# Bayesian Meta Analysis of Ivermectin Effectiveness in Treating Covid-19 Disease

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# Bayesian Meta Analysis of Ivermectin Effectiveness in Treating Covid-19 Disease

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## Abstract

A recent peer reviewed meta-analysis evaluating ivermectin (Bryant et al, 2021) concluded that this antiparasitic drug is a cheap and effective treatment for reducing Covid-19 deaths. These conclusions were in stark contrast to those of a later study (Roman et al, 2021). Although (Roman et al, 2021) applied the same classical statistical approach to meta-analysis, and produced similar results based on a subset of the same trials data used by (Bryant et al), they claimed there was insufficient quality of evidence to support the conclusion Ivermectin was effective. This paper applies a Bayesian approach, to a subset of the same trial data, to test several causal hypotheses linking Covid-19 severity and ivermectin to mortality and produce an alternative analysis to the classical approach. Applying diverse alternative analysis methods which reach the same conclusions should increase overall confidence in the result. We show that there is overwhelming evidence to support a causal link between ivermectin, Covid-19 severity and mortality, and: i) for severe Covid-19 there is a 90.7% probability the risk ratio favours ivermectin; ii) for mild/moderate Covid-19 there is an 84.1% probability the risk ratio favours ivermectin. Also, from the Bayesian meta-analysis for patients with severe Covid-19, the mean probability of death without ivermectin treatment is 22.9%, whilst with the application of ivermectin treatment it is 11.7%. The paper also highlights advantages of using Bayesian methods over classical statistical methods for meta-analysis.

## 1. Introduction

A recent meta-analysis of the trials evaluating ivermectin (Bryant et al., 2021) was widely welcomed by those who have argued that this antiparasitic drug is a cheap and effective treatment for Covid-19 infections. The study concluded:

> *"Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally."*

These conclusions stand in stark contrast to those of a later meta-analysis (Roman et al., 2021) which looked at a subset of the trials. They concluded:

> *"In comparison to SOC or placebo, IVM did not reduce all-cause mortality, length of stay or viral clearance in RCTs in COVID-19 patients with mostly mild disease. IVM did not have effect on AEs or SAEs. IVM is not a viable option to treat COVID-19 patients."*

This conclusion is not, however, based on the results of the statistical analysis of the data, which were very similar to those of (Bryant et al., 2021); instead, as claimed in (Fordham & Lawrie, 2021) it was based on a somewhat vague and possibly biased subjective assessment of the quality of the trials themselves. Moreover, (Crawford, 2021) has highlighted errors in the data and the analysis carried out by (Roman et al., 2021).

This paper applies a Bayesian approach, to a subset of the same trial data, to test several causal hypotheses linking Covid-19 severity and ivermectin to mortality. Applying diverse alternative analysis methods, which reach the same conclusions, should increase overall confidence in the result.

A Bayesian approach also brings with it several advantages over the classical statistical approaches applied to this trials data thus far. Firstly, it allows the evaluation of competing causal hypotheses; so here we test whether Covid-19 mortality is independent of Covid-19 severity, treatment or both treatment and severity. Also, given that a causal link can be established, a Bayesian approach can explicitly evaluate the strength of impact of that causal link on mortality. These advantages can be obtained within a Bayesian meta-analysis framework using a hierarchical model which can also take account of 'zero' frequency results which are not estimable in the classical statistical framework. Finally, the Bayesian approach to confidence intervals leads to the ability to directly interpret confidence intervals in a way that does not rely on notions of repeated trials, making them easier to understand.

## 2. Trials Data Used

The trials data analysed in our meta-analysis is summarised in Table 1 and is based on (Bryant et al., 2021) Figure 4 (which also provides the full references to the individual studies). In contrast to (Bryant et al., 2021), we have made the following necessary changes:

- We have excluded the study by (Niaee 2020)[1] in our analysis because a) the placebo control applied in that group was not a true placebo; and b) the severe Covid-19. patients were not separated from the mild/moderate Covid-19 patients in the trial.
- The ivermectin group of the (Lopez-Medina 2021) trial had zero deaths in 200 patients, not zero in 275 as stated in (Bryant et al., 2021).

