Inferring efficacy of Astrazeneca vaccine in phase III trials using JAGS

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Abstract

On March 22, 2021, Astrazeneca released the results of the phase III trial of their vaccine. From their analysis, it turned out that the vaccine efficacy at preventing symptomatic COVID-19 is 79% and the efficacy against severe or critical disease and hospitalisation is 100% [1]. The results were presented with no uncertainty and, because of how efficacy is defined, do not indicate the likelihood that the next patient will be protected by the vaccine. This created confusion not only in the media, but more importantly about how people interpreted these results, even those with specialized backgrounds. For this reason, I attempted to extrapolate, from the few published data, the full probability density (*pdf*) of efficacy. The work is based on a previous one concerning the early stages of vaccine trials [2], and through the implementation of a simple model based on a Bayesian Network, processed through Markov Chain Monte Carlo techniques. For inferred efficacy I found $(78.0 \pm 4.0)\%$ (mean $\pm$ standard dev) at preventing symptomatic COVID-19. On the other hand, as far as severe disease is concerned, from the published data, it is impossible to determine a definite conclusion for the efficacy of the vaccine. In particular, I studied how the lack of information on the number of severe placebos drastically changes our knowledge of vaccine efficacy pdf. The results published by Asrazeneca are in agreement with the modal values of the distributions obtained, and this leads us to believe that the method used is consistent with their analysis, however, statements about efficacy against severe cases have been sloppy and have led to important misunderstanding.

Contents

1 Introduction

On March 22, 2021, Astrazeneca released phase III trial results for its vaccine. The results claimed an efficacy of preventing symptomatic COVID-19 of 79% and an efficacy against severe or critical disease and hospitalisation of 100% [1]. However this results were presented without any type of uncertainty, and generated confusion in their interpretation both in the media and in people with a more or less technical background, as had already happened with previous results [2]. From the few data published by Astrazeneca, I tried to reconstruct a plausible *pdf* of the two efficacies presented. This is only for instructive purposes and to give a more precise statistical meaning to the claimed results. However, as far as severe disease is concerned, from the published data, it is impossible to determine a definite conclusion for the efficacy of the vaccine. Infact, without the knowledge of the number of placebo with sever disease ($n_{P_{I_s}}$) we can say nothing about the efficacy of the vaccine. In particular, our belief in the plausibility of 100% efficacy depends heavily on this number. If the number of severe placebos were equal to 0, certainly the vaccine's efficacy against severe cases would be 100%, but not because of a direct action of the vaccine so much as that the disease does not develop severe cases. As the number of severe placebos observed increases, so does our confidence in the efficacy of the vaccine, however without knowing this number it is impossible to determine firm conclusions from the analysis. So it becomes very interesting to develop a framework where this uncertainty of ours is properly represented.

	vaccine - placebo	n_{tot_I}	ϵ_1	$n_{V_{I_s}}$	ϵ_2
AZD1222	$21.633 - 10.816$	141	79%	0	100%

Table 1: Astrazeneca's data. n_{tot_I} is the total number of infected, ϵ_1 is the efficacy against symptomatic COVID-19, n_{V,I_s} is the number of severe disease into the group of vaccined and ϵ_2 is the efficacy against severe disease.

As we can see in the Table 1, for this phase of the trial, a ratio of 2:1 was chosen between the vaccinated and placebo groups. In this case the efficacy is defined as

$$\epsilon = 1 - \frac{n_{V,s}}{n_{P,s}} \frac{N_P}{N_V} \tag{1}$$

where $n_{V,s}$ and $n_{P,s}$ are the number of patients with symptoms vaccinated and placebo, respectively, and N_V and N_P are the sample size of vaccined and placebo. Using eq.1 and the claimed efficacy for symptomatic COVID-19 in Table 1, we can extrapolate the value of the number of symptomatic vaccined observed $n_{V,I} = 42$ and the number of symptomatic placebo observed $n_{P,I} = 99$.
With these data we can start the analysis of the model through a Markov Chain Monte Carlo (MCMC) implemented through the library *rjags* of **R**, based on the software JAGS (just another Gibbs sampler).
The paper is organized as follow. in Sec. 2 I will present a Bayesian network to model in an approximate way the causal and probabilistic relationships between the quantities of interest. In this section we will focus on the efficacy against the symptomatic COVID-19 and I will present the results based on MCMC algorithms. In Sec. 4 I will present an extended model in order to incorporate the efficacy for severe disease into the first model, and I will present the results obtained. Finally, in Sec. 5 I will discuss all the results obtained.

