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Bayesian Non-Linear Models for the Bactericidal Activity of Tuberculosis Drugs

by

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Declaration of Authorship

I, Divan Aristo Burger, declare that this thesis titled, 'Bayesian Non-Linear Models for the Bactericidal Activity of Tuberculosis Drugs' and the work presented in it are my own. I confirm that:

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- Where I have consulted the published work of others, this is always clearly attributed.
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Abstract

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Trials of the early bactericidal activity (EBA) of tuberculosis (TB) treatments assess the decline, during the first few days to weeks of treatment, in colony forming unit (CFU) count of *Mycobacterium tuberculosis* in the sputum of patients with smear-microscopy-positive pulmonary TB. Profiles over time of CFU data have conventionally been modeled using linear, bilinear or bi-exponential regression. This thesis proposes a new biphasic nonlinear regression model for CFU data that comprises linear and bilinear regression models as special cases, and is more flexible than bi-exponential regression models. A Bayesian nonlinear mixed effects (NLME) regression model is fitted jointly to the data of all patients from clinical trials, and statistical inference about the mean EBA of TB treatments is based on the Bayesian NLME regression model. The posterior predictive distribution of relevant slope parameters of the Bayesian NLME regression model provides insight into the nature of the EBA of TB treatments; specifically, the posterior predictive distribution allows one to judge whether treatments are associated with mono-linear or bilinear decline of log(CFU) count, and whether CFU count initially decreases fast, followed by a slower rate of decrease, or *vice versa*. The fit of alternative specifications of residuals, random effects and prior distributions is explored. In particular, the conventional normal regression models for log(CFU) count versus time profiles are extended to provide a robust approach which accommodates outliers and potential skewness in the data. The deviance information criterion and compound Laplace-Metropolis Bayes factors are calculated to discriminate between models. The biphasic model is fitted to time to positivity data in the same way as for CFU data.

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Contents

Abbreviations

Abbreviation	Definition
AFB	Acid-fast bacilli
AmB	Amphotericin
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BCI	Bayesian credibility interval
CFU	Colony forming unit
CI	Confidence interval
CPO	Conditional posterior ordinate
CV	Coefficient of variation
DIC	Deviance information criterion
EBA	Early bactericidal activity
HIV	Human immunodeficiency virus
HRZE	Isoniazid, rifampicin, pyrazinamide and ethambutol
ICPO	Reciprocal of CPO
LLOQ	Lower limit of quantification
log(CFU)	logarithm of CFU
MCMC	Markov Chain Monte Carlo
MDG	Millennium Development Goal
MDR	Multi-drug resistant

Abbreviation	**Definition**
MDR-TB	Multi-drug resistant TB
MGIT	Mycobacteria Growth Indicator Tube
ML	Maximum likelihood
NE	Not estimable
NLME	Non-linear mixed effects
NR	Not reported
PA-824	Pretomanid
PK	Pharmacokinetics
REML	Restricted maximum likelihood
SD	Standard deviation
SE	Standard error
SSCC	Serial sputum colony count
TB	Tuberculosis
TB Alliance	The Global Alliance for TB Drug Development
TMC207	Bedaquiline
TTP	Time to positivity
ULOQ	Upper limit of quantification
XDR-TB	Extensively drug resistant TB

Notation

Mathematical

Abbreviation	**Definition**
$\text{EBA}(t_1 - t_2)$	EBA from Day t_1 to Day t_2
	CFU count: Daily rate of change in log(CFU) count from Day t_1 to Day t_2
	TTP: Daily percentage change in TTP from Day t_1 to Day t_2
$\text{BA}(t_1 - t_2)$	Bactericidal activity from Day t_1 to Day t_2
v_{50}	Time at which percentage change from baseline in CFU count reaches 50%
$P(X) \propto P(Y)$	$P(Y)$ is proportional to $P(X)$
$\Gamma(x)$	Gamma function ($x > 0$)
$\Gamma_p(x)$	Multivariate gamma function (p-variate) ($x > 0$)
$\boldsymbol{h} = (h_1, h_2, \ldots, h_z)'$	Boldface signifies a vector or matrix
$\text{diag}\,(h_1, h_2, \ldots, h_z)$	Matrix with diagonal entries $h_1, h_2, \ldots, h_z$, for which the remainder entries are set to 0
I_h	Identity matrix of order $h \times h$
e or $\exp(1)$	Napier's constant ($e \approx 2.72$)
$\text{etr}\,(A)$	exp(trace of the matrix A)

Abbreviation	**Definition**
π	Ratio of a circle's perimeter to its diameter ($\pi \approx 3.14$)
$\log(x)$	Natural logarithm of x or $\log_e(x)$
$\log_a(x)$	Logarithm of x to the base of a
$I(x)$	Indicator function taking the value 1 if x is true, and 0 otherwise
$\text{step}\,(x)$	Function taking the value 0 if $x \leq 0$, and 1 otherwise

Probabilistic

Abbreviation	**Definition**
i.i.d.	Independent and identically distributed
$P(\boldsymbol{\theta})$	Generic prior density of $\boldsymbol{\theta}$
$P(\boldsymbol{\theta}\|\boldsymbol{x})$	Generic posterior density of $\boldsymbol{\theta}$ given the data $\boldsymbol{x}$
$P(X\|\boldsymbol{\theta})$	Density function of variable X, conditional on parameter $\boldsymbol{\theta}$
$Y \sim P(Y\|\boldsymbol{\theta})$	Variable Y is distributed with density $P(Y\|\boldsymbol{\theta})$
f_N	Density function of the standard normal distribution
f_{N_p}	Density function of the standard p-variate normal distribution
F_N	Cumulative distribution function of the standard normal distribution
$\mathrm{E}(X)$	Expected value of variable X
$\mathrm{Var}(X)$	Variance of variable X
$\mathrm{Cov}(X, Y)$	Covariance between variable X and Y
$\mathrm{CV}(X)$	Coefficient of variation for variable X
ρ_{XY}	Correlation coefficient between variable X and Y

