Non-Linear Fractional Polynomial for Estimates of Long-Term Persistence of Induced HPV Antibodies: A Hierarchical Bayesian Approach:

Supplementary Web Appendix

—blinded—

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1 Probability of protection for anti-HPV-18 antibodies

In this appendix, we discuss the results for the analysis of the anti-HPV-18 antibodies and we present also model diagnostics to the fitted models for both anti-HPV-16 antibodies and anti-HPV-18 antibodies.

Figure 1 shows the histogram of the posterior probability above a threshold value for anti-HPV-18 antibodies. There are 118 subjects who have $\widehat{\pi}_{ij}$=1 above a threshold τ=2.446 while 86 subjects have a $\widehat{\pi}_{ij}$=0 over 50 years. Moreover, there are 186 subjects whose posterior probability above threshold is between 0 and 1; $0 < \widehat{\pi}_{ij} < 1$. If we use the threshold τ=1.355, all of the subjects except two subjects have a posterior probability above a threshold more than 0.5 over 50 years. The left panel of Figure 2 shows the sorted posterior probabilities above a threshold τ=2.446 while the right panel shows the posterior probabilities above the threshold τ=2.446 for subjects who had above/below threshold value for 10 years. Clearly, among 212 (54.4%) subjects who had above the threshold value, 133 subjects have $\widehat{\pi}_{ij} = 1$ while 79 subjects have $0.48 < \widehat{\pi}_{ij} < 1$. On the other hand, among 178 (45.6%) subjects who had below the threshold value, 83 subjects have $\widehat{\pi}_{ij} = 0$ while 95 subjects have $0 < \widehat{\pi}_{ij} < 0.5$ for 10 years.

Figure 3 shows the long term prediction for some selected subjects while Figure 4 indicates their posterior distribution of the probability above the threshold τ=1.355 for these subjects. We can clearly see that the first two subjects have a log antibody level below the threshold τ=1.355, whereas the other two subjects

have a log antibody level above the threshold τ=1.355 for 50 years.

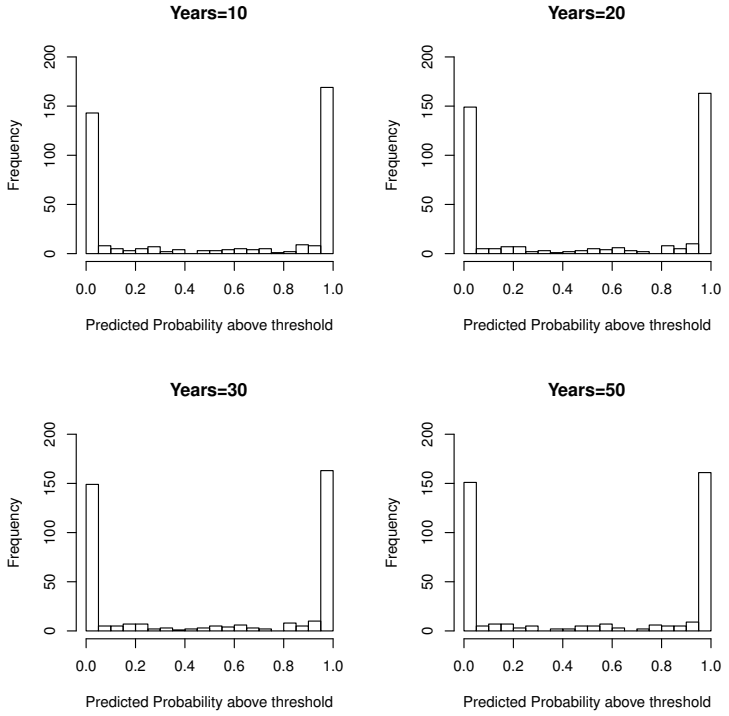

Figure 1: *The posterior probability above a threshold=2.446 at 10,20, 30 and 50 years for anti-HPV-18 antibodies using non-linear fractional polynomial model.*