2 Model for efficacy against symptomatic COVID-19

The causal model on which the analysis is based is shown in Fig. 1. At the extremes of the Bayesian network we have the data observed during the trial, at the top the number of the sample of vaccinated (N_V) and placebo (N_P), in the base, the number of symptomatic in the group of vaccinated (n_{V_I}) and in the group of placebo (n_{P_I}). One of the first problems is to understand how to probabilistically connect these two layers of the graph. As shown in Ref. [2], one way to

simplistically schematize the process is to define an assault probability p_a that takes into account all possible factors that determine the probability of becoming infected. This probability is the same for the vaccinated and placebo and creates an additional layer in the graph where we have the unobserved amounts of the "assaulted" number of infected in the two groups of vaccinated (n_{V_a}) and placebo (n_{P_a}). The vaccinated group, is protected with some efficacy ϵ_1 from symptomatic COVID-19, so, not all of the assault group will end up being infected, but they will have a $1-\epsilon_1$ probability of being infected. Different discussion for placebos, where placebo efficacy is zero, so the connection between n_{P_a} and n_{P_I} is deterministic and was indicated with a dotted line.

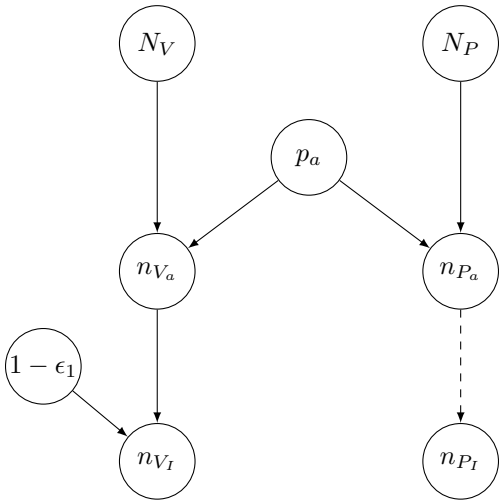

Figure 1: Bayesian Network for the model of test III trial, vaccine vs placebo.

To solve the ϵ_1 *pdf* problem via *rjags* we now only need to define how the nodes in the graph are connected to each other. Basically, we just define the pdf of the quantities of interest and *rjags* does the "dirty" work for us. The two "assaulted" quantities are related to their relatives as follow

$$n_{V_a} \sim \text{Binom}(N_V, p_a) \tag{2}$$

$$n_{P_a} \sim \text{Binom}(N_P, p_a). \tag{3}$$

Instead the number of vaccined infected is related to his relatives as

$$n_{V_I} \sim \text{Binom}(n_{V_a}, 1-\epsilon_1). \tag{4}$$

We can translate this into **R** code

```
write("
model {
  nP.I   ~ dbin(pA, nP)
  nV.A  ~ dbin(pA, nV)
  nV.I ~ dbin(ffe1, nV.A)      # ffe1 = 1 - eff1
  pA ~ dbeta(1,1)
  ffe ~ dbeta(1,1)
  eff1 <- 1 - ffe1
}
", model)
```

In the first three rows we have the three functions defined above, while the last two rows are the *prior* of p_a and ϵ_1. We chose a uniform prior for both quantities, modeled via a Beta function of parameters $\{1,1\}$. By providing the data for N_V, N_P, n_{V_I} and n_{P_I}, we can finally calculate the *pdf* of our interest.