Distributions

Abbreviation	**Definition**
$N(\theta, \sigma^2)$	Normal distribution with mean θ and variance σ^2
$TN(\theta, \sigma^2)I(.)$	Truncated normal distribution with mean θ and scale parameter σ^2, truncated over the parameter space as per $I(.)$
$SN(\theta, \sigma^2, \delta)$	Skew normal distribution with mean θ, scale parameter σ^2 and skewness parameter δ
$T(\theta, \sigma^2, v)$	Student t distribution with mean θ, scale parameter σ^2 and v degrees of freedom
$ST(\theta, \sigma^2, \delta, v)$	Skew Student t distribution with mean θ, scale parameter σ^2, skewness parameter δ and v degrees of freedom
$N_p(\boldsymbol{\theta}, \Sigma)$	Multivariate normal distribution (p-variate) with mean vector $\boldsymbol{\theta}$ and covariance matrix Σ
$TN_p(\boldsymbol{\theta}, \Sigma)$I(.)	Multivariate truncated normal distribution (p-variate) with mean vector $\boldsymbol{\theta}$ and scale matrix Σ, truncated over the parameter space as per $I(.)$
$SN_p(\boldsymbol{\theta}, \Sigma, \boldsymbol{\delta})$	Skew multivariate normal distribution (p-variate) with mean vector $\boldsymbol{\theta}$, scale matrix Σ and skewness vector $\boldsymbol{\delta}$
$T_p(\boldsymbol{\theta}, \Sigma, v)$	Multivariate Student t distribution (p-variate) with mean vector $\boldsymbol{\theta}$, scale matrix Σ and v degrees of freedom
$U(a, b)$	Uniform distribution with bounded range a to b
$G(a, b)$	Gamma distribution with shape and scale parameters a and b, respectively
$W_p(a, A)$	Wishart distribution (p-variate) with a degrees of freedom and inverse scale matrix A

Preface

In accordance with the regulations for the degree of Doctor of Philosophy from the University of the Free State, the author of this thesis presents a summary of contents of the thesis indicating how this work constitutes a contribution to knowledge.

Chapter 1 provides an overview of the burden and treatment of tuberculosis (TB), and a brief description of the assessment of early bactericidal activity (EBA) and sterilization of TB drugs, characterized by the rate of change in colony forming unit (CFU) count and time to positivity (TTP). Decline in log(CFU) count during a particular treatment period (e.g. 14 days) typically is bilinear or biphasic over time. The argument is made that some form of nonlinear regression modeling is required to reflect this biphasic nature of log(CFU) versus time profiles. A literature review suggests that CFU count conventionally has been regressed on a by-patient basis, and that nonlinear mixed effects (NLME) regression modeling for CFU count was introduced only recently. NLME regression modeling of CFU count has been based on the bi-exponential regression model. However, the bi-exponential regression model is not appropriate for log(CFU) versus time profiles that are decreasing slowly during the early phase of treatment, followed by a faster decline. Other important aspects (applicable to both the regression modeling of CFU count and TTP against time) which require further research are discussed. In conclusion this chapter argues that nonlinear regression methods for log(CFU) versus time data published in literature require some modification and generalization.

Chapter 2 formulates a generalized mixed effects regression model for CFU data and discusses various regression functions which might appropriately describe

log(CFU) count over time. These underlying regression functions are derived based on the principle that the rate of change in CFU count at a given time is proportional to the corresponding CFU count, but importantly, the proportionality factor is allowed to change over time. The linear, conventional bilinear and the bi-exponential regression functions are introduced, and a new biphasic nonlinear regression model (called the "differential hyperbolic tangent regression model") that comprises linear and bilinear regression models as special cases is proposed. The new nonlinear regression model is argued to be more flexible than bi-exponential regression models. Furthermore, estimation of and inference on model parameters from a Bayesian perspective are suggested.

Chapter 3 presents statistical methods for the assessment of CFU data based on the regression models defined in Chapter 2. The proposed statistical methods include the modeling of CFU data on a by-patient basis using the new proposed biphasic regression model, and the implementation of the models as Bayesian NLME regression models fitted jointly to data of all patients from a given trial. Unlike methods described in previous literature, model parameters are estimated from the data, rather than determined through visual inspection. The Bayesian implementation of these mixed effects regression models includes the following contributions:

- The specification of priors for small variance components is challenging. The use of a so-called "default" Wishart prior for the covariance matrix of the random intercept and slope parameters is proposed.
- The posterior predictive distribution of relevant slope parameters is suggested to provide insight into the nature of the EBA of TB treatments.
- Distributions other than the normal distribution are introduced for both the residuals and random coefficients of the proposed model. In this way, the conventional normal regression models for log(CFU) count versus time profiles are extended to provide a robust approach which accommodates outliers caused by laboratory error. In particular, the Student t distribution for residuals and random coefficients allows for heavier tails than the normal distribution. These

models are further adapted to allow for the modeling of potential skewness through the skew Student t distribution.

- DIC statistics and compound Laplace-Metropolis Bayes factors are introduced to discriminate between different mixed effects regression models. The calculation of Bayes factors, especially with regard to the associated multidimensional integrals, is known to be challenging and cumbersome. A workaround is introduced through which marginal likelihoods can be calculated relatively easily using an adapted approach in SAS® and the R project. This approach (in particular, the programming code available in the appendices of this thesis) can be generalized and used by practitioners for other applications of Bayesian mixed effects regression models.

In Chapter 4, results of an extensive empirical investigation of the suitability of the proposed model based on a large number of CFU versus time profiles are presented, including applications of the methodology in Chapter 3 to CFU data of recently published clinical trials.

In Chapter 5, the methodology for modeling of CFU data is extended to the analysis of TTP data. Results of an extensive empirical investigation of the suitability of the proposed model based on a large number of TTP versus time profiles are presented, including applications of the methodology in Chapter 3 to TTP data of recently published clinical trials.

Chapter 6 provides a discussion of the results of this study, lists some possible shortcomings of the proposed methods (including suggestions), and highlights some topics for future research. The final conclusion section provides an outline of analysis methods for practitioners.

Chapter 1

Introduction

1.1 Burden and Treatment of Tuberculosis

Tuberculosis (TB), or more specifically *Mycobacterium tuberculosis*, is an infectious disease which primarily manifests in the lungs of infected individuals (Lawn and Zumla, 2011). Symptoms of TB infected patients include chest pain, prolonged cough and coughing up of blood. TB can cause meningitis (Kim and Kim, 2009) and damage to the kidneys and bones when the patient's immune system is compromised (Herrmann and Lagrange, 2005).

TB is the second leading cause of human mortality worldwide within its class of infectious diseases, after infection with the human immunodeficiency virus (HIV) (WHO, 2013). In 2012, an estimated 8.6 million incidences of TB were reported globally, and Asia and Africa were the continents with the highest reported incidence (WHO, 2013).

