direction = "two-sided", null = 50)` to compute the odds that with our priors and our posteriors what are the odds that the vaccine is more than 50% effective (two tailed to be conservative). The answer is the odds given are data are more than 400,000:1 that the vaccine is more than 50% effective. Overwhelming evidence.

```
prior <- distribution_normal(60000, mean = 50, sd = 15)
bayesfactor_parameters(pfizer_results$diff_rate, prior, direction = "two-sided", nu
```

```
## Loading required namespace: logspline
```

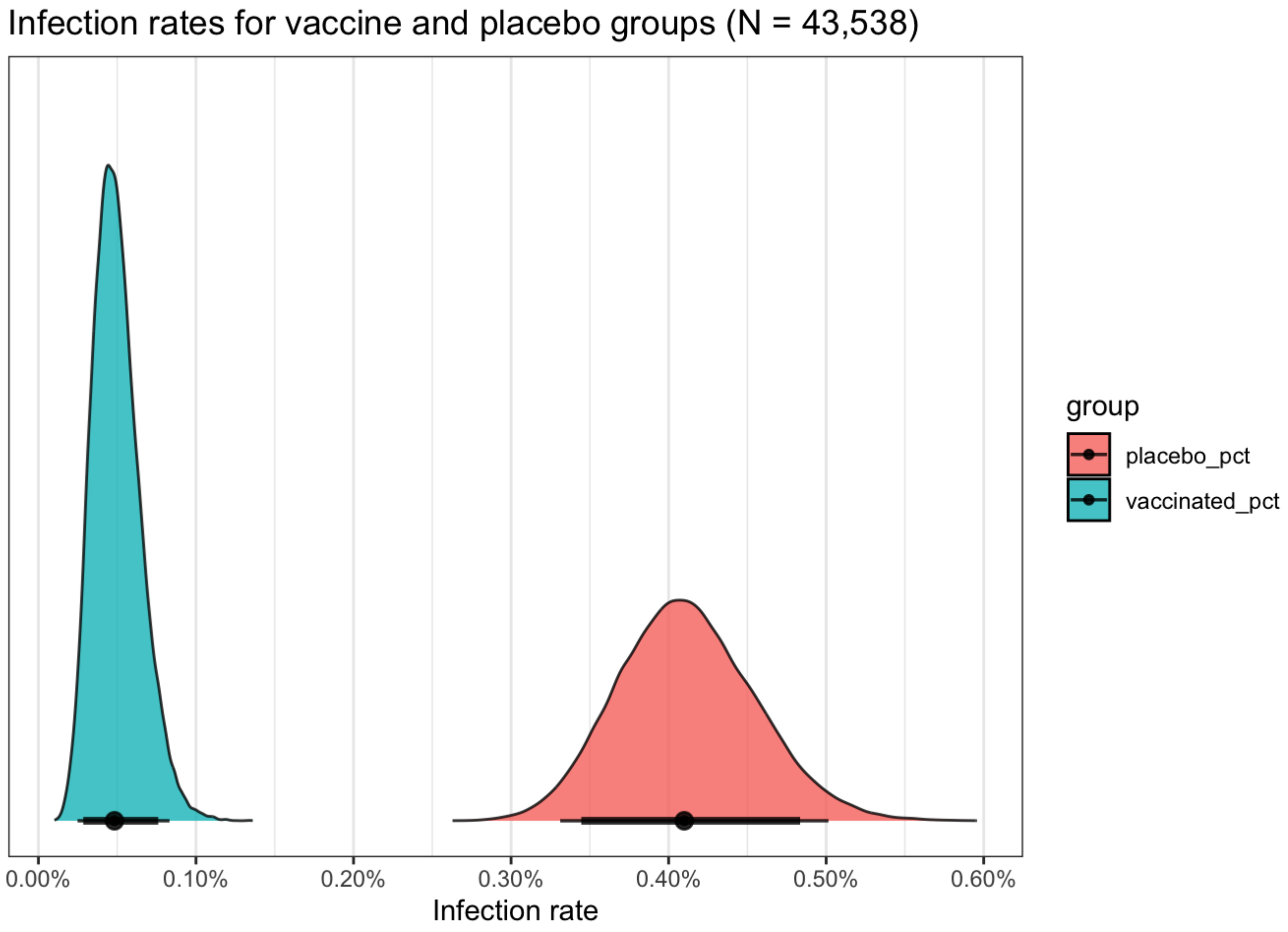
```
## # Bayes Factor (Savage-Dickey density ratio)
##
## BF
## ---------
## 4.159e+05
##
## * Evidence Against The Null: [50]
```

```
plot(bayesfactor_parameters(pfizer_results$diff_rate, prior, direction = "two-sided
)
```



For extra credit don't forget from my earlier posts that if you want the ultimate in custom control over your plots `ggdist` can be your ally. `ggdist` has a variety of nice functions for summarizing and displaying draws and chains. `stat_halfeye` not only plots it as a density curve but allows us to add per group credible intervals. A "quick" example.

```
pfizer_results %>%
   select(placebo_pct:vaccinated_pct) %>%
   tidyr::pivot_longer(everything(), names_to = "group") %>%
   ggplot(aes(x = value, fill = group)) +
   ggdist::stat_halfeye(.width = c(0.89, 0.95),
                        alpha = .8,
                        slab_colour = "black",
                        slab_size = .5) +
   ggtitle("Infection rates for vaccine and placebo groups (N = 43,538)") +
   xlab("Infection rate") +
   scale_x_continuous(labels = scales::label_percent(scale = 1),
                      breaks = seq.int(0, .6, .1)) +
   theme(axis.title.y = element_blank(),
        axis.text.y = element_blank(),
        axis.ticks.y = element_blank(),
        panel.grid.major.y = element_blank(),
        panel.grid.minor.y = element_blank())
```



What have we learned?

- The Pfizer vaccine appears to be tremendously effective. Let's hope that the safety data is equally good. There will be a lot more analysis needed on a variety of factors like age, race, and gender as data accumulates.
- **DBDA** is a timeless resource full of great information for data scientists and statisticians. But there are a lot faster and more elegant ways to code in `r` these days. Hopefully I've shown you a few while still honoring the book.

Done

I'm done with this topic for now. Fantastic news for humanity in the race for a vaccine.

Hope you enjoyed the post. Comments always welcomed. Especially please let me know if you actually use the tools and find them useful.

Keep counting the votes! Every last one of them!

Chuck

how-to, r

Bayes, COVID, credible interval, dplyr, functions, ggplot2, kable, MCMC, r, tidyr, warpspeed

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Yongduek Seo • a minute ago

Good to read this. This article shows something that is very much useful and informative in regard to considering the Pfizer data.

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