2.1 Results

The behavior of the program is conceptually simple. Once the number of iterations and the variables to be "monitored" have been chosen, *rjags* samples the entire range of possibilities and returns a list of numbers of the chosen variables which can then be statistically analyzed. The code to do this is just as simple

```
data <- list(nP=nP, nV=nV, nP.I=nP.I, nV.I=nV.I)
jm <- jags.model(model, data)
update(jm, 100)
to.monitor <-  c('pA', 'eff1', 'nV.A')
chain <- coda.samples(jm, to.monitor, n.iter=nr)
chain.df <- as.data.frame( as.mcmc(chain) )
```

The results obtained are summarized in the Fig. 2.1 and table 2 below

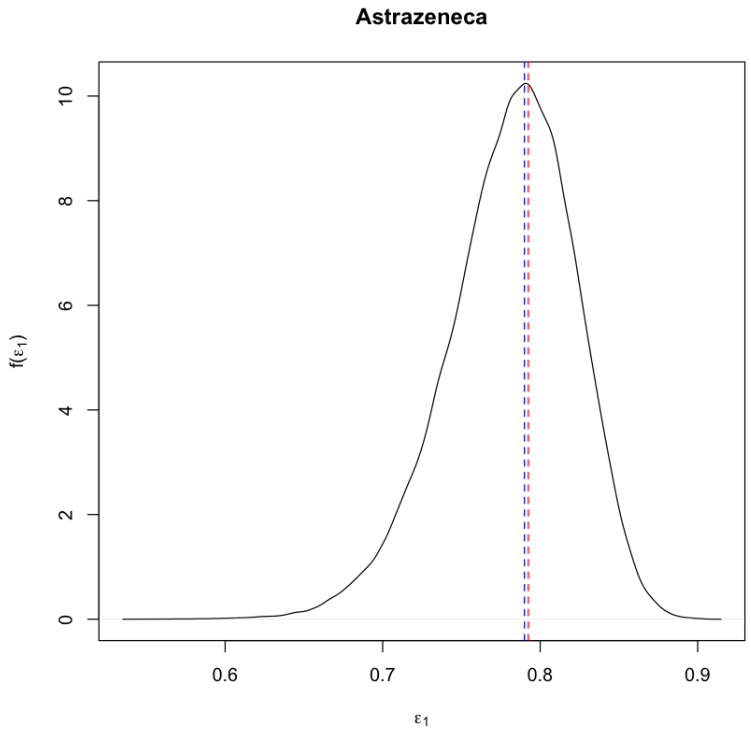

Figure 2: Efficacy against symptomatic COVID-19. The red line is the modal value of the distribution and the blue line is the value claimed by Astrazeneca.

	mean ± SD	centr. 95% cred. int.	modal value	published value
AZD1222	$(78.0 \pm 4.0)\%$	$[0.69 - 0.85]$	79.3%	79%

Table 2: MCMC results vs. Astrazeneca's data. The modal value is practically the same.

The red dashed line in Fig. 2.1 correspond to the modal value of the distribution, instead the blue one is the value published by Astrazeneca. As we can see their are practically the same value. However, it is important to emphasize that the most important value is not the modal value but the mean with standard deviation. These two values best summarize the information of

the efficacy distribution. If we ask ourselves what will be the probability that a new vaccinated patient will not develop the symptoms of COVID-19 we should calculate

$$P(NS|A, V, \text{data}, H) = \int_0^1 \epsilon_1 \cdot f(\epsilon_1|\text{data}, H) d\epsilon_1 \tag{5}$$

where NS denotes a non symptomatic vaccined person, who was not in the starting sample, and H indicates all the hypoteses we have done. The integral is exactly the definition of the average of the efficacy and not the modal value.
Another interesting point to verify is the mean and standard deviation of n_{V_a}, i.e. the unobserved node, which we expect to be about $\frac{N_V}{N_P} n_{P_a} \sim 2n_{P_a}$. The value obtained is 197 ± 25, and is comparable with what we expect.