Mitchison and Davies (2008) stated that for "the first time in thirty years, the anti-TB drug development pipeline may be on the verge of delivering significant advances in therapy". In the recent past, however, many anti-TB drugs in the form of monotherapy have proven to be ineffective against drug resistant TB (Yang et al., 2011). Drug resistance against TB is mainly caused by non-adherence to the administration of prescribed TB medication (Amuha et al., 2009). Moreover,

drug resistant TB strains are contagious, and therefore have the ability to spread from one person to another (Van Rie et al., 2000). Combinations of anti-TB drugs have therefore been introduced for more effective eradication of drug resistant TB (Diacon et al., 2012a). Although many successful treatments for TB have been developed over the years, multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) pose a worldwide challenge, and research needs to be done on the successful treatment and containment of these particular forms of TB (Jassal and Bishai, 2010).

Among other problems associated with TB infection, some anti-TB drugs do not have the ability to eliminate TB, due to their lack of bactericidal activity against persistent microorganisms (Koul et al., 2011). Furthermore, TB is more likely to reoccur in HIV patients, due to those patients' increased susceptibility to infections in general (Lawn and Zumla, 2011). An extensive range of therapeutics is generally required for the treatment of MDR-TB and XDR-TB, usually involving a longer duration of treatment (WHO, 2012).

The World Health Organization recognized the global need to fight TB infection during 1993 (WHO, 2012). Consequently, the WHO formed the Stop TB Strategy in 2006 whose goals, in line with the Millennium Development Goals (MDGs), include the reduction of TB prevalence by 2015 (WHO, 2012). The document published by WHO (2012) provides a status report on the numerous MDG targets, showing that substantial progress towards the reduction of TB infections and deaths due to TB has been made. This report, however, recognizes that "the global burden of TB remains enormous", and that the number of MDR-TB infections is still increasing.

First line anti-TB drugs, namely those drugs which are initially provided to TB patients, include isoniazid, rifampicin, pyrazinamide and ethambutol (Laurenzi et al., 2007). More expensive second line anti-TB drugs, provided to patients when they show resistance to the first-line drugs, include streptomycin, capreomycin, kanamycin, amikacin, ethionamide, para-aminosalicylic acid, cycloserine, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin and clofazimine (Laurenzi et al., 2007). A patient is considered suffering from MDR-TB when resistant to both isoniazid and rifampicin, whereas XDR-TB is defined as drug

resistance to isoniazid, rifampicin, fluoroquinolone and at least one of three injectable second line anti-TB drugs, e.g. capreomycin, kanamycin and amikacin (WHO, 2012).

Among new anti-TB drugs currently under development are delamanid, bedaquiline (or TMC207) and pretomanid (or PA-824) (Matteelli et al., 2014; Diacon et al., 2015). Migliori and Sotgiu (2012) stated that the results of an early phase clinical trial (Diacon et al., 2012a) suggest that combination therapy of moxifloxacin, PA-824 and pyrazinamide might provide a potential breakthrough in the fight against TB and MDR-TB. PA-824 has been developed by The Global Alliance for TB Drug Development (TB Alliance), which is a nonprofit organization established for the development of new anti-TB drugs. Migliori and Sotgiu (2012) pointed out that, among other advantages, the new combination therapy of moxifloxacin, PA-824 and pyrazinamide, still under development, could have less drug interaction potential with HIV antiretroviral treatments than combination treatments which include rifampicin.

As Diacon et al. (2012a) state, "ideally [new treatment] regimens would contain new drugs able to combat tuberculosis resistant to currently available drugs, especially multidrug-resistant (MDR) tuberculosis ...". Thus one of the challenges in early development of new TB treatments is to identify promising combinations of drugs for subsequent testing in pivotal clinical trials. Since the treatment regimens may involve combinations of three or four drugs, including one or more novel molecules, potentially large numbers of regimens need to be screened. One way to do so efficiently and cost effectively is to assess the early bactericidal activity (EBA) of those regimens.

1.2 Early Bactericidal Activity and Sterilization

1.2.1 Colony Forming Unit Count

The EBA of TB drugs is conventionally characterized by the daily rate of change (decline), during the first few days to weeks of treatment, in count of colony

forming units (CFUs) in the sputum of patients with smear-microscopy-positive pulmonary TB (Diacon et al., 2012a). An early definition of EBA was the "fall in counts/mL sputum/day [of CFUs] during the first two days of treatment" (Mitchison and Sturm (1997) as cited in Donald and Diacon (2008)). *In vitro* studies have suggested that anti-TB drugs eradicate a fixed proportion of TB bacteria per unit time (Gillespie et al., 2002), at least over suitably short time intervals, which would imply an exponential decay in CFU count. Conventionally, therefore, EBA has been characterized by the daily rate of decline in the logarithm of CFU count, i.e. log(CFU) count (Jindani et al., 1980) (note that an exponential decay in CFU count on the original scale translates to a constant rate of decline in log(CFU) count). Thus, EBA characterizes the potency of anti-TB drugs (against TB bacteria) during the first few days of treatment. Most anti-TB drugs, such as isoniazid (Jindani et al., 1980; Mitchison and Sturm, 1997), cause a relatively fast decline in log(CFU) count during the initial phase of treatment, therefore eradicating most of the TB bacteria during the first few days of treatment.

In contrast to the concept of EBA, the sterilization property of TB drugs refers to the rate of decline in log(CFU) count after the initial phase of treatment (i.e. the rate of decline once the majority of TB bacteria have been eradicated) (Brindle et al., 2001). More specifically, the sterilization phase of anti-TB drugs refers to the sterilizing activity against persistent TB microorganisms surviving the first few days of treatment (Brindle et al., 2001).

As mentioned above, the potency of most anti-TB drugs has been characterized in the past by the EBA during the first 2 days of treatment (also known as "standard EBA"). Jindani et al. (2003) argued that, despite being cost effective and of short duration, "standard EBA" trials might fail to measure the sterilizing activity of TB drugs: For example, monotherapy of pyrazinamide has been shown to be less bactericidal than that of isoniazid and streptomycin during the first few days of treatment (EBA), but proves to eradicate TB bacteria at about the same rate afterwards (sterilization). Thus, even though pyrazinamide has weak EBA, its sterilizing activity proves to be better than that of isoniazid and streptomycin (Brindle et al., 2001; O'Brien, 2002). Based on these findings, Jindani et al. (2003) suggested the extension of "standard EBA" trials to a treatment period of

at least 5 to 7 days, in order to evaluate the sterilization activity of anti-TB drugs. Currently, in fact, the treatment and profile period for EBA trials typically is 14 days, with collection of one or two pre-treatment and, often daily, post-treatment overnight sputum samples (Diacon et al., 2012a). EBA trials are conducted for the evaluation of new anti-TB drugs during early stages of development, such as in "early Phase II" trials (Diacon et al., 2012a).