Also note that the ivermectin and control groups of the (Ravkirti et al., 2020) study have 55 and 57 patients respectively not 57 and 58 as stated in (Roman et al., 2021).

| | **Severe Covid-19 trials** | | | |
|---|---|---|---|---|
| | Ivermectin | | Control | |
| | Total | Deaths | Total | Deaths |
| Elgazaar 2020 | 100 | 2 | 100 | 20 |
| Fonseca 2021 | 52 | 12 | 115 | 25 |
| Gonzalez 2021 | 36 | 5 | 37 | 6 |
| Hashim 2020 | 11 | 0 | 22 | 6 |
| Okumus 2021 | 36 | 6 | 30 | 9 |
| | | | | |
| | **Mild/moderate Covid-19 trials** | | | |
| | Ivermectin | | Control | |
| | Total | Deaths | Total | Deaths |
| Ahmed 2020 | 45 | 0 | 23 | 0 |
| Babalola 2020 | 42 | 0 | 20 | 0 |
| Chaccour 2020 | 12 | 0 | 12 | 0 |
| Elgazaar 2020 | 100 | 0 | 100 | 4 |
| Hashim 2020 | 48 | 0 | 48 | 0 |
| Lopez-Medina 2021 | 200 | 0 | 198 | 1 |
| Mahmud 2020 | 183 | 0 | 180 | 3 |
| Mohan 2021 | 100 | 0 | 52 | 0 |
| Petkov 2021 | 50 | 0 | 50 | 0 |
| Ravikirti 2021 | 55 | 0 | 57 | 4 |
| Rezai 2020 | 35 | 1 | 34 | 0 |
| Total | 1225 | 30 | 1138 | 89 |

Table 1: Trial data used in this Bayesian Meta-analysis

## 3. The Bayesian Meta-analysis

The Bayesian meta-analysis approach has several stages involving learning from data, determining which causal hypotheses best explain this data, selecting the 'best' hypothesis and then using this to estimate its impact. The stages are linked as follows:

A. Learn the mortality probability distribution from relevant trials for each hypothesis of concern using a hierarchical Beta-Binomial model.
B. For each causal hypothesis use the model in stage A to learn the mortality probability distributions relevant to that causal hypothesis.
C. For each causal hypothesis use the learnt probability distributions from stage B to predict the observed data and calculate the likelihood of observing the data.
D. For all causal hypotheses compute the posterior probability of each hypothesis given the likelihood of observing the data under that hypothesis and select the most likely causal hypothesis that explains the data.
E. Estimate the magnitude of impact of the relevant variables, under the selected 'best' hypothesis, on mortality.

[1] The full citations references for the studies are provided in (Bryant et al 2021) and are not repeated here.

Full details and results are given in the Appendix. For further background information on this type of Bayesian analysis see (Fenton & Neil, 2018).

The four hypotheses being tested (denoted $H1 - H4$) about the causal connections between variables deaths ($D$), Covid-19 Severity ($S$), and Treatment ($T$), are as follows:

$H1$: $P(D)$ – death is independent of Covid-19 severity or treatment

$H2$: $P(D|S)$ – death is dependent on Covid-19 severity only

$H3$: $P(D|T)$ – death is dependent on treatment only

$H4$: $P(D|S,T)$ – death is dependent on Covid-19 severity and treatment

These hypotheses are shown graphically in Figure 1.