3 Infer the number of infected in a new sample

Now that we have the full ϵ_1 *pdf*, we can ask, given a new sample of vaccinated people N'_V, what is the expected number of infected given the efficacy of the vaccine. Obviously this number will depend not only on the initial sample but also on the details of the assault probability of the new sample p'_a, the analysis is for educational purposes only.
This scenario is implemented by a Bayesian network that is an extension of 1

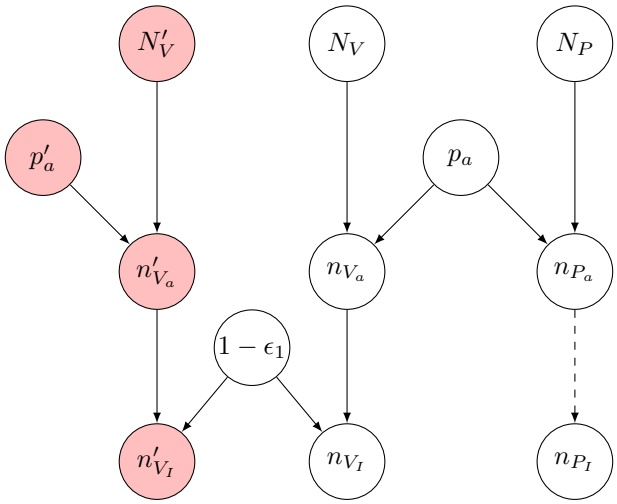

Figure 3: Bayesian Network for the number of infected in a new sample.

The model in *rjags*

```
 write("
model {
  nP.I   ~ dbin(pA, nP)
  nV.A  ~ dbin(pA, nV)
  nVn.A ~ dbin (pan, nVn)

  pA ~ dbeta(1,1)
  nV.I ~ dbin(ffe, nV.A)
  ffe ~ dbeta(1,1)
  nVn.I ~ dbin(ffe, nVn.A)
  eff <- 1 - ffe
}
", model)
```

Choosing an initial sample of $N'_V = 100.000$ vaccinees and a $p'_a = 1\%$, without deep rationale. The result we get, is shown in Fig. 3

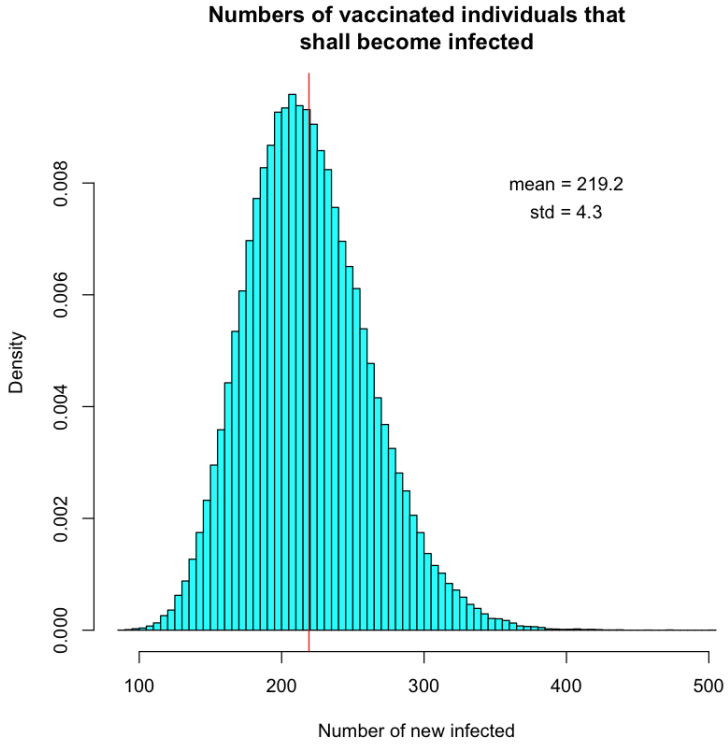

Figure 4: Distribution of the predicted number of vaccinated infectees.

4 Model for efficacy against severe disease

In order to study efficacy for severe symptoms, we need only extend the causal model in Fig. 1.