Conventionally (see for example Botha et al. (1996)), the EBA in a given patient over a given time interval, say from Day t_1 to Day t_2, i.e. EBA$(t_1 - t_2)$, was expressed as follows:

$$\text{EBA}(t_1 - t_2) = -\frac{\log(\text{CFU}_{t_2}) - \log(\text{CFU}_{t_1})}{t_2 - t_1} \tag{1.1}$$

Here $\log(\text{CFU}_{t_1})$ and $\log(\text{CFU}_{t_2})$ are the observed log(CFU) counts at Day t_1 and Day t_2, respectively, where $0 \leq t_1 < t_2 \leq T$, and T is the length of the profile period over which sputum samples are collected.

Values that are routinely reported for such EBA TB trials include EBA(0-14), EBA(0-2), EBA(0-7), EBA(2-14) and EBA(7-14).

Alternatively (see for example Jindani et al. (2003)), EBA$(t_1 - t_2)$ was expressed as follows:

$$\text{EBA}(t_1 - t_2) = -\frac{\hat{f}(t_2) - \hat{f}(t_1)}{t_2 - t_1} \tag{1.2}$$

where $f(t)$ is a suitable regression function for log(CFU) count against time, and $\hat{f}(t_1)$ and $\hat{f}(t_2)$ are the associated fitted values at Day t_1 and Day t_2, respectively.

Thus, the method for the calculation of EBA given in Equation (1.1) is model-free, i.e. EBA$(t_1 - t_2)$ is characterized by the rate of decrease between two observed data points collected on Day t_1 and Day t_2. As opposed to Equation (1.1), the method for calculation of EBA by Equation (1.2) is model-based.

The model-based estimate of EBA$(t_1 - t_2)$ in Equation (1.2) has two potential advantages over the model-free estimate in Equation (1.1): Firstly, the EBA estimate

in Equation (1.1) uses information from only two CFU counts, namely those observed at Day t_1 and Day t_2; in contrast, the whole series of observed CFU counts may be used to estimate $f(t_1)$ and $f(t_2)$, with potential gains in precision for the model-based EBA estimate in Equation (1.2). Secondly, the model-free EBA estimate for a given time interval $(t_1 - t_2)$ can only be calculated if CFU counts are in fact available for these particular times; in contrast, the model-based estimate can be calculated (e.g. by extrapolating the curve over time interval $[t_1 - t_2]$) even if CFU counts have not been observed at Day t_1 and Day t_2, either because the study design did not specify data collection at those times, or because of missing data. The fitting of regression models (as in Equation (1.2)) allows for by-patient EBA to be estimated from a single model, thus avoiding fits of piecewise regression lines to successive data points (as is implied by Equation (1.1)).

From Equation (1.1) and Equation (1.2) it can be seen that the potency of a given drug against TB bacteria becomes larger as $\text{EBA}(t_1 - t_2)$ increases.

When a linear relationship (by-patient) between log(CFU) count and time is assumed, with intercept α and rate of decrease λ (assuming $\lambda > 0$), respectively, then $\hat{f}(t_1)$ and $\hat{f}(t_2)$ in Equation (1.2) can be expressed as follows:

$$\hat{f}(t) = \hat{\alpha} - \hat{\lambda} \cdot t \tag{1.3}$$

where $\hat{\alpha}$ and $\hat{\lambda}$ are the linear regression estimates of the intercept and slope parameters α and λ, respectively. Given Equation (1.3), $\text{EBA}(t_1 - t_2)$ in Equation (1.2) can be simplified as follows:

$$\text{EBA}(t_1 - t_2) = \hat{\lambda} \tag{1.4}$$

Thus, if the decay of CFU count over the *whole* interval $[0, T]$ is exponential (equivalently, log-linear), the EBA estimate in Equation (1.2) over all sub-intervals $(t_1 - t_2)$ of $[0, T]$ is constant, and equal to minus one times the slope of the linear regression line of log(CFU) versus time.

Equation (1.1) can be viewed as special case of Equation (1.4) when setting $\hat{\lambda}$ to be the rate of decrease between two observed data points collected on Day t_1 and Day t_2, i.e.:

$$\hat{\lambda} = \frac{\log(\text{CFU}_{t_2}) - \log(\text{CFU}_{t_1})}{t_2 - t_1} \tag{1.5}$$

1.2.2 Time to Positivity

Alternatively to CFU count, the potency of TB drugs can be evaluated using the time to sputum culture, i.e. the time it takes for a given sputum sample to yield a positive Mycobacteria Growth Indicator Tube (MGIT) culture after start of incubation. This time is referred to as time to positivity (TTP) (e.g. expressed in hours). If no positive MGIT culture is reported by a certain number of hours, the sputum sample status is assigned a "negative" value for the collection day at which the given sputum sample has been collected (Bark et al., 2013). Liquid culture results can thus be reported quantitatively, and TTP in liquid culture is considered more sensitive than solid culture being used to derive CFU count (Diacon et al., 2012b). In liquid culture, the opportunity to count colonies of bacteria is not available, but the time it takes for growth in liquid culture to register as a positive readout (TTP) is inversely related to the bacterial load of such cultures (Diacon et al., 2012b; Bark et al., 2013). Thus, alternatively to the EBA from solid media (CFU count), EBA can also be characterized by liquid media (TTP) (Diacon et al., 2010).

Similar to CFU count, a preliminary investigation of TTP data collected over time has suggested that both TTP and log(TTP) data increase linearly or bilinearly over time (Diacon et al., 2012a). Given the inverse relationship between log(CFU) count and log(TTP), the (model-fitted) EBA over a certain time interval, based on log(TTP), can be calculated similarly to that based on log(CFU) count, namely:

$$\text{EBA}_L(t_1 - t_2) = \frac{\hat{f}(t_2) - \hat{f}(t_1)}{t_2 - t_1} \tag{1.6}$$

where $f(t)$ is a suitable regression function for log(TTP) against time, and $\hat{f}(t_1)$ and $\hat{f}(t_2)$ are the associated fitted values at Day t_1 and Day t_2, respectively.

The EBA with respect to TTP can also be expressed as a daily percentage change in log(TTP) from Day t_1 to Day t_2, i.e.:

$$\text{EBA}(t_1 - t_2) = 100 \cdot \left(e^{\text{EBA}_L(t_1 - t_2)} - 1\right) \tag{1.7}$$

Similarly, expressing Equation (1.7) on a model-free basis (Equation (1.1)), one obtains:

$$\text{EBA}(t_1 - t_2) = 100 \cdot \left(\left[\frac{\text{TTP}_{t_2}}{\text{TTP}_{t_1}}\right]^{t_2 - t_1} - 1\right) \tag{1.8}$$

Here TTP_{t_1} and TTP_{t_2} are the observed TTP values at Day t_1 and Day t_2, respectively.