2 Model Diagnostics

For both anti-HPV-16 antibodies and anti-HPV-18 antibodies, convergence diagnostics were constructed using trace plots, Brooks-Gelman-Rubin (BGR) plots, and potential scale reduction factor ($\widehat{R}$; Brooks and Gelman, 1998). The results for the trace plots for anti-HPV-16 antibodies and anti-HPV-18 antibodies are shown in Figure 5 and Figure 6, respectively, while the BGR plots are displayed in Figure 7 and Figure 8, respectively. Table 1 shows the result of $\widehat{R}$. We can clearly see that all the model diagnostics methods show good convergence. As a practical rule of thumb, a 97.5% quantile of $\widehat{R} \leq 1.2$ is sufficient to claim convergence (Smith, 2007). Hence, the estimates of $\widehat{R}$ in Table 1 show rapid convergence and efficient mixing of the chains for all the parameters. Note that the notations sigma.bo, sigma.b1, sigma, and rhom in the figures denote the variance of the random intercept, random slope, measurement error and the correlation between the

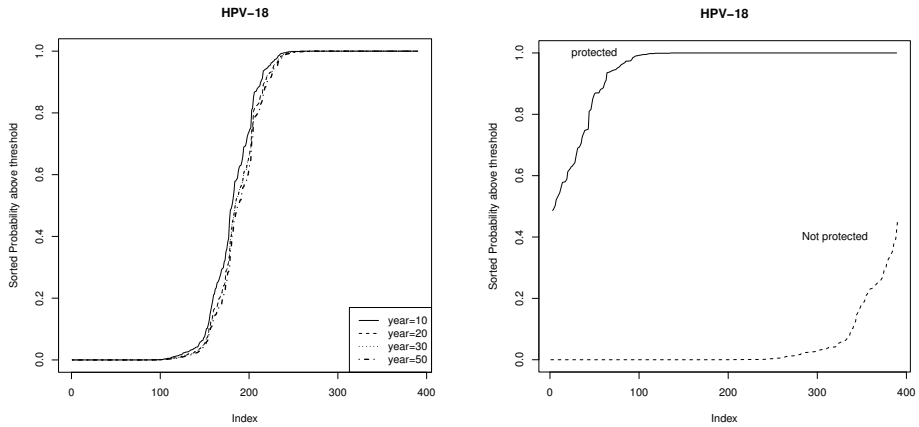

Figure 2: *anti-HPV-18 antibodies; Subject-specific sorted posterior probability above a threshold 2.446 (Left Panel) and posterior probability above a threshold 2.446 for 10 years for subjects who had above/below a threshold value (Right Panel) using non-linear fractional polynomial model. Index represents the number of subjects.*

random intercept and the random slope, respectively, and p1 shows the power parameter.

3 Modeling the Mean Antibody Using a Modified Power-law Model

To investigate the robustness of the inferences drawn from the non-linear fractional polynomial (NLFP) model, we considered the modified power-law model proposed by Fraser *et al.* (2007). These authors extended the power-law model to account for two populations of B-cells, including activated and memory B-cells, which impose a long-term antibody plateau. Their model is given by:

$$Y_{ij} = b_{0i} + \log[(1-\pi)(c+t_{ij})^{-b_{1i}} + \pi] + \varepsilon_{ij},$$

where $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$ and π is the relative level of antibody produced in the long-term memory plateau (between 0 and 1). A value of $\pi > 0$ shows long-term antibody persistence. The parameter β_0 is the peak log level, β_1 is the decay rate, and c is an arbitrary small constant (often set to zero). The modified power-law model enforce an asymptote for the antibody levels at $t_{ij} \to \infty$ and, as a result, the expected value of individual antibody level reaches a constant value in the long run. Note that for $\pi = 0$, the modified power-law model is reduced to standard power-law model.