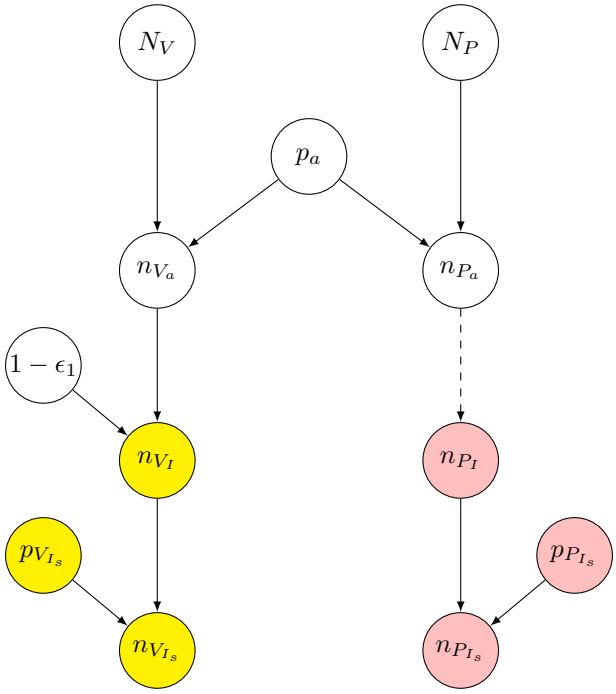

Figure 5: Extended Bayesian Network for the efficacy against severe disease.

Where $n_{V_{I_s}}$ and $n_{P_{I_s}}$ are the number of infected individuals with severe disease, vaccinated and placebo, respectively. $p_{V_{I_s}}$ and $p_{P_{I_s}}$ are the probability of being infected with severe disease on individuals vaccinated and placebo, respectively. Again we use binomial distribution for probabilistic connection

$$n_{V_{I_s}} \sim \text{Binom}(n_{V_I}, p_{V_{I_s}}) \quad (6)$$

$$n_{P_{I_s}} \sim \text{Binom}(n_{P_I}, p_{P_{I_s}}). \quad (7)$$

Note how the group of colored nodes is disconnected from the rest of the neural network, because n_{V_I} and n_{P_I} are observed data.
We can implement the entire model on *rjags*

```
write("
model {
  nP.I   ~ dbin(pA, nP)
  nV.A  ~ dbin(pA, nV)
  pA ~ dbeta(1,1)
  nV.I ~ dbin(ffe1, nV.A)
  ffe1 ~ dbeta(1,1)
  eff1 <- 1 - ffe1

  pS_P ~ dbeta(1,1)
  pS_V ~ dbeta(1,1)
  nV.S ~ dbin(pS_V,nV.I)
  nP.S ~ dbin(pS_P,nP.I)
  eff2 <- 1 - pS_V
}
", model)
```

where we have defined the efficacy $\epsilon_2 = 1 - p_{V_{I_s}}$. Now providing the data we can calculate the *pdf* of our interest as in Sec. 2.

4.1 Results

The results obtained are summarized in the Fig. 4.1 and table 5 below.

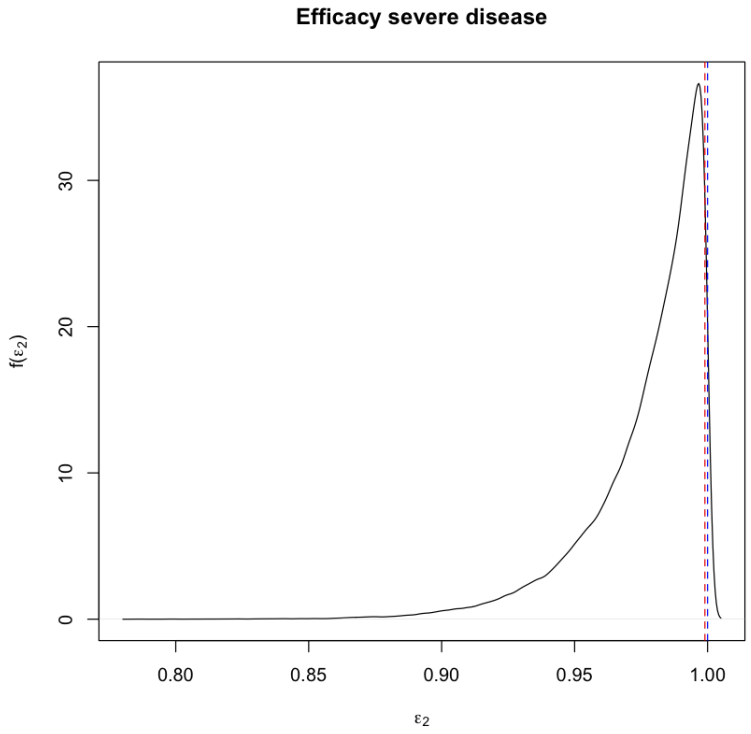

Figure 6: Efficacy against severe disease. The red line is the modal value of the distribution and the blue line is the value claimed by Astrazeneca.

	mean ± SD	centr. 95% cred. int.	modal value	published value
AZD1222	$(97.7 \pm 2.3)\%$	$[0.92 - 1.00]$	100%	100%

Table 3: MCMC results vs. Astrazeneca's data. The modal value is practically the same.