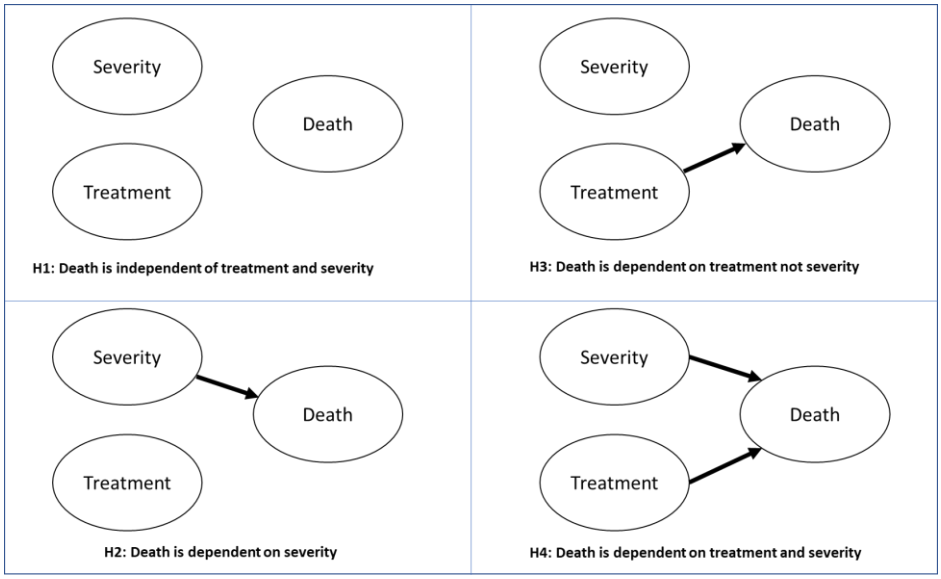


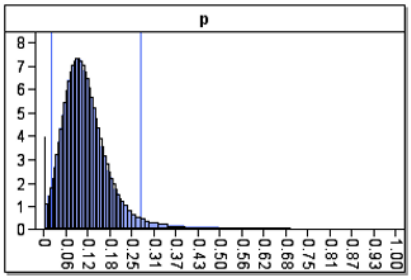

Figure 1: Causal hypotheses $H1 - H4$

From applying the analysis stages, A to D, the resulting posterior probability of these hypotheses being true given the data is:

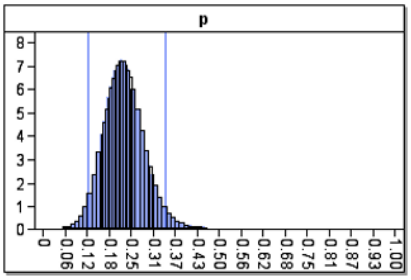
$$P(H1\,|Data) = 0, P(H2\,|Data) = 0.0092, P(H3\,|Data) = 0, P(H4\,|Data) = 0.9908$$

Hence, there is extremely convincing evidence that Covid-19 severity and treatment causally influence mortality.

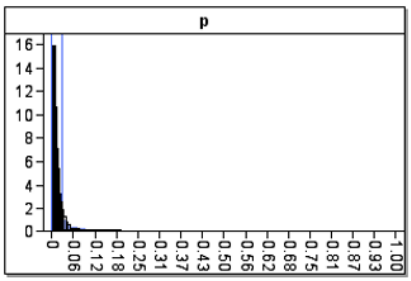
To estimate the magnitude of the impact of Covid-19 severity, $S$, and Treatment, $T$, on death, $D$ we need to compute $H4$: $P(D|S,T)$. Figure 2 shows the marginal probability distributions for mortality for each of the combinations of severity and treatment and Table 2 shows the mean and 95% confidence intervals.



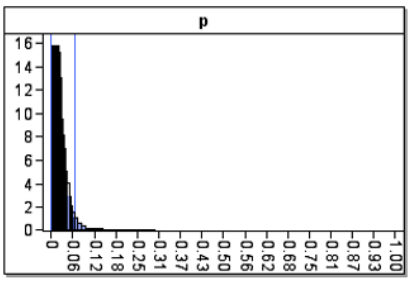

$H4\text{: } P(D = True|S = Severe, T = Ivermectin)$




$H4\text{: } P(D = True|S = Severe, T = Control)$




$H4\text{: } P(D = True|S = Mild/Moderate, T = Ivermectin)$



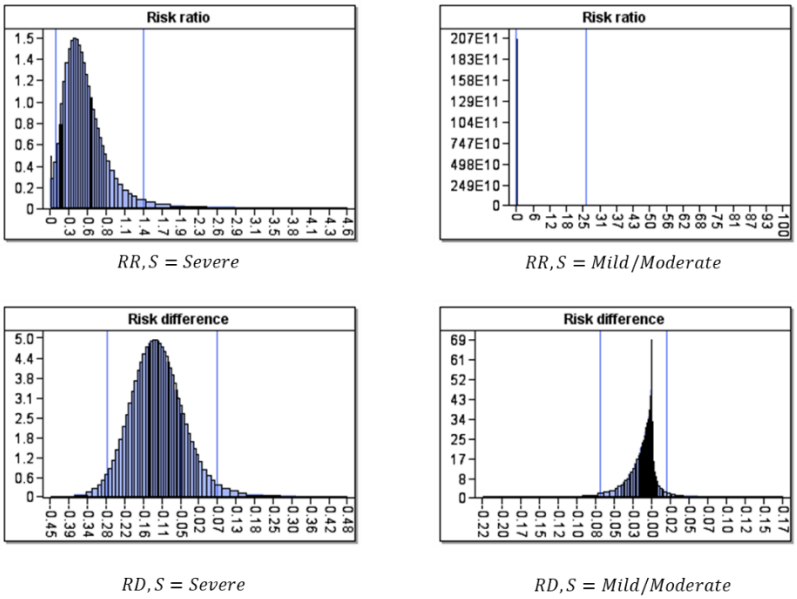

$H4\text{: } P(D = True|S = Mild/Moderate, T = Control)$

Figure 2: Posterior marginal probability distributions for mortality from meta-analysis