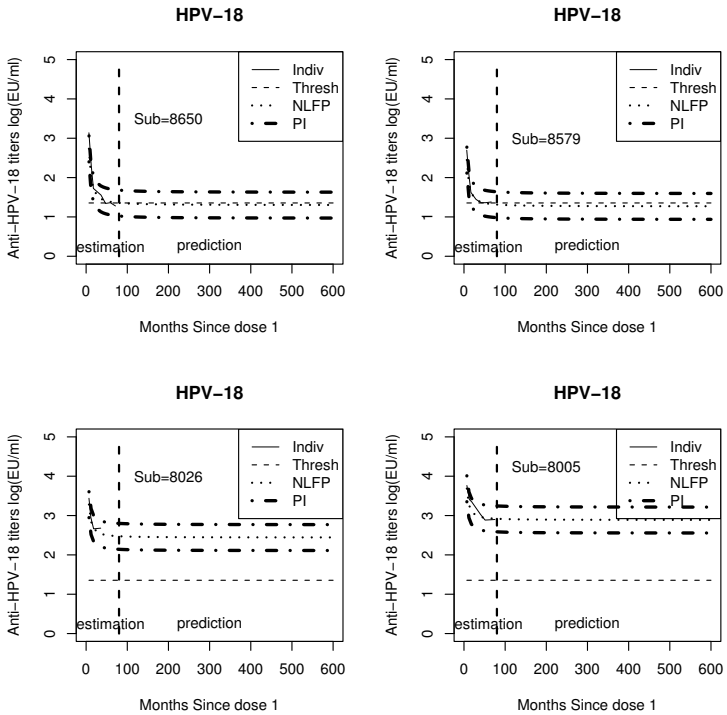

Figure 3: *Long term (50 Years) prediction with posterior predictive interval of some selected subjects for anti-HPV-18 antibodies using non-linear fractional polynomial model.*

Similar to the non-linear fractional polynomial model, an independent normal prior was used for β_0 and β_1, whereas a gamma prior was employed for the precisions, $\sigma_\varepsilon^{-2} \sim G(0.01, 0.01)$. Further, we assumed a uniform prior distribution for π, $\pi \sim \mathrm{U}(0,1)$. For the subject-specific parameters, b_{0i} and b_{1i}, we specified a bivariate normal distribution prior, i.e.,

$$\begin{bmatrix} b_{0i} \\ b_{1i} \end{bmatrix} \sim MVN\left(\begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}, \mathbf{D} = \begin{bmatrix} \sigma_{b_0}^2 & \rho_{b_0 b_1}\sigma_{b_0}\sigma_{b_1} \\ \rho_{b_0 b_1}\sigma_{b_0}\sigma_{b_1} & \sigma_{b_1}^2 \end{bmatrix} \right).$$

We assumed an inverse Wishart prior distribution for the covariance matrix $\mathbf{D}$, i.e.,

$$\mathbf{D}^{-1} \sim \mathrm{Wishart}(R_D, 2).$$

Here R_D is 2×2 identity matrix.

We implemented the modified power-law model using a Markov Chain Monte Carlo (MCMC) sampling procedure with three chains of 100,000 iterations, a burn-in length of 20,000 and thinning equal to 100. The trace plot, Brooks, Gelman, and Rubin's (BGR) plot (Figures 13 and 14), and estimated potential scale

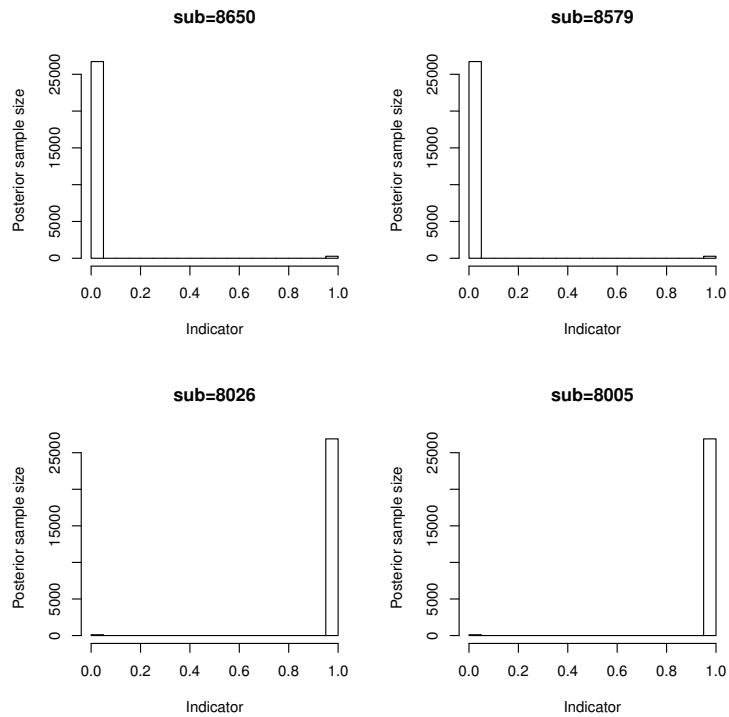

Figure 4: *The posterior distribution of the probability above the threshold τ=1.355 for some selected subject for anti-HPV-18 antibodies using non-linear fractional polynomial model.*

reduction factor (Table 2) show good convergence for all the model parameters.

