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A Bayesian Model for Evaluating Influenza Antiviral Efficacy in Household Studies with Asymptomatic Infections (Supplementary Materials)

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1. Specific Considerations for the Oseltamivir Trials

1.1 *Identification of clinical symptom onset*

We need a definition of ILI to identify the time of symptom onset, i.e., the first day of an ILI episode, which provides information for the infection time of a symptomatic influenza case. The two oseltamivir trials collected the same set of symptoms: temperature, three respiratory symptoms (cough, nasal congestion, sore throat) and four constitutional symptoms (headache, aches/pains, chills/sweats, fatigue). However, the two primary analyses use different definitions of ILI. Welliver et al. (2001) used body temperature $\geqslant 37.2^{\circ}$C plus at least one respiratory symptom and at least one constitutional symptom, whereas Hayden et al. (2004) used body temperature $\geqslant 37.8^{\circ}$C plus either cough or nasal congestion. We refer to the former as the Welliver definition and the latter as the Hayden definition. There are other definitions of ILI as well. For example, in the analysis of a zanamivir trial, Monto et al. (2002) used at least two symptoms of fever ($\geqslant 37.8^{\circ}$C), cough, headache, sore throat, and myalgia.

Halloran et al. (2007) used the Hayden definition for Osel I and the Welliver definition for Osel II. In Yang et al. (2006), the Welliver definition was used for Osel II, but the symptom onset dates in Osel I were

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determined by the source providing the data, and the exact definition of ILI was not clear. We use the same definition as in Halloran et al. (2007) for comparability between our and previous results. Other definitions are also explored in sensitivity analyses. We assume the incubation period takes discrete distributions (1 day:0.21, 2 days:0.58, 3 days:0.21) (Elveback, 1976), where $l : \rho$ stands for $\Pr(\tilde{t}_{hi} = \hat{t}_{hi} + l | \hat{t}_{hi}) = \rho$. We allow multiple ILI episodes for the same person, but two different episodes have to be sufficiently distant from each other so that each candidate infection day can be associated with at most a single ILI episode. Hence, we assume that there must be at least 7 days without any symptom preceding each ILI episode. Let $\tilde{t}_{hik}$ denote the k^{th} symptom onset day of person (h, i), $k = 1, \ldots, m_{hi}$, where m_{hi} is the total number of ILI episodes for this individual. Redefine $\tilde{t}_{hi}$ as a mapping from $\{t : \underline{T_h} \leqslant t \leqslant \overline{T_h}\}$ to $\{\tilde{t}_{hik} : k = 1, \ldots, m_{hi}\}$:

$$\tilde{t}_{hi}(t) = \begin{cases} \tilde{t}_{hik}, & \exists \tilde{t}_{hik}, \text{ such that } \Pr(\tilde{t}_{hik}|t) > 0 \\ \infty, & \text{otherwise.} \end{cases}$$

That is, $\tilde{t}_{hi}(t)$ is the symptom onset day if the infection of subject (h, i) occurs on day t. The function $\tilde{t}_{hi}(\cdot)$ is defined on $\{t : \underline{T_h} \leqslant t \leqslant \overline{T_h}\}$ because the true infection day $\hat{t}_{hi}$ is a latent variable and will be sampled over this range.

1.2 *Identification of candidate infection days*

To use our method, it is necessary to identify Ω_{hi}, the collection of candidate infection days for infected individuals, which in turn requires specific links between $C(\boldsymbol{y}_{hi}|\hat{t}_{hi})$ and lab-test results. We divide the time period for each individual into two intervals: $[\underline{T_h}, 0]$ and $[1, \overline{T_h}]$, and refer to the former as the pre-baseline period and the latter as the post-baseline period. All intervals considered here are sets of integers. We assume the baseline swab collected on day 1 is fully indicative of the infection status in the pre-baseline period. Given that the individual is not infected during the pre-baseline period, the infection status during the post-baseline period is jointly determined by both swabs collected after day 1 (follow-up swabs) and the HI titers; however, swabs are considered determinant while HI titers are considered supplementary. We do not consider the sensitivity and specificity of the lab-tests.