| | **Median** | **Mean** | **95% CI** |
|---|---|---|---|
| $P(D = True\|S = Severe,\ T = Ivermectin)$ | 0.107 | 0.117 | (0.019, 0.275) |
| $P(D = True\|S = Severe,\ T = Control)$ | 0.227 | 0.229 | (0.125, 0.349) |
| $P(D = True\|S = Mild/Moderate,\ T = Ivermectin)$ | 0.0003 | 0.004 | (1.4E-6, 0.0036) |
| $P(D = True\|S = Mild/Moderate,\ T = Control)$ | 0.012 | 0.0178 | (7.18E-5, 0.068) |

Table 2: Mean and 95% confidence intervals.

The $RR$ is the estimated mortality probability of ivermectin patients divided by the estimated mortality probability of control patients. One of the advantages of the Bayesian approach is that the shape and scale of the probability distribution for $RR$ can be directly calculated and inspected whilst making minimal statistical assumptions. Figure 3 shows the marginal probability distribution of $RR$. Note that the probability distribution $RR$ for mild/moderate Covid-19 is heavily asymmetric because the lower bounds for treatment variable, $T$, includes zero, hence producing a zero-division computational overflow. For this reason, classical statistical methods cannot easily estimate this quantity. However, we can instead use an arithmetically alternative measure that does not suffer from this defect, risk difference, $RD = ivermectin - control$. The marginal probability distribution for $RD$ is also shown in Figure 3 and for mild/moderate Covid-19 there is a clear modal spike around zero, and most of the probability mass is closer to zero difference, but for severe Covid-19 most of the probability mass is further from zero difference. This suggests our confidence in the evidence for ivermectin treatment for severe Covid-19 is stronger than for mild/moderate Covid-19.




$RR, S = Severe$ $RR, S = Mild/Moderate$

$RD, S = Severe$ $RD, S = Mild/Moderate$

Figure 3: Posterior marginal probability distributions for $RR$ and $RD$ from meta-analysis

If the $RR$ is less than one, then this provides support for the hypothesis that the treatment is effective (the lower the number the more effective) and if the upper bound of the confidence interval for the $RR$ is less than one then it is concluded that the treatment is effective with that level of confidence (95% in this case). From the marginal probability distributions shown in Figure 2, we compute the risk ratio, $RR$, dependent on the severity of Covid-19 shown in Table 3.

| | **Severe** | **Mild to Moderate** |
|---|---|---|
| $P(RR < 1)$ | 90.7% | 84.1% |

Table 3: Probability of risk ratio, $RR < 1$ , favouring ivermectin vs control

The $RR$ results of (Bryant et al., 2021) and (Roman et al., 2021) together with the $RR$ results from our Bayesian analysis are shown in Table 4.

| | ***RR* *** | ***RR*** **95% CI** |
|---|---|---|
| Roman et al, 2021 (all mild or moderate cases) | 0.37 | (0.12, 1.13) |
| Bryant et al, 2021 (mild or moderate cases) | 0.24 | (0.06, 0.94) |
| Bryant et al, 2021 (severe cases) | 0.51 | (0.22, 1.14) |
| Bryant et al, 2021 (all cases) | 0.38 | (0.19, 0.73) |
| Bayesian analysis, 2021 (mild or moderate cases) | 0.34 | (0.00, 26.0) |
| Bayesian analysis, 2021 (severe cases) | 0.48 | (0.08, 1.46) |

Table 4: Summary of risk ratio results in (Roman et al, 2021),
(Bryant et al, 2021) and this Bayesian meta-analysis

## 4. Conclusions

This Bayesian meta-analysis has shown that the posterior probability for the hypothesis of a causal link between, Covid-19 severity ivermectin and mortality is over 99%. From the Bayesian meta-analysis estimates the mean probability of death of patients with severe Covid-19 to be 11.7% (CI 12.6 – 34.75%) for those given ivermectin compared to 22.9% (CI 1.83 – 27.62%) for those not given ivermectin. For the severe Covid-19 cases the probability of the

risk ratio being less than one is 90.7% while for mild/moderate cases this probability it is 84.1%.