The posterior summary statistics using the modified power-law model are shown in Table 2. For both anti-HPV-16 and anti-HPV-18 antibodies, the DIC value for the non-linear fractional polynomial (NLFP) is smaller than that of the modified power-law (MPL) model, indicating that the NLFP fits to the data better than the MPL model.

Figure 9 shows the long-term posterior predicted means for anti-HPV-16 and anti-HPV-18 antibodies using the MPL model. The results are comparable with the results obtained from the non-linear fractional polynomial model (also for probabilities of being above a threshold, see Figures 10, 11, and 12).

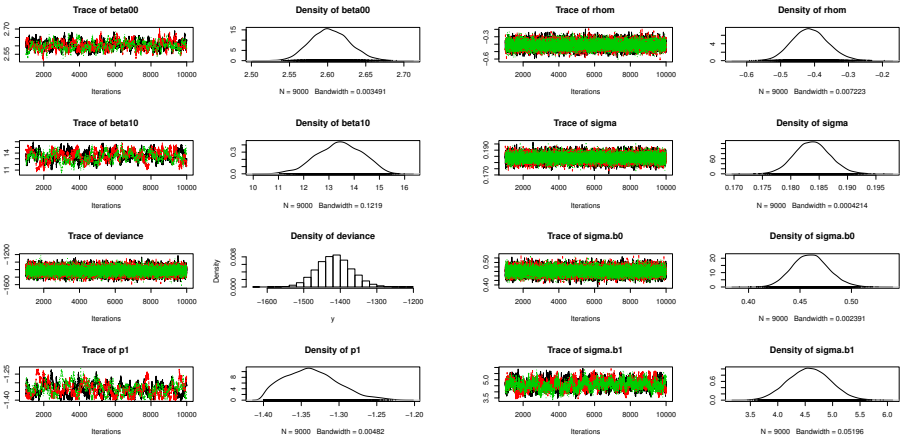

Figure 5: *Trace plot for anti-HPV-16 antibodies for non-linear fractional polynomial model.*

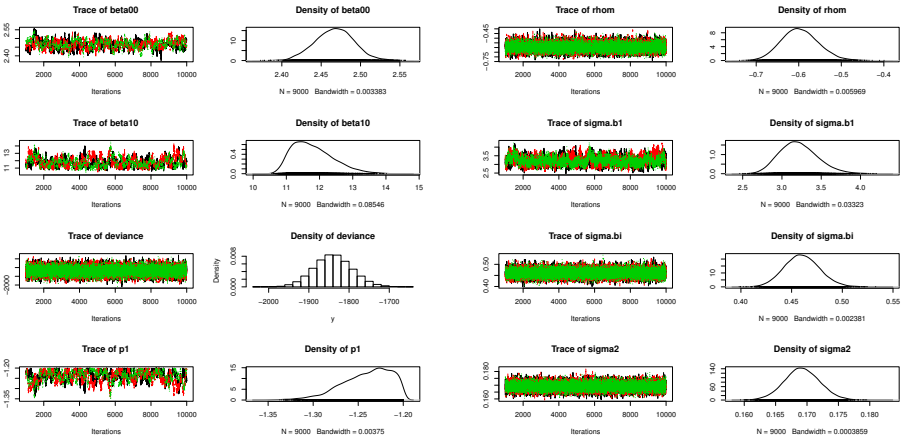

Figure 6: *Trace plot for anti-HPV-18 antibodies for non-linear fractional polynomial model.*