Before introducing the specific rules, two principle assumptions about lab-tests are made:

- A positive nasal/throat swab drawn on day t indicates that infection occurred in the period $\{s : t - \delta \leqslant s \leqslant t - 1\}$, without considering other information.
- A 4-fold increase in HI titers indicates that infection occurred in the post-baseline period given that the subject is susceptible at baseline.

When a subject has multiple positive swabs, we only consider the first one and discard the subsequent ones. Assume $\underline{T_h} < 1 - \delta$. Let $I(\cdot)$ be the indicator function. The following rules are used to identify $C(\boldsymbol{y}_{hi}|\hat{t}_{hi})$ and thus Ω_{hi}:

1. If the baseline (day 1) swab is positive, then $C(\boldsymbol{y}_{hi}|t) = I\big(t \in [1 - \delta, 0]\big)$; else, subject (h, i) is susceptible at the beginning of day 1.
2. Given the baseline swab is negative, if the first positive follow-up swab is drawn on day $t^\star$, consider the following possibilities defined by the location of $[t^\star - \delta, t^\star - 1]$ relative to $[1, \overline{T_h}]$:
   - If $t^\star - 1 \leqslant \overline{T_h}$, then $C(\boldsymbol{y}_{hi}|t) = I\big(t \in [t^\star - \delta, t^\star - 1] \cap [1, \overline{T_h}]\big)$.
   - If $t^\star - \delta \leqslant \overline{T_h} < t^\star - 1$, check HI titers. If there is a 4-fold increase in HI titers, $C(\boldsymbol{y}_{hi}|t) = I\big(t \in [t^\star - \delta, t^\star - 1] \cap [1, \overline{T_h}]\big)$; else, $C(\boldsymbol{y}_{hi}|t) = 0$ for all $t \in [1, \overline{T_h}]$.

- If $t^\star - \delta > \overline{T_h}$, check HI titers. If there is a 4-fold increase in HI titers, $C(\boldsymbol{y}_{hi}|t) = I\big(t \in [1, \overline{T_h}]\big)$; else, $C(\boldsymbol{y}_{hi}|t) = 0$ for all $t \in [1, \overline{T_h}]$.

3. Given the baseline swab is negative, if all follow-up swabs are negative or there is no follow-up swab, check HI titers. If there is a 4-fold increase in HI titers, $C(\boldsymbol{y}_{hi}|t) = I\big(t \in [1, \overline{T_h}]\big)$; else, $C(\boldsymbol{y}_{hi}|t) = 0$ for all $t \in [1, \overline{T_h}]$.

While the choice of δ seems arbitrary, it should at least (1) be biologically reasonable, and (2) allow Ω_{hi} to be non-empty for infected subjects. In a meta-analysis of human influenza challenge studies, Carrat et al. (2008) found the average duration of viral shedding among 375 participants to be 4.8 days (95% CI:4.31, 5.29). We set $\delta = 7$ for the major analysis, and perform sensitivity analysis for different values of δ.

The determination of $\overline{T_h}$ is affected by both the duration of symptom diary and the last day of specimen collection. For Osel II, we assume the duration of symptom diary is 14 days, starting from day 1. For subjects whose symptom diary stopped at day 7 due to absence of ILI in the first week, we assume no ILI occurred from day 8 to day 14. It probably takes several days for the HI titer level to reach a 4-fold increase after infection, hence it is reasonable to set $\overline{T_h} = 14$ as the second blood draw for HI titers was on day 21. Similarly, we set $\overline{T_h} = 23$ for Osel I as the second blood draw for HI titers was on day 30, although the symptom diary was recorded up to day 30.

2. PRIOR DISTRIBUTIONS

As the information in the data about the relative infectivity curve is very limited and the shape parameters, a and b, are highly dependent, we adopt a reparameterization in the form of $A = a + b$ and $B = \frac{a}{a+b}$ to improve the convergence rate and to reduce auto-correlation. For all parameters except for A, we use flat priors over their domains at the natural scale for the primary analysis:

$$
\begin{aligned}
\pi(\gamma_0) &\propto I(0 < \gamma_0 < \infty) \\
\pi(\gamma_1) &\propto I(0 < \gamma_1 < \infty) \\
\pi(\alpha_{uv}) &\propto I(-\infty < \alpha_{uv} < \infty), \quad (u, v) \in \{(0,0), (0,1), (1,0)\} \\
\pi(\theta_{Rx}) &\propto I(0 < \theta_{Rx} < \infty) \\
\pi(\phi_{Rx}) &\propto I(0 < \phi_{Rx} < \infty) \\
\pi(\theta_{\text{Age}}) &\propto I(0 < \theta_{Age} < \infty) \\
\pi(\phi_{\text{Age}}) &\propto I(0 < \phi_{Age} < \infty) \\
\pi(A) &\propto exp\{-\frac{1}{2}(\log(A-2) - \log(2))^2\}, \quad A > 2 \\
\pi(B) &\propto I(0 < B < 1)
\end{aligned}
$$