The results obtained are in agreement with those published by Astrazeneca, however, in this case we made strong hires. First, by interpreting $1-p_{V_{I_s}}$ as the efficacy of the vaccine, we assumed that the entire group of infected people can develop severe symptoms and the fact that they do not manifest them is completely attributable to the action of the vaccine. This is certainly not the case. We can implement a more sophisticated model to account for the fact that not all of the initial sample should necessarily develop severe symptoms. Essentially we are saying that the quantity we have interpreted as efficacy is actually the product of two quantities, one is effectively the efficacy of the vaccine, the other is the probability of having severe symptoms. To update the model we need to introduce a new probability that will be in common between the placebo and infected nodes and that is the probability that an infected person will experience severe symptoms. In this model we are imagining that the action of the vaccine is a counterattack to the manifestation of

these symptoms and is not instead a shield. In essence, the *a priori* probability of having severe symptoms does not change whether we are vaccinated or not, but it does change our response to this possibility.

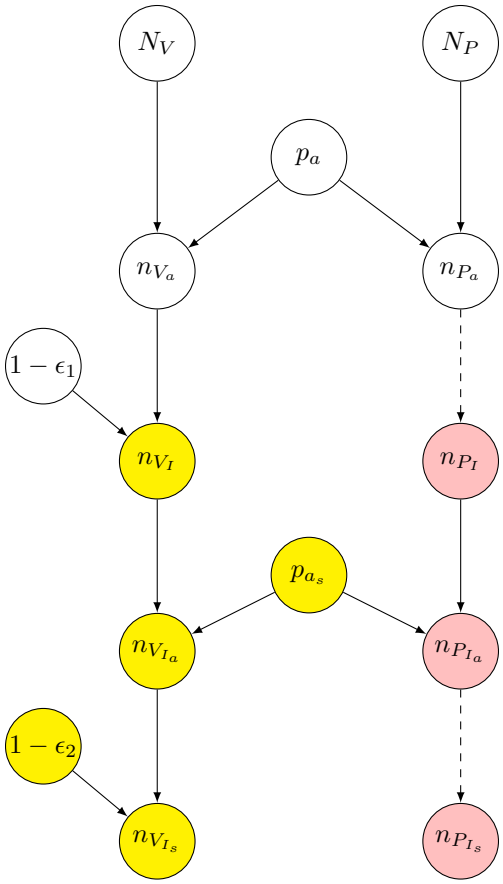

Figure 7: Bayesian Network for "counterattack" vaccine .

In this other model, the inference about efficacy depends on our knowledge of the number of severals in the placebo case. So it would be interesting to make the dotted line connecting the placebo assaulted with the severals, a probabilistic connection like the others. In this way we model the fact that although Astrazeneca did not release all the data, we can have a *prior* knowledge about the number of severities they found during the trial. Specifically, we can assume that the number of severals is around 10% of those infected. We can also ask ourselves how our belief about the value of efficacy changes as the number of placebos with severe symptoms changes.