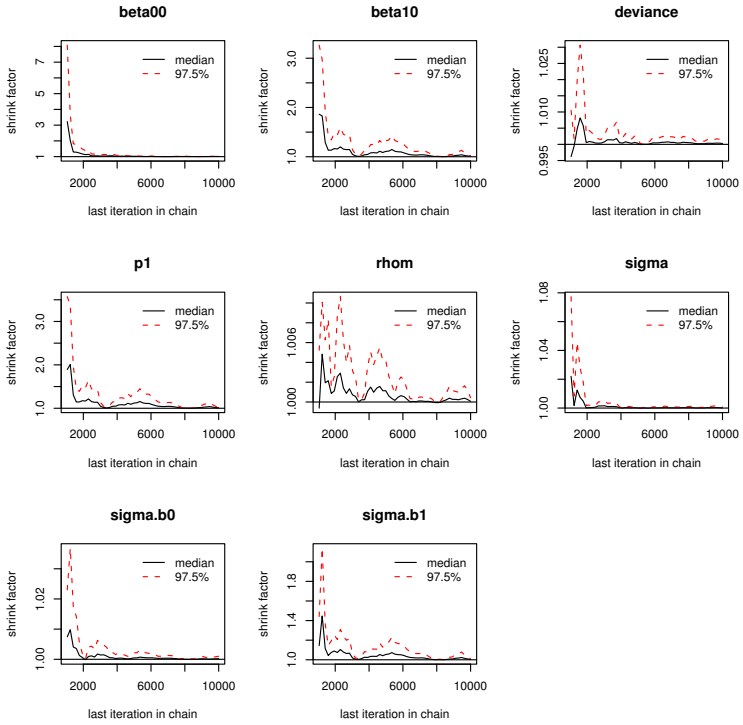

Figure 7: *Brooks, Gelman and Rubin's plot for anti-HPV-16 antibodies for non-linear fractional polynomial model.*

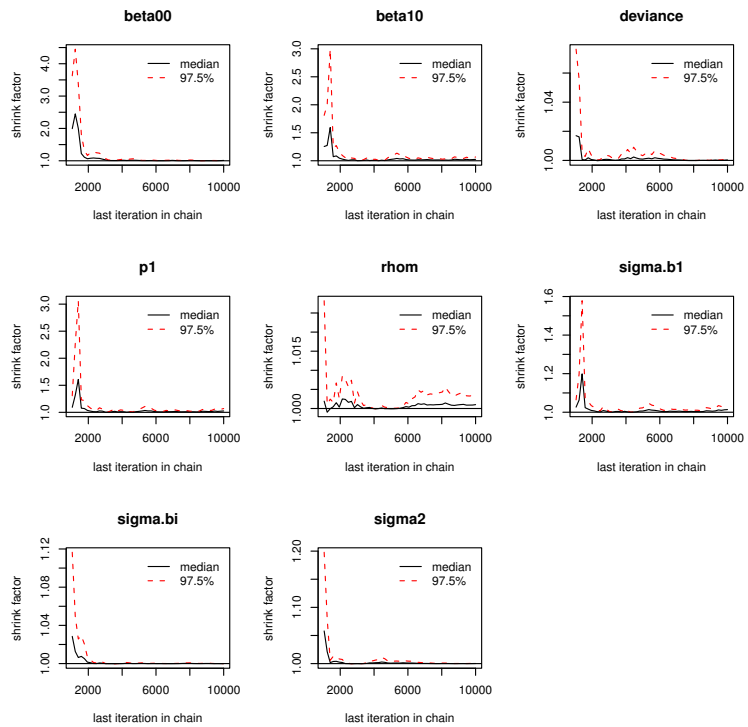

Figure 8: *Brooks, Gelman and Rubin's plot for anti-HPV-18 antibodies for non-linear fractional polynomial model.*

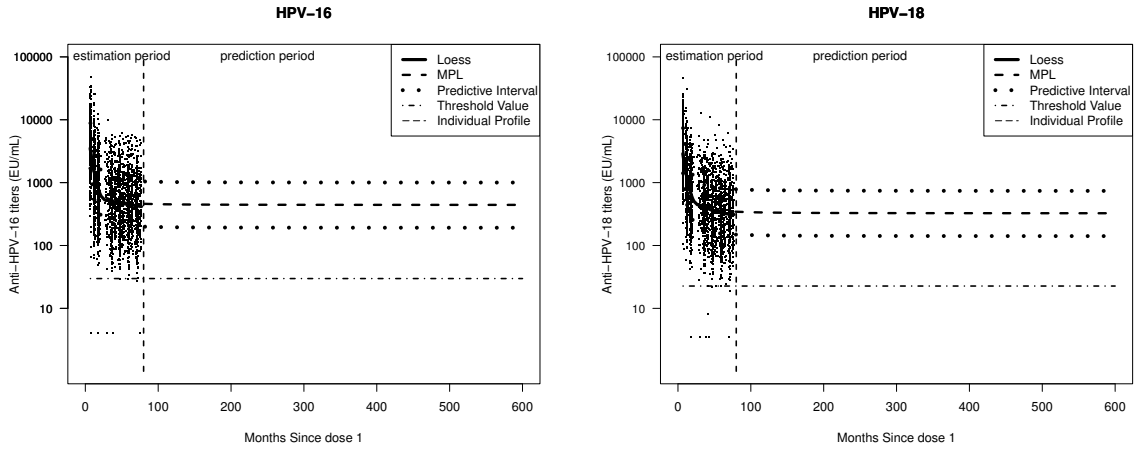

Figure 9: *Long-term prediction with posterior predictive interval over 50 years for anti-HPV-16 (left panel) and anti-HPV-18 antibodies (right panel) using the modified power-law model.*