An informative prior is used for A such that it has mode at 4, based on the empirical values of a and b. A minimum value of 2 is imposed on A to ensure that most samples of a and b are larger than 1 so that the relative infectivity curve has a bell shape.

Highly informative priors are investigated in sensitivity analyses. It should be noted that these flat priors are noninformative in the sense that each possible value in the domain is equally weighted, but such noninformativeness is not invariant to transformation in general. Our purpose of using flat priors at the natural scale is to make justifiable comparison of the Bayesian estimates with likelihood-based estimates in previous analyses.

3. MCMC SAMPLING SCHEME

3.1 *Sampling parameters*

Let $\boldsymbol{\omega}(-\beta)$ denote the collection of parameters without β. Take the common risk γ_0 as an example. Given the current value of ${\gamma_0}^{old}$, we sample ${\gamma_0}^{new}$ from the proposal distribution Log-Normal$({\gamma_0}^{old}, d^2_{\gamma_0})$, and accept ${\gamma_0}^{new}$ with the probability

$$\alpha = \min\left\{1, \frac{\Pr\left(\boldsymbol{y}, \hat{\boldsymbol{t}}, \tilde{\boldsymbol{t}}, {\gamma_0}^{new}, \boldsymbol{\omega}(-\gamma_0)\right)}{\Pr\left(\boldsymbol{y}, \hat{\boldsymbol{t}}, \tilde{\boldsymbol{t}}, {\gamma_0}^{old}, \boldsymbol{\omega}(-\gamma_0)\right)} \times \frac{{\gamma_0}^{new}}{{\gamma_0}^{old}}\right\}.$$

The value of d_{γ_0} is chosen to reach an acceptance rate of $0.3 - 0.4$.

3.2 *Monitoring the convergence of the chains*

To obtain the joint posterior distribution of all the parameters, a burn-in period of 10000 iterations is adopted on three parallel MCMC chains. Convergence in the joint posterior distribution of all parameters is diagnosed on three parallel chains using the scale reduction factor defined as $\sqrt{\hat{R}} = \sqrt{\frac{M-1}{M} + \frac{1}{M}\frac{V}{W}}$ in Gelman and Rubin (1992), where M is the number of runs, and V and W are the between-sequence and within-sequence variances respectively. Convergence is considered as reached if $\sqrt{\hat{R}} < 1.1$ for all parameters. After convergence, we go over the last 5000 iterations and randomly choose one chain per iteration to read in the samples. We report the results for all parameters based on these 5000 samples.

4. ADDITIONAL SENSITIVITY ANALYSIS

The standard analysis to which all sensitivity analyses are compared is given in column 2 of Table 4 in the main text and is also added to each sensitivity analysis table to facilitate comparison. In general, the posterior estimates for γ_1, AVE_{Si} (via θ_{Rx}), θ_{Age} and ϕ_{Age} are relatively robust to various assumptions and prior believes.

4.1 *Sensitivity to the definition of ILI (Table S1)*

We consider two ILI definitions different from the one used in our primary analysis:

1. Use the Hayden definition for both Osel I and Osel II. The Welliver definition can not be applied to Osel I because constitutional symptoms were missing for many subjects in that study.

2. A weaker definition that lowers the temperature threshold of the Hayden definition: body temperature $\geqslant 37.2^{\circ}$C plus either cough or nasal congestion.

We refer to the first one as the Hayden definition and the second one as the weak definition. The incubation period takes discrete distributions (1 day:0.21, 2 days:0.58, 3 days:0.21) for the Hayden definition and (1 day:0.5, 2 days:0.5) for the weak definition. The distribution for the weak definition is based on some challenge studies (Fritz et al., 1999; Hayden et al., 1999) in which one or more symptoms generally appeared in the first two days after inoculation of influenza viruses.