1.3 Need for Nonlinear Regression Models

As mentioned above, over a suitably short time interval a TB drug typically eradicates a fixed proportion of TB bacteria per unit time, implying exponential decline of CFU count over the time interval in question. Empirically, an exponential decline of CFU count (or a linear decline in log(CFU) count) has indeed been observed for most TB regimens, at least during the first few days of treatment, and certainly during the first two days. Thus, EBA(0-2) can be estimated from a simple linear regression of log(CFU) versus time (see Equation (1.2)) (Brindle et al., 2001; Jindani et al., 2003; Dietze et al., 2008). However, when the profile period of EBA trials, and associated EBA calculations, covers time intervals significantly longer than 2 days, say 14 days, then the assumption of a constant rate of decay over the whole time interval generally is no longer valid. In fact, for many TB drugs, a significant difference between the rate of decline over the first two days of treatment compared to the subsequent days has been observed (Donald and Diacon, 2008): Usually, during the first few days of treatment, log(CFU) count declines with a fast rate, followed by a slower rate of decline during the second

phase. The decline in log(CFU) count can therefore be biphasic (Mitchison and Davies, 2008) over a 14-day treatment period. Thus, for EBA trials with longer profile periods, estimation of EBA generally requires some form of nonlinear modeling that appropriately reflects the biphasic nature of the regression of log(CFU) count against time.

Given that CFU counts over time are closely (or in fact, inversely) related to TTP, the argument made above in essence also applies to the modeling of log(TTP) over time.

1.4 Serial Sputum Colony Count

In pivotal Phase III TB trials for application of drug registration, the proportion of patients with positive sputum culture after 6 months of treatment, and the proportion of patients experiencing relapse within a two-year follow-up period (after trial completion) are the standard efficacy endpoints (Mitchison, 2006; Mitchison and Davies, 2008). These clinical endpoints, therefore, can only be assessed in clinical programs comprising relatively lengthy and expensive trials (Mitchison, 2006; Phillips and Fielding, 2008; Wallis et al., 2009).

Any surrogate markers (or biomarkers) for the aforementioned efficacy endpoints should, among other requirements, closely relate to the disease being treated (Weir and Walley, 2006). Furthermore, those biomarkers must have the ability to predict the outcome of a given disease in the long run, such as relapses (recurrence). Thus, an appropriate surrogate marker for measuring the effectiveness of TB treatments may shorten the duration of anti-TB drug development, and may predict efficacy or inefficacy early during a given TB drug's development phase (Katz, 2004).

Sputum culture status ("positive" or "negative") after two months of treatment has been shown to be the best validated surrogate marker for the aforementioned primary efficacy TB endpoints (Mitchison, 1993, 1996). Limitations of this surrogate marker, however, are that large sample sizes are required for hypotheses testing, and its lack of association with relapse within individual patients (Weiner

et al., 2010). Two alternative surrogate markers, namely TTP and rate of decline in CFU count per milliliter (mL) (or also referred to as serial sputum colony count (SSCC)), both being assessed over 2 months of weekly or bi-weekly intervals, overcome problems associated with the two-month sputum culture status as surrogate marker (Weiner et al., 2010; Burman et al., 2008; O'Brien, 2002). The disadvantage of measuring TTP and CFU count is that they require assays of multiple sputum plates per sputum sample, dilution of samples, long waiting periods for culture growth, a labor intensive counting process of CFUs (Berthet et al., 1998), and the proneness of sputum samples to contamination (Sloan et al., 2012).

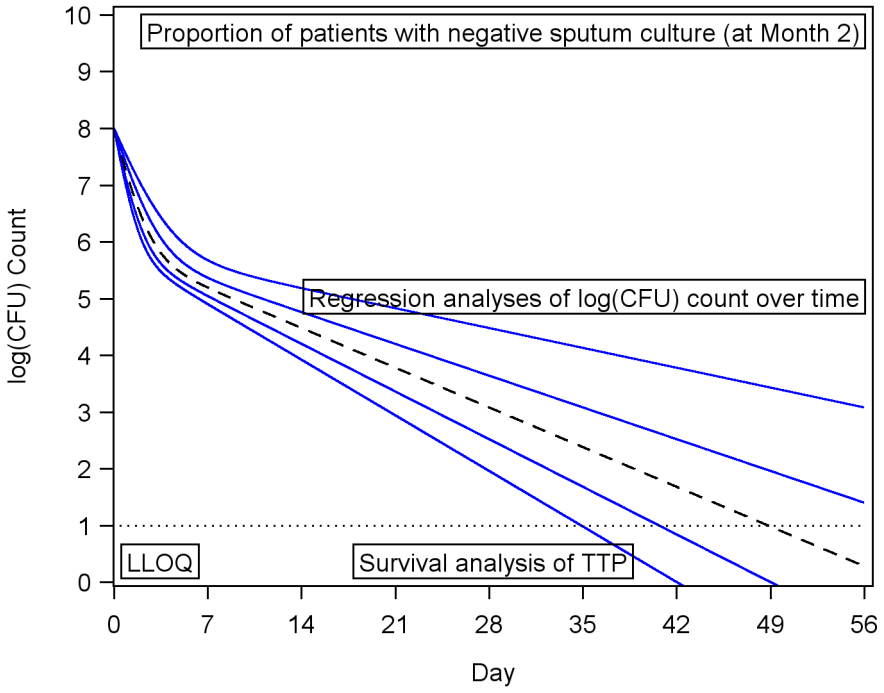
"SSCC" trials can therefore be viewed as extended EBA trials (in terms of treatment duration), and similarly to EBA trials, "SSCC" trials are expected to show a rapid rate of decline in log(CFU) count during the initial phase of treatment, as opposed to the terminal phase of treatment. Such "SSCC" trials are conducted for the evaluation of new anti-TB drugs during later stages of development, such as in "late Phase II" trials, specifically designed to assess the sterilizing activity of anti-TB drugs, before entering the pivotal stage of the development program (i.e. Phase III).

Figure 1.1, adapted from Mitchison and Davies (2008), provides a summary of the relationship between the following standard efficacy endpoints of 8-week extended bactericidal activity trials:

- Regression analyses of log(CFU) count over time.
- Survival analysis of TTP.
- Proportion of patients with negative (or positive) sputum culture (after two months of treatment).

In Figure 1.1, the solid blue lines represent the decline in log(CFU) count in individual patients. The dashed black line represents the mean decline in log(CFU) count of all patients. The dotted black line represents the applicable lower limit of quantification (LLOQ) used for log(CFU) count. The efficacy endpoints indicated in this figure are are all shown to be surrogate markers of the efficacy endpoints of pivotal Phase III TB trials.