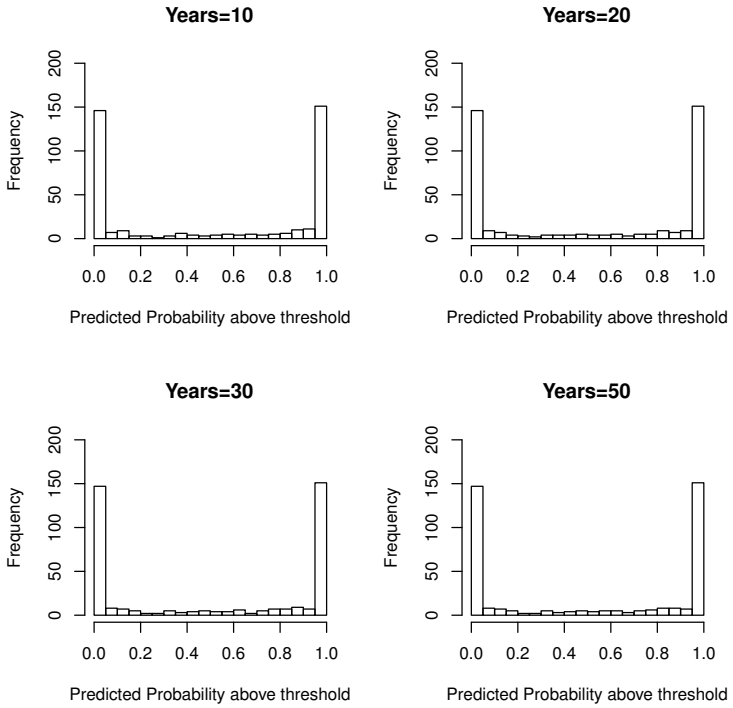

Figure 10: *The posterior probability above a threshold=2.621 at 10,20, 30 and 50 years for anti-HPV-16 antibodies using the modified power-law model.*

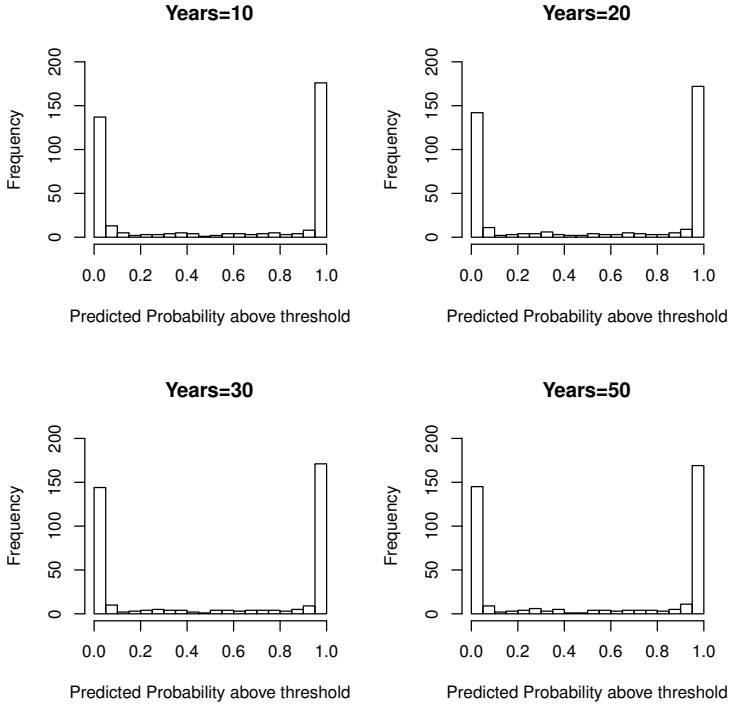

Figure 11: *The posterior probability above a threshold=2.446 at 10,20, 30 and 50 years for anti-HPV-18 antibodies using the modified power-law model.*