The estimates for γ_1, AVE_{Si}, θ_{Age} and ϕ_{Age} are not sensitive to the ILI definition, whereas the estimates for all other parameters are. In particular, results for definition 3 are quite different from those for definitions 1 and 2. With definition 3, the probabilities of developing ILI are similar between treatment

combinations, and thus the efficacies for pathogenicity approach 0. Overall, regardless of the ILI definition, the prophylaxis for the susceptible significantly reduced susceptibility to infection and symptomatic infection but did not change pathogenicity, and antiviral therapy for infectives reduced pathogenicity and the risk of symptomatic infection in the contacts, but was not able to reduce the risk of viral transmission.

4.2 *Sensitivity to the distribution of the incubation period (Table S2)*

We change the distribution of the incubation period to {1 day: 0.7, 2 days: 0.2, 3 days: 0.1} and {1 day: 0.1, 2 days: 0.2, 3 days: 0.4, 4 days: 0.3} to reach a shorter mean duration of 1.4 days and a longer mean duration of 2.9 days, respectively. A longer mean duration of the incubation period seems to be associated with slightly higher γ_0 and γ_1, but does not affect the estimates for the pathogenicity parameters and the efficacies.

4.3 *Sensitivity to the range of potential infection time that a positive lab-test can indicate (Table S3)*

We have assumed that a positive nasal/throat swab collected on day t indicates an infection day between $t-\delta$ and $t-1$, where $\delta = 7$ in the primary analysis. We change the value of δ to 5 days and 10 days respectively, but identify no appreciable differences except for minor impacts on the estimates for γ_0.

4.4 *Sensitivity to the prior distribution (Table S4)*

In the primary analysis, priors are changed for one parameter at a time. However, changes in the prior of one parameter may influence the posterior distribution of other parameters. Here we investigate the sensitivity of the Bayesian estimates by changing the priors from flat to non-flat for three subsets of parameters, one subset at a time while keeping the priors of other parameters unchanged: the infection rates (γ_0 and γ_1), the pathogenicity parameters (α_{00}, α_{01} and α_{10}), and the antiviral effects (θ_{Rx} and ϕ_{Rx}). The non-flat priors have the same form as those used for Figure 3 in the primary analysis, with μ corresponding to the 99^{th} percentile of the flat-prior-based posterior distribution reflecting strong prior belief in extremely large values.

The third column of Table S1 suggests that, when the infection rates are believed to be high, their posterior estimates go up moderately for γ_1 and substantially for γ_0. The strong prior in infeciton rates also lead to increase in AVE_{Ii} and decreases in θ_{Age} and ϕ_{Age}. The impact on the estimates of other parameters is limited.

According to the fourth column, strong prior information about the pathogenicity parameters does play a significant role in the posterior distributions of the pathogenicity parameters themselves and related efficacy measures, AVE_{Sp}, AVE_{Ip}, AVE_{Sd} and AVE_{Id}, but does not affect much the estimates for other parameters and efficacy measures.

The last column shows that strong prior belief in large values for θ_{Rx} and ϕ_{Rx}, i.e., towards null or adverse antiviral effects, has moderate influence on the estimates for γ_1, AVE_{Si} (via θ_{Rx}), AVE_{Sd} and AVE_{Id}, but decreases the posterior estimates for AVE_{Ii} substantially. We also observe minor increases in the posterior estimates for ϕ_{Age}. Pathogenicity parameters seem to be insensitive to the prior belief about the antiviral effects, and consequently so do AVE_{Sp} and AVE_{Ip}.

Table S1. *Analysis of sensitivity to the definition of ILI. Distribution of the incubation period is {1 day: 0.21, 2 days: 0.58, 3 days: 0.21} for the Hayden definitions and is {1 day:0.5, 2 days:0.5} for the weak definition. Estimates are presented as Median (95% CS).*