Figure 1.1: Relationship Between Efficacy Endpoints in Extended Bactericidal Activity Trials



1.5 Literature on Statistical Analysis of Early Bactericidal Activity Trials

1.5.1 Colony Forming Unit Count

This section reviews literature on the different types of regression models that have been fitted to CFU and log(CFU) count. The review includes a short description of the techniques applied for estimation of the relevant model parameters, where indicated.

1.5.1.1 Linear Regression Models

Botha et al. (1996)

Objectives

Botha et al. (1996) investigated the EBA of the monotherapy of 1200 mg ethambutol and 2000 mg pyrazinamide, and of combination therapy of one tablet per 10 kg body weight of 80 mg isoniazid, 120 mg rifampicin and 250 mg pyrazinamide in 28 previously untreated TB patients.

Study Design

Patients assigned to monotherapy of ethambutol or combination therapy of isoniazid, rifampicin and pyrazinamide received daily doses for two consecutive days; 16-hour sputum samples were collected pre-treatment (i.e. Day 0) and on Day 1 and Day 2, relative to the first dose of treatment. Patients assigned to monotherapy of pyrazinamide received daily doses for three consecutive days; 16-hour sputum samples were collected pre-treatment (i.e. Day 0) and on Day 1, Day 2 and Day 3 relative to the first dose of treatment.

Methodology

For each treatment group, the mean $\log_{10}$(CFU) count was reported for each treatment day (i.e. Day 0, Day 1, Day 2 and Day 3). For each patient, the rate of decline in $\log_{10}$(CFU) count over 2 days after treatment, i.e. EBA(0–2), was calculated according to Equation (1.1), hence using the model-free approach. The mean EBA and corresponding 95% confidence intervals (CIs) were reported by treatment group, based on an one-way analysis of variance (ANOVA) of the EBA data.

Dietze et al. (2001)

Objectives

Dietze et al. (2001) conducted a 6-month open-label, randomized, active controlled Phase II clinical trial whose objective was to assess the safety, pharmacokinetics (PK) and bactericidal activity of rifalazil in 65 patients with newly diagnosed TB.

Study Design

Patients were randomized to either daily 300 mg isoniazid as monotherapy (16 patients); daily 300 mg isoniazid and 450 mg or 600 mg rifampicin, depending on the patients' weight, as combination therapy (16 patients); daily 300 mg isoniazid and once-weekly 10 mg rifalazil as combination therapy (17 patients); and daily 300 mg isoniazid and once-weekly 25 mg rifalazil as combination therapy (16 patients). Patients received treatment for 14 days as per randomization schedule: Isoniazid and rifampicin administered daily; Rifalazil administered once-weekly on Day 1 and Day 8.

Two 12-hour pooled sputum samples were collected pre-treatment which constituted the baseline measurement collected on Day 1. Post-treatment 12-hour pooled sputum samples were collected on Day 3, Day 4, Day 8, Day 11, Day 14, Day 15, Day 28, relative to the first dose of treatment.

Methodology

The change from baseline in log(CFU) count was calculated for Day 15 (i.e. $\log_{10}(\text{CFU}_{15}) - \log_{10}(\text{CFU}_1)$) for each patient. Pooled sputum samples collected on Day 14 were used when Day 15 samples were missing. Summary statistics were reported for the change from baseline in log(CFU) count at Day 15, and an ANOVA was used to compare change from baseline in log(CFU) count between treatment groups.

Brindle et al. (2001)

Objectives

Brindle et al. (2001) performed a 28-day retrospective analysis in 122 newly diagnosed TB patients in order to show that the sterilizing activity of anti-TB drugs is more appropriately assessed through observation periods longer than 2 days of treatment (i.e. extended "standard" EBA trials; see Section 1.4).

Study Design

Patients either received combination therapy of streptomycin, thiacetazone and isoniazid (67 patients) or combination therapy of streptomycin, isoniazid, rifampicin and pyrazinamide (55 patients). Both regimens were administered daily for 28 days.

Twelve-hour sputum samples were collected before dosing on Day 0 as the pre-treatment sample, and post-treatment samples were collected on Day 2, Day 7, Day 14 and Day 28.

Methodology

Values for EBA(0–2), EBA(2–7), EBA(7–14), EBA(14–28) and EBA(2–28) were calculated model-free as in Equation (1.1). In addition, by-patient linear regression analysis, to characterize EBA for the overall treatment period, was performed providing patients had at least 2 post-treatment samples. The sign of the individual linear regression coefficients was reversed in order to obtain EBA values. Summary statistics by treatment group were reported both for the respective EBA values and the estimated individual linear regression coefficients. The EBA values and estimates of regression coefficients were compared by means of ANOVA (2-way; unbalanced), fitting treatment group and HIV status (either positive or negative). Prior to the ANOVA, the EBA values and estimated individual linear regression coefficients were normalized by transformation (in cases where the Shapiro-Wilk

test showed departure from the normality assumption). More specifically, the estimated individual linear regression coefficients were normalized "using the mean symmetry version of the Box-Cox transformation".

Jindani et al. (2003)

Objectives

Jindani et al. (2003) investigated the bactericidal and sterilizing activities of 22 different dose combinations of isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, either administered as monotherapy or as combination therapy, in previously untreated TB patients over a study period of 14 days.

Study Design

Patients received either monotherapy of 150 mg isoniazid, 300 mg isoniazid, 600 mg isoniazid, 5 mg/kg (body weight) rifampicin, 10 mg/kg rifampicin, 20 mg/kg rifampicin, 2000 mg pyrazinamide or 1000 mg streptomycin, or combination therapy of 300 mg isoniazid, 10 mg/kg rifampicin, 2000 mg pyrazinamide, 25 mg/kg ethambulol or 1000 mg streptomycin in various different combinations. Patients were dosed daily for 14 consecutive days.

Two pre-treatment overnight sputum samples were collected and used for the calculation of CFU count at Day 0. In addition, overnight sputum samples were collected on Day 2, Day 4, Day 6, Day 8, Day 10, Day 12 and Day 14, relative to the first dose of treatment.

Methodology

Model-free EBA values (Equation (1.1)) and model-based regression slopes (Equation (1.2)) were calculated over the available data points. The by-patient EBA values and regression slopes were summarized per treatment group by descriptive statistics and analyzed using ANOVA and multiple regression.

Dietze et al. (2008)

Objectives

Dietze et al. (2008) report results of a 7-day clinical trial which assessed the early and extended bactericidal activity of linezolid, compared to isoniazid, in 30 newly diagnosed TB patients.