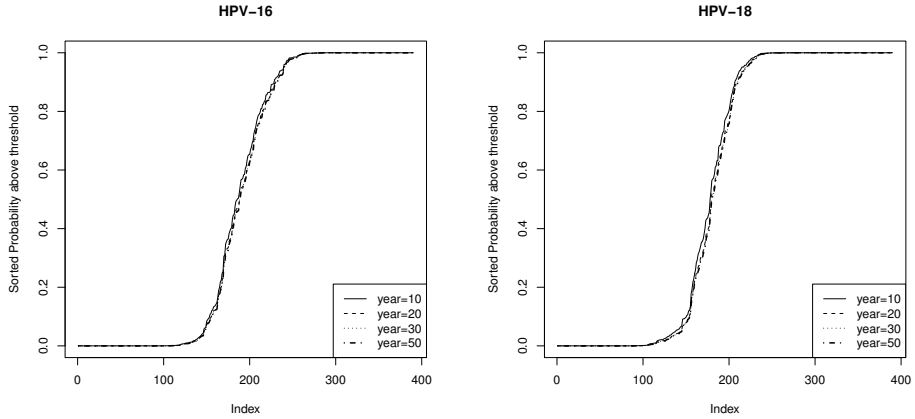

Figure 12: *Subject-specific sorted posterior probability of being above a threshold for anti-HPV-16 antibodies (Left Panel) and for anti-HPV-18 antibodies (Right Panel) using modified power-law model. Index represents the number of subjects.*

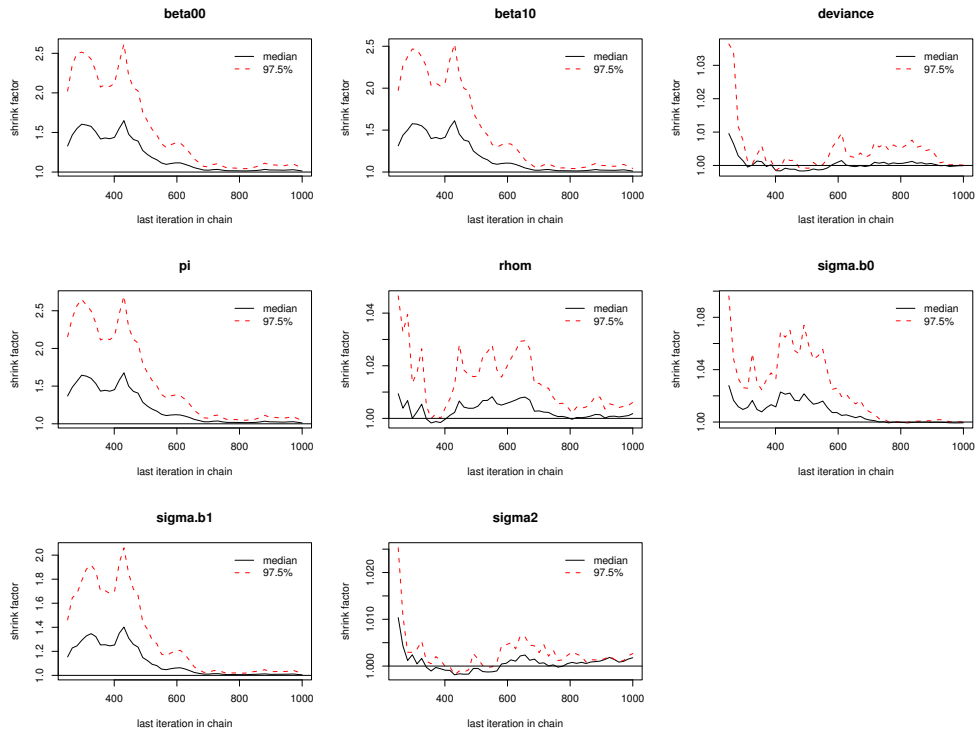

Figure 13: *Brooks, Gelman and Rubin's plot for anti-HPV-16 antibodies for modified power-law model.*