Parameter	Standard	Hayden Definition	Weak Definition
γ_0	0.00046 (0.00006,0.0017)	0.00053 (0.00007,0.0019)	0.0017 (0.00062,0.0040)
γ_1	0.021 (0.011,0.038)	0.020 (0.010,0.037)	0.018 (0.0092,0.034)
η_{00}	0.49 (0.33,0.66)	0.41 (0.25,0.58)	0.53 (0.38,0.68)
η_{01}	0.30 (0.095,0.58)	0.21 (0.056,0.49)	0.49 (0.25,0.74)
η_{10}	0.080 (0.018,0.22)	0.079 (0.018,0.21)	0.38 (0.18,0.65)
AVE_{Si}	0.61 (0.36,0.78)	0.61 (0.36,0.77)	0.58 (0.30,0.76)
AVE_{Ii}	-0.21 (-0.94,0.29)	-0.17 (-0.89,0.29)	0.086 (-0.65,0.56)
AVE_{Sp}	0.38 (-0.32,0.81)	0.48 (-0.36,0.86)	0.088 (-0.54,0.53)
AVE_{Ip}	0.84 (0.53,0.96)	0.80 (0.39,0.95)	0.28 (-0.44,0.68)
AVE_{Sd}	0.77 (0.42,0.93)	0.80 (0.40,0.95)	0.62 (0.25,0.83)
AVE_{Id}	0.80 (0.38,0.96)	0.78 (0.23,0.95)	0.36 (-0.38,0.76)
θ_{Age}	1.07 (0.64,1.87)	1.07 (0.65,1.87)	1.03 (0.63,1.79)
ϕ_{Age}	1.05 (0.64,1.69)	1.04 (0.63,1.79)	1.11 (0.63,1.89)

Table S2. *Analysis of sensitivity to the distributions of the incubation period. The short period has the distribution {1 day: 0.7, 2 days: 0.2, 3 days: 0.1}, and the long period has the distribution {1 day: 0.1, 2 days: 0.2, 3 days: 0.4, 4 days: 0.3}. Estimates are presented as Median (95% CS).*

Parameter	Standard	Short	Long
γ_0	0.00046 (0.00006,0.0017)	0.00046 (0.00006,0.0017)	0.00053 (0.00008,0.0019)
γ_1	0.021 (0.011,0.038)	0.020 (0.0096,0.034)	0.026 (0.013,0.046)
η_{00}	0.49 (0.33,0.66)	0.50 (0.33,0.67)	0.49 (0.32,0.66)
η_{01}	0.30 (0.095,0.58)	0.30 (0.10,0.58)	0.31 (0.096,0.60)
η_{10}	0.080 (0.018,0.22)	0.079 (0.018,0.21)	0.079 (0.017,0.22)
AVE_{Si}	0.61 (0.36,0.78)	0.61 (0.38,0.78)	0.60 (0.33,0.77)
AVE_{Ii}	-0.21 (-0.94,0.29)	-0.18 (-0.96,0.29)	-0.22 (-1.03,0.26)
AVE_{Sp}	0.38 (-0.32,0.81)	0.40 (-0.28,0.80)	0.37 (-0.41,0.80)
AVE_{Ip}	0.84 (0.53,0.96)	0.84 (0.53,0.96)	0.84 (0.52,0.96)
AVE_{Sd}	0.77 (0.42,0.93)	0.77 (0.44,0.93)	0.75 (0.38,0.93)
AVE_{Id}	0.80 (0.38,0.96)	0.81 (0.39,0.96)	0.80 (0.33,0.96)
θ_{Age}	1.07 (0.64,1.87)	1.06 (0.64,1.81)	1.05 (0.63,1.80)
ϕ_{Age}	1.05 (0.64,1.69)	1.07 (0.66,1.75)	0.99 (0.61,1.63)

Table S3. *Analysis of sensitivity to δ, the range of potential infection time that a positive lab-test can indicate. Estimates are presented as Median (95% CS).*