In our view this Bayesian analysis, based on the statistical study data, provides sufficient confidence that ivermectin is an effective treatment for Covid-19 and this belief supports the conclusions of (Bryant et al., 2021) over those of (Roman et al., 2021).

The paper has also highlighted the advantages of using Bayesian methods over classical statistical methods for meta-analysis, which is especially persuasive in providing a transparent marginal probability distribution for both risk ratio $RR$ and risk difference, $RD$. Furthermore, we show that using $RD$ avoids the estimation and computational issues encountered using $RR$ , thus making full and more efficient use of all evidence.

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## Appendix

The stages in the analysis are organised as follows:

A. Learn the mortality probability distribution from relevant trials for each hypothesis of concern using a Beta-Binomial hierarchical model.
B. For each causal hypothesis use the model in stage A to learn the mortality probability distributions relevant to that causal hypothesis.
C. For each causal hypothesis use the learnt probability distributions from stage B to predict the observed data and calculate the likelihood of observing that data.
D. For all causal hypotheses compute the posterior probability of each hypothesis given the likelihood of observing the data under that hypothesis and select the most likely causal hypothesis that explains the data.
E. Estimate the magnitude of impact of the relevant variables, under that hypothesis, on mortality.

For each hypothesis and combination of Covid-19 severity and treatment variable state we learn the corresponding mortality probability distribution using a hierarchical Beta-Binomial model (where $m$ is the number of studies, $n_i$ is the number of patients and $x_i$ is the number of deaths in study $i$):

$$P(p) = \sum_{\alpha,\beta,p_i,x_i} P(p|\alpha,\beta)P(\alpha,\beta)\left\{\prod_{i=0}^{m} P(x_i|n_i,p_i)P(p_i|\alpha,\beta)\right\}$$

$$P(x_i|n_i,p_i) = \binom{n_i}{p_i} {p_i}^{x_i}(1-p_i)^{n_i-x_i}$$

$$p_i \sim Beta(\alpha,\beta)$$

$$\alpha,\beta \sim Uniform(0,100)$$

where the mortality probability, $p$, is determined by two parameters, $\alpha$ and $\beta$ that model the global distribution of $p_i$ variables across the studies, where each $p_i$ is determined by its local data $(n_i, x_i)$.

An example of the structure of the Bayesian model used in steps A to C is shown in Figure 4, as a Bayesian Network, where we learn the probability distribution for $p \equiv P(D = True|S = Severe,\ T = Ivermectin)$ from the $m = 5$ relevant studies using data pairs $(n_i, x_i)$ for deaths and number of subjects in given trial.

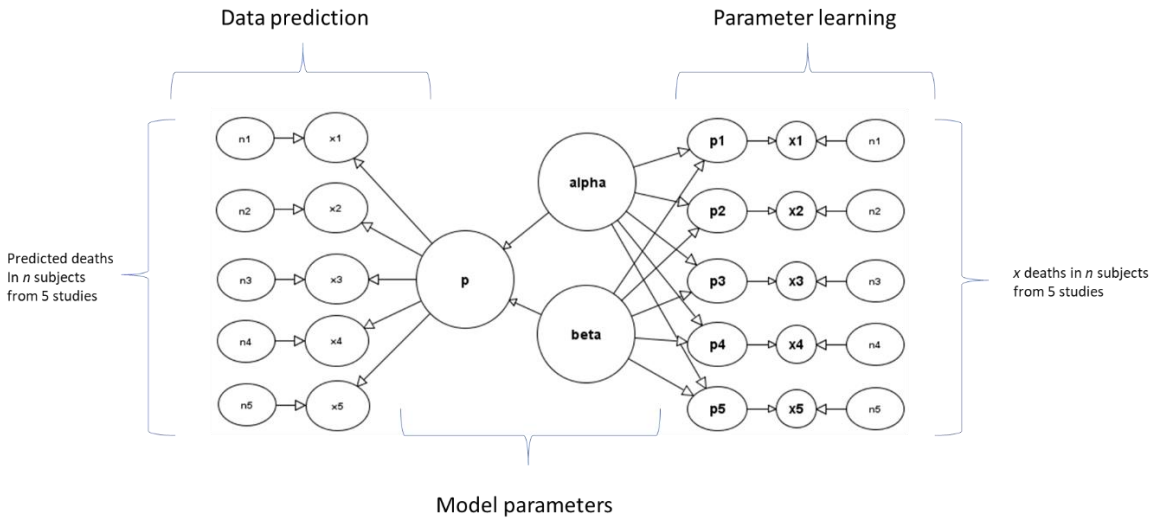


Figure 4: Meta analysis Bayesian Network

Once we have learnt $P(p|\alpha,\beta)$ from the data we need to determine how well the learnt distribution explains that data under each hypothesis $H1-H4$. Note that each hypothesis has a different number of mortality probability parameters, $p$,determined by the number of states for each variable for that hypothesis. So, for $H1: P(D)$ we only have one probability to determine. For $H2: P(D|S)$ we have two mortality probabilities to consider, one for severe Covid-19 and another for mild-moderate Covid-19, and so on.