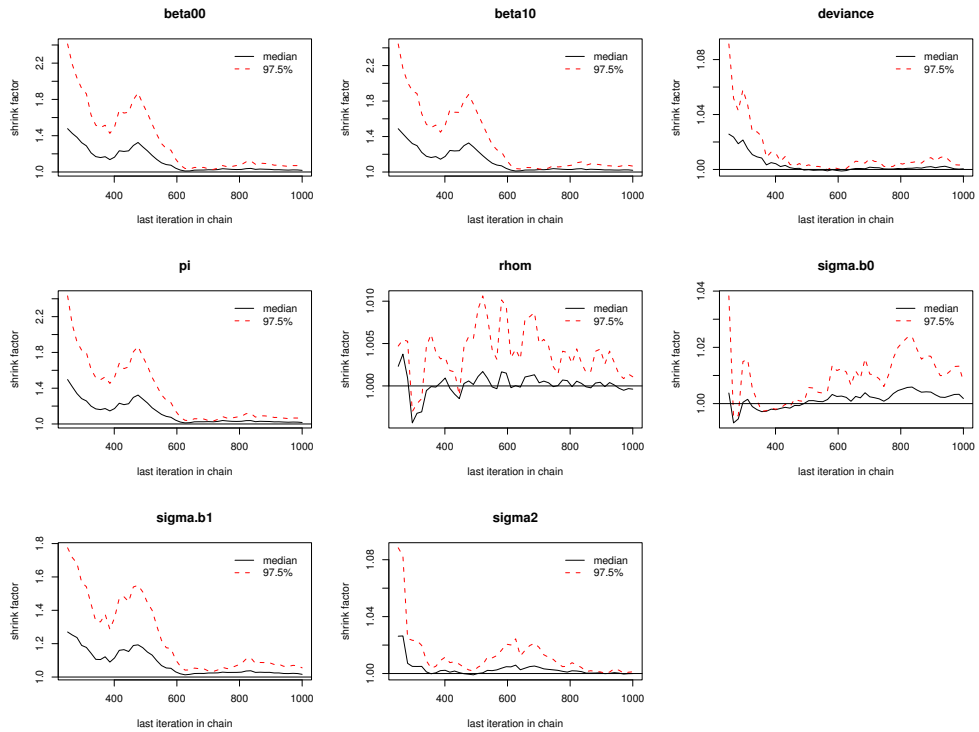

Figure 14: *Brooks, Gelman and Rubin's plot for anti-HPV-18 antibodies for modified power-law model.*

Table 1: *Estimate of the potential scale reduction factor ($\widehat{R}$).*

	anti-HPV-16 antibodies		anti-HPV-18 antibodies	
Parameter	Point est.	97.5% quantile	Point est.	97.5% quantile
$\beta 0$	1.01	1.02	1.01	1.03
$\beta 1$	1.01	1.02	1.02	1.06
σ	1.00	1.00	1.00	1.00
σ_{b_0}	1.00	1.00	1.00	1.00
σ_{b_1}	1.00	1.01	1.01	1.04
ρ_{12}	1.00	1.00	1.00	1.00
p	1.01	1.02	1.03	1.07
deviance	1.00	1.00	1.00	1.00

Table 2: *Posterior summary statistics of the modified power-law model for anti-HPV-16 and anti-HPV-18 antibodies.*

	HPV-16					HPV-18				
Parameters	mean	sd	MC error	95 % CI	$\widehat{R}$	mean	sd	MC error	95% CI	$\widehat{R}$
β_0	6.672	0.106	0.008	(6.455,6.872)	1.01	6.444	0.096	0.008	(6.252,6.625)	1.02
β_1	1.828	0.049	0.004	(1.725,1.92)	1.01	1.731	0.046	0.004	(1.641,1.818)	1.02
σ_{b_0}	0.453	0.017	3.86E-4	(0.420,0.489)	1.00	0.448	0.016	0.0003	(0.418,0.482)	1.00
σ_{b_1}	11.44	1.198	0.074	(9.183,13.91)	1.00	7.846	0.781	0.051	(6.412,9.441)	1.02
σ_ε	0.185	0.003	6.104E-5	(0.179,0.191)	1.00	0.171	0.003	6.42E-5	(0.166,0.177)	1.00
$\rho_{b_0 b_1}$	-0.388	0.054	0.001	(-0.489,-0.274)	1.00	-0.583	0.046	8.24E-4	(-0.668,-0.485)	1.00
π	0.018	0.002	1.39E-4	(0.014,0.022)	1.01	0.019	0.002	1.46E-4	(0.016,0.023)	1.02
DIC	-752.71					-1182.24				