Parameter	Standard ($\delta = 7$)	$\delta = 5$	$\delta = 10$
γ_0	0.00046 (0.00006,0.0017)	0.00055 (0.00007,0.0020)	0.00045 (0.00007,0.0017)
γ_1	0.021 (0.011,0.038)	0.020 (0.0099,0.038)	0.021 (0.011,0.038)
η_{00}	0.49 (0.33,0.66)	0.49 (0.32,0.65)	0.50 (0.33,0.67)
η_{01}	0.30 (0.095,0.58)	0.30 (0.098,0.59)	0.31 (0.098,0.58)
η_{10}	0.080 (0.018,0.22)	0.079 (0.017,0.22)	0.079 (0.018,0.22)
AVE_{Si}	0.61 (0.36,0.78)	0.61 (0.36,0.78)	0.61 (0.36,0.77)
AVE_{Ii}	-0.21 (-0.94,0.29)	-0.15 (-0.98,0.31)	-0.21 (-1.0,0.28)
AVE_{Sp}	0.38 (-0.32,0.81)	0.37 (-0.35,0.80)	0.38 (-0.30,0.81)
AVE_{Ip}	0.84 (0.53,0.96)	0.83 (0.52,0.96)	0.84 (0.54,0.96)
AVE_{Sd}	0.77 (0.42,0.93)	0.76 (0.42,0.93)	0.76 (0.43,0.93)
AVE_{Id}	0.80 (0.38,0.96)	0.81 (0.39,0.96)	0.81 (0.37,0.96)
θ_{Age}	1.07 (0.64,1.87)	1.06 (0.64,1.86)	1.04 (0.64,1.76)
ϕ_{Age}	1.05 (0.64,1.69)	1.04 (0.62,1.77)	1.05 (0.63,1.70)

Table S4. *Analysis of sensitivity of posterior estimates to the prior distributions by changing a subset of priors while keeping other priors flat. The new prior mode for each parameter in this subset corresponds to the 99^{th} percentile of the posterior distribution based on the flat prior. Estimates are presented as Median (95% CS).*

		Parameters for which priors are changed		
Parameter	Standard	γ_0 and γ_1 [a]	α_{00}, α_{01} and α_{10} [b]	θ_{Rx} and ϕ_{Rx} [c]
γ_0	0.00046 (0.00006,0.0017)	0.00091 (0.00033,0.0022)	0.00046 (0.00007,0.0017)	0.00044 (0.00006,0.0017)
γ_1	0.021 (0.011,0.038)	0.029 (0.019,0.044)	0.020 (0.011,0.036)	0.016 (0.0090,0.029)
η_{00}	0.49 (0.33,0.66)	0.48 (0.32,0.64)	0.54 (0.42,0.65)	0.50 (0.34,0.67)
η_{01}	0.30 (0.095,0.58)	0.30 (0.10,0.58)	0.45 (0.24,0.67)	0.30 (0.097,0.59)
η_{10}	0.080 (0.018,0.22)	0.078 (0.016,0.21)	0.13 (0.055,0.26)	0.079 (0.017,0.21)
AVE_{Si}	0.61 (0.36,0.78)	0.63 (0.39,0.79)	0.61 (0.36,0.78)	0.50 (0.30,0.65)
AVE_{Ii}	-0.21 (-0.94,0.29)	-0.066 (-0.73,0.36)	-0.21 (-0.97,0.26)	-0.53 (-1.13,-0.077)
AVE_{Sp}	0.38 (-0.32,0.81)	0.37 (-0.36,0.80)	0.17 (-0.27,0.53)	0.40 (-0.29,0.81)
AVE_{Ip}	0.84 (0.53,0.96)	0.84 (0.53,0.97)	0.76 (0.52,0.90)	0.84 (0.54,0.97)
AVE_{Sd}	0.77 (0.42,0.93)	0.77 (0.44,0.93)	0.68 (0.39,0.85)	0.70 (0.31,0.91)
AVE_{Id}	0.80 (0.38,0.96)	0.83 (0.44,0.97)	0.70 (0.32,0.89)	0.76 (0.26,0.95)
θ_{Age}	1.07 (0.64,1.87)	0.83 (0.55,1.26)	1.06 (0.66,1.79)	1.05 (0.64,1.75)
ϕ_{Age}	1.05 (0.64,1.69)	0.91 (0.56,1.45)	1.06 (0.67,1.74)	1.13 (0.70,1.81)

a: $\mu_{(\sigma)} = \log(0.00197)_{(0.832)}$ for γ_0 and $\log(0.0408)_{(0.324)}$ for γ_1.
b: $\mu_{(\sigma)} = 0.802_{(0.357)}$ for α_{00}, $0.764_{(0.724)}$ for α_{01} and $-0.825_{(0.786)}\alpha_{10}$.
c: $\mu_{(\sigma)} = \log(0.711)_{(0.269)}$for θ_{Rx}, $\log(2.097)_{(0.26)}$ for ϕ_{Rx}.

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