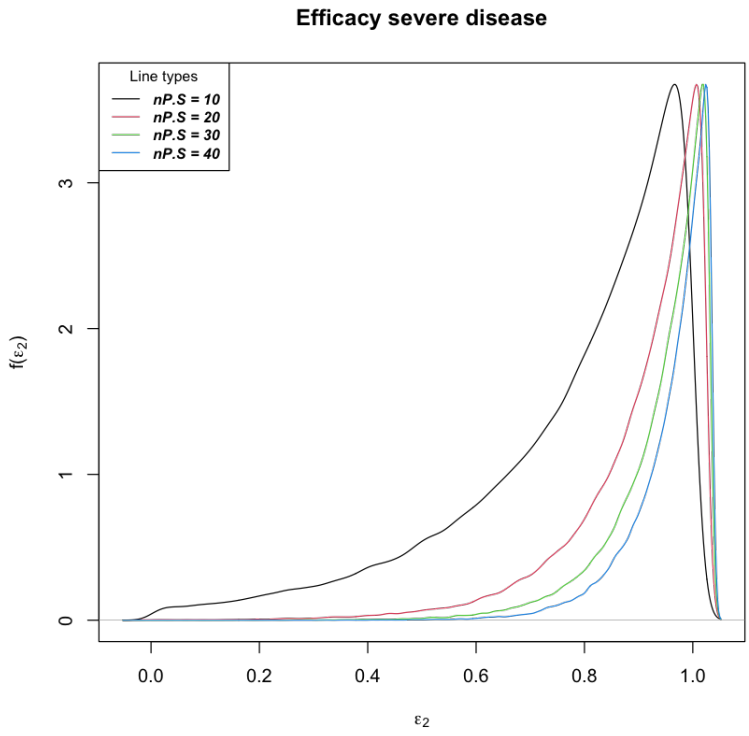

Figure 8: Efficacy against severe disease with $SD_{n_{Ps}} = 3$. As the number of placebos with severe symptoms increases, the probability density of efficacy converges toward 100%.

n_{P_s}	mean $\pm$ SD	centr. 95% cred. int.
10	$(77.5 \pm 20.8)\%$	$[0.21 - 0.99]$
20	$(88.1 \pm 11.9)\%$	$[0.56 - 1.00]$
30	$(92.2 \pm 7.8)\%$	$[0.72 - 1.00]$
40	$(94.2 \pm 5.8)\%$	$[0.79 - 1.00]$

Table 4: Variation of the results increasing the number of placebos with severe symptoms.

As the number of placebos with severe symptoms observed increases, so does our belief in Astrazeneca's published value.

In the case of severe symptoms, the results published by Astrazeneca are too few to draw firm conclusions. Results on vaccine efficacy also depend on the number of severe placebos that were observed, and without knowing this number, we cannot rely even on the modal value they stated. On the other hand this is not surprising, if the number of severe placebos was zero, we should conclude that the disease does not produce severe cases at all, and therefore the administration of the vaccine would not have any positive effect to fight a symptom that cannot occur. Since this is not the case, it would have been appropriate to also report the number of severe placebos and to state the mean and standard deviation of the efficacy distribution and not the modal value, which has limited statistical significance.

5 Conclusions

In this paper, I have alternatively analyzed the results published by Astrazeneca for educational purposes. On the one hand it is interesting to see how from few data available it is possible to reconstruct plausible results for the quantities of interest, on the other hand this approach allows us to have a greater understanding of the results that have been obtained. The results I obtained are in agreement with those published, particularly with the modal value of the *pdfs*. This is not a surprising fact but rather a consequence of Bayes' theorem applied to Bernoulli processes, in particular to the difference between $P(x|n,p)$ and $P(p|n,x)$, where p is the probability of success, x is the number of succes and n the number of trials.
For the efficacy against symptomatic COVID-19 I found an efficacy of $(78.0 \pm 4.0)\%$ with central 95% credible interval of $[0.69 - 0.85]$ that cover the published result of 79%. For the case of severe symptoms, the issue is more complicated. I built a model for the efficacy that related the nodes of the placebo and that of the vaccinated, however, the results published by Astrazeneca do not allow to draw firm conclusions on the efficacy of the vaccine. In particular, I showed how as the number of severe placebos observed changes, our confidence in the stated value decreases. If we decrease this number enough, the modal value of the distribution does not coincide anymore with the one published by Astrazeneca. It is therefore important to publish the results correctly in order to understand the analysis that has been done.

References

[1] AstraZeneca PLC, News Release, 22 March 2021,https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html

[2] G. D'Agostini and A. Esposito, *"What is the probability that a vaccinated person is shielded from Covid-19? A Bayesian MCMC based reanalysis of published data with emphasis on what should be reported as 'efficacy"',* arXiv:2102.11022v1[stat.AP]