Study Design

Patients were randomized to receive either 300 mg isoniazid once daily (10 patients), 600 mg linezolid once daily (10 patients) or 600 mg linezolid twice daily (10 patients) for 7 days.

Two pre-treatment overnight sputum samples were collected, which constituted the CFU count at Day 0. In addition, overnight sputum samples were collected on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6 and Day 7, relative to the first dose of treatment.

Methodology

The mean change from baseline in $\log_{10}$(CFU) count (relative to Day 0) was summarized for each treatment day. Values for EBA(0–2) and EBA(2–7) were calculated in analogy to Jindani et al. (2003), and between-treatment comparisons made use of multiplicity-adjusted parametric and nonparametric ANOVA. Within-treatment correlation between the respective EBA and PK endpoints was explored by linear regression.

1.5.1.2 Bilinear Regression Models

Diacon et al. (2010)

Objectives

Diacon et al. (2010) report a 14-day clinical trial whose objectives included the evaluation of the safety, tolerability, PK and EBA of various doses of PA-824 in 69 previously untreated TB patients. EBA was characterized by the evaluation of CFU count and TTP.

Study Design

Patients were randomized to receive either daily double-blind monotherapy of 200 mg PA-824 (15 patients), 600 mg PA-824 (15 patients), 1000 mg PA-824 (16 patients), 1200 mg PA-824 (15 patients) or open-label combination therapy of standard treatment (isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE)) (8 patients) for 14 days. The latter treatment regimen served as the control group for this study.

Two 16-hour overnight sputum samples were collected pre-treatment and were used for the calculation of CFU count at Day 0. In addition, overnight sputum samples were collected daily from Day 1 up to Day 4, and every second day from Day 6 up to Day 14. From each sample, four CFU counts were made available. The four CFU counts (per patient and sample) were averaged and used for the calculation of the $\log_{10}$(CFU) count of a given study day.

Methodology

The mean change from baseline in $\log_{10}$(CFU) count (relative to Day 0), and corresponding 95% CIs, were calculated for each treatment day (i.e. Day 1 up to Day 14). The method for calculation of the 95% CIs is not specified in this article. Model-based (Equation (1.2)) values for EBA(0–14), EBA(0–2) and EBA(2–14)

were calculated for each patient. In contrast to earlier work where simple linear regression was used, a bilinear regression model was fitted to the daily $\log_{10}$(CFU) counts of each patient in this study. The method of estimation of the regression parameters (intercept, slopes and change point (or node)) is not specified in this article. Mean EBA values were reported for each treatment group. In addition, the change from baseline in mean $\log_{10}$(CFU) count (per sample day) was modeled through bilinear regression (over time) by treatment group.

Diacon et al. (2012a)

Objectives

Diacon et al. (2012a) report a Phase II, partially double-blind, randomized clinical trial to assess the 14-day EBA, safety, tolerability and PK of various combinations of TMC207, pyrazinamide and moxifloxacin, compared to Rifafour e-275®, in a total of 85 previously untreated drug susceptible TB patients. EBA was characterized by the evaluation of CFU count and TTP.

Study Design

Patients were randomized to receive either monotherapy of TMC207 (15 patients), combination therapy of TMC207 and pyrazinamide (15 patients), combination therapy of TMC207 and PA-824 (15 patients), combination therapy of PA-824 and pyrazinamide (15 patients), combination therapy of PA-824, moxifloxacin and pyrazinamide (15 patients) or Rifafour e-275® (10 patients). The control group consisted of patients receiving standard TB treatment with combination therapy of isoniazid, rifampicin, pyrazinamide and ethambutol (Rifafour e-275®).

Treatment was administered for 14 consecutive days, for which the dosing regimen is detailed in "Panel 1: Treatment Groups" of the article.

Two 16-hour overnight sputum samples collected pre-treatment were used for the calculation of the baseline (Day 0) CFU count. Post-treatment 16-hour overnight

sputum samples were collected daily from Day 1 up to Day 14, relative to the first dose of treatment.

Methodology

Values for EBA(0–14), EBA(0–2), EBA(0–7), EBA(2–14) and EBA(7–14) were calculated as weighted slopes from individual bilinear regression fits (Equation (1.2) (model-based)). The node (or change point) was identified visually, and assumed to be the same for all patients in a given treatment group. The EBA was compared between treatment groups by Holm's method. In addition, the change from baseline in mean $\log_{10}$(CFU) count was modeled through bilinear regression (over time) by treatment group.

Diacon et al. (2012c)

Objectives

Diacon et al. (2012c) report a 14-day dose finding clinical trial whose objectives included the evaluation of the safety, tolerability, PK and EBA of various doses of PA-824 in 69 previously untreated TB patients. EBA was characterized by the evaluation of CFU count and TTP.

Study Design

Patients were randomized to receive either daily doses of 50 mg PA-824 (15 patients), 100 mg PA-824 (15 patients), 150 mg PA-824 (15 patients), 200 mg PA-824 (16 patients) or Rifafour e-275® (8 patients) (control group) for 14 days.

Sputum samples were collected daily from Day 0 up to Day 4, and every second day from Day 6 up to Day 14. From each sample, four CFU counts were made available, and were averaged (per patient) for the calculation of the $\log_{10}$(CFU) count of a given study day.

Methodology

Model-based (Equation (1.2)) values for EBA(0–14), EBA(0–2) and EBA(2–14) were calculated for each patient. A bilinear regression model was fitted to the daily $\log_{10}$(CFU) counts of each patient in this study. The method of estimation of the regression parameters (intercept, slopes and change point (or node)) is not specified in this article. Mean EBA values were reported for each treatment group. In addition, the change from baseline in mean $\log_{10}$(CFU) count was modeled through bilinear regression (over time) by treatment group.

Diacon et al. (2013)

Objectives

Diacon et al. (2013) report a 14-day dose finding clinical trial whose objectives included the evaluation of the safety, tolerability, PK and EBA of various doses of TMC207 in 68 previously untreated TB patients. EBA was characterized by the evaluation of CFU count and TTP.

Study Design

Patients were randomized to receive either daily doses of 100 mg TMC207 (15 patients), 200 mg TMC207 (15 patients), 300 mg TMC207 (15 patients), 400 mg TMC207 (15 patients) or Rifafour e-275® (8 patients) (control group) for 14 days. Loading doses for each of the treatment regimens containing TMC207 were provided during the first two days of treatment.

Two 16-hour overnight sputum samples were collected pre-treatment and were used for the calculation of CFU count at Day 0. In addition, overnight sputum samples were collected daily from Day 1 up to Day 8, and every second day from Day 10 up to Day 14.