As the number of mortality probability parameters to be estimated under each hypothesis increases the smaller the amount of data available to estimate each one. This leads to greater variance in predictions of the data when there are more parameters and, thus, models with more parameters are penalised by Occam's razor.

To test the predictions of the data under each hypothesis, $H_i$, we use Bayes:

$$P(H_i|Data) \propto P(Data|H_i)P(H_i)$$

Here we assume the prior probabilities $P(H_i)$ are uniform and we can calculate $P(Data|H_i)$ as:

$$P(Data|H_i) = \prod_{i=0}^{m} P\left(x_i|n_i, p_{H_i}\right)$$

which is simply the product of likelihoods over all trials data, using the learnt $p_{H_i}$ variables for the given hypothesis. Given the uniform prior assumption the posterior belief in each causal hypothesis is simply: $P(H_i|Data) = P(Data|H_i)$. The results are shown in Table 5.

| Hypothesis | Summary statistics for learnt $p$ distributions | | | | Likelihood of Data given $p$ | | | |
|---|---|---|---|---|---|---|---|---|
| | | Median | Mean | 95% CI | | Likelihood | Joint likelihood | Posterior probability |
| *H1* | *P(Death)* | 1.11% | 5.78% | (0, 35.8) | *P(Data)* | 2.97E-28 | 2.97E-28 | 0.000 |
| *H2* | *P(Death \| C = Severe)* | 16.52% | 17.20% | (5.5, 33.13) | *P(Data \| C = Severe)* | 5.65E-13 | 1.29E-21 | 0.009 |
| | *P(Death \| C = Mild/Moderate)* | 0.31% | 0.86% | (0, 4.74) | *P(Data \| C = Mild/Moderate)* | 2.29E-09 | | |
| *H3* | *P(Death \| T = Ivermectin)* | 0.04% | 3.37% | (0, 23.35) | *P(Data \| T = Ivermectin)* | 4.30E-11 | 6.86E-28 | 0.000 |
| | *P(Death \| T = Control)* | 3.63% | 7.62% | (0, 37.82) | *P(Data \| T = Control)* | 1.60E-17 | | |
| *H4* | *P(Death \| S = Severe, T = Ivermectin)* | 10.74% | 11.71% | (1.93, 27.62) | *P(Data \| S = Severe, T = Ivermectin)* | 2.17E-06 | 1.40E-19 | 0.991 |
| | *P(Death \| S = Mild/Moderate, T = Ivermectin)* | 0.03% | 0.42% | (0, 3.13) | *P(Data \| S = Mild/Moderate, T = Ivermectin)* | 1.24E-02 | | |
| | *P(Death \| S = Severe, T = Control)* | 22.65% | 22.91% | (12,6, 34.75) | *P(Data \| S = Severe, T = Control)* | 3.95E-06 | | |
| | *P(Death \| S = Mild/Moderate, T =Control)* | 1.20% | 1.78% | (0, 6.89) | *P(Data \| S = Mild/Moderate, T = Control)* | 1.32E-06 | | |

Table 5: Summary statistics of distributions and resulting likelihood predictions

The above description takes us up to stage D and established the support for each causal hypothesis. Here there was overwhelming support for hypothesis $H4$ and hence we use the causal structure for this hypothesis to compute the necessary impact statistics at stage E:

- compute the risk ratio ($RR$).
- Compute the risk difference ($RD$).
- determine the probability of the risk ratio being less than one.

The relevant computations here are:

$$RR = \frac{p_{ivermectin}}{p_{control}}$$

$$RD = p_{ivermectin} - p_{control}$$

$$P(RR < 1) = \int_0^1 f(RR)\, dRR$$

All calculations are carried out using AgenaRisk Bayesian network software (Agena Ltd, 2021). All models used are available on request and all can be run in the free trial version of AgenaRisk.