Methodology

Values for EBA(0–14), EBA(0–2), EBA(2–14) and EBA(7–14) were calculated as weighted slopes from individual bilinear regression fits (Equation (1.2) (model-based)). The node (or change point) was identified visually, and assumed to be the same for all patients in a given treatment group. The EBA was compared between treatment groups by Holm's method. In addition, the mean $\log_{10}$(CFU) count (per sample day) was modeled through bilinear regression (over time) for each treatment group.

1.5.1.3 Repeated Measures Linear Regression Models

Hafner et al. (1997)

Objectives

Hafner et al. (1997) investigated the optimization of the methodology for obtaining accurate EBA estimates. This trial's primary objective was to compare EBA, over 2 and 5 days of treatment, between results quantified by both acid-fast bacilli (AFB) smears and CFU-cultured agar plates, obtained from either 10-hour overnight, 2-hour early morning and 12-hour combined sputum samples.

Study Design

The clinical trial was carried out in 16 evaluable TB patients. All patients were treated daily with combination therapy of 300 mg isoniazid and 50 mg pyridoxine for 5 days. The first two days of the trial constituted the baseline period.

The 10-hour overnight and 2-hour early morning sputum samples were collected on each study day. The two mycobacterial loads were quantified as the CFU count on agar plates (CFU/mL) and AFB in smears (AFB/mL) for each sputum sample. The weighted average of the 10-hour overnight and 2-hour early morning sputum

sample was used for the calculation of the 12-hour combined mycobacterial load (CFU/mL and AFB/mL).

Methodology

The EBA was characterized by the change from baseline in $\log_{10}$(CFU) count on Day 2 and Day 5, in both CFU and AFB. The analysis included the characterization of EBA as the slope from a repeated measures linear regression model fitted to data from the 5-day treatment period. The repeated measures linear regression model accounted for between-patient and within-patient variation of $\log_{10}$(CFU) count. The effect of collection volume, collection duration and presence of cavitation on the $\log_{10}$(CFU) count were also explored. The adjusted mean $\log_{10}$(CFU) count and corresponding 95% CIs were presented for each sample type.

1.5.1.4 Nonlinear Regression Models

Gillespie et al. (2002)

Objectives

Gillespie et al. (2002) suggested the use of exponential decay models for the assessment of EBA in TB patients. They fitted the models to data from a previously published clinical trial, and to data acquired from additional patients recruited in accordance with the previously published clinical trial's inclusion and exclusion criteria.

Study Design

In total, 16 patients received either rifampicin (2 patients), isoniazid (9 patients) or ciprofloxacin (5 patients). Details of the dosing and sputum sampling schedule were not provided in this article (a reference to the article discussing the conduct of the previously published clinical trial was provided).

Methodology

Two exponential decay models were investigated, namely a single-exponential decay model and bi-exponential decay model. In the notation of Gillespie et al. (2002), the single-exponential decay model was defined as follows:

$$\mathrm{V}_t = \mathrm{M} \cdot e^{-k \cdot t} + S \tag{1.9}$$

where V_t is the viable CFU count at time t, M the CFU population susceptible to the test drug, S the persistent CFU population prone to solely the sterilizing anti-TB drugs, and k the daily rate of decline in CFU count for the CFU population susceptible to the test drug.

The bi-exponential decay model was defined as an extension of the single-exponential decay model in the following format:

$$\mathrm{V}_t = \mathrm{M} \cdot e^{-k \cdot t} + \mathrm{S} \cdot e^{-f \cdot t} \tag{1.10}$$

where f is the daily rate of decline in CFU count for the persistent CFU population prone to solely the sterilizing anti-TB drugs.

The goodness of fit for each of the exponential decay models was assessed by r^2, and the two models were compared by means of an F test.

The time at which the percentage change from baseline in CFU count reaches 50% (v_{50}) was calculated for each patient.

The paper of Gillespie et al. (2002) addresses the problem of outliers and unreliable CFU counts, and provides an iterative method, based on the goodness of fit measure r^2, for excluding such problematic data points for appropriate modeling (as described by the exponential decay curves) of the true clinical variability of a given anti-TB drug.

The paper does not provide detail on the estimation of the model parameters.

The EBA(0–2) from both the iterative single-exponential decay model and model-free approach (Equation (1.1)) was calculated. The mean EBA(0–2) and corresponding 95% CI were reported for each of the methods by treatment group.

Gosling et al. (2003a)

Objectives

Gosling et al. (2003a) applied the iterative single-exponential decay model, proposed by Gillespie et al. (2002) (Equation (1.9)), to assess the decline in CFU count from three previously published clinical trials over a treatment period of either 5, 7 or 14 days.

Study Design

In total, 85 patients were evaluated who received either 300 mg isoniazid (31 patients), 600 mg isoniazid (4 patients), 10 mg/kg rifampicin (8 patients), 20 mg/kg rifampicin (8 patients), 2000 mg pyrazinamide (9 patients), 1000 mg streptomycin (4 patients), 25 mg/kg ethambutol (4 patients), 2000 mg para-aminosalicylic acid (4 patients), 150 mg thiacetazone (8 patients), 750 mg ciprofloxacin (5 patients). Detail on the sputum sampling schedule was not provided (references to the articles discussing the conduct of the previously published clinical trials were provided).

Methodology

The quantity v_{50} was calculated for each patient and compared between treatment groups by means of the Kruskal-Wallis nonparametric ANOVA. Mean v_{50} and corresponding standard errors (SEs) were reported for each treatment group.

Gosling et al. (2003b)

Objectives

Gosling et al. (2003b) report a clinical trial of the 5-day bactericidal activity of moxifloxacin, isoniazid and rifampicin in 43 TB patients.

Study Design

Patients were randomized to receive either daily treatment with 300 mg isoniazid (16 patients), 600 mg rifampicin (13 patients) or 400 mg moxifloxacin (14 patients) for 5 consecutive days.

The mean CFU count from two pre-treatment overnight 16-hour sputum samples was taken as the baseline (Day 0) CFU count. Post-treatment overnight 16-hour sputum samples were collected daily for 5 days.

Methodology

The iterative single-exponential decay model discussed by Gillespie et al. (2002) and Gosling et al. (2003a) was used for the calculation of v_{50}. Similar to Gosling et al. (2003a), the Kruskal-Wallis nonparametric ANOVA was used to compare v_{50} between treatment groups. Mean v_{50} and corresponding 95% CIs were reported for each treatment group. The model-free EBA(0–2) was calculated for each patient, and compared between treatment groups by means of the Kruskal-Wallis nonparametric ANOVA. The mean EBA(0–2) and corresponding 95% CIs were presented for each treatment group.

Jindani et al. (2003)

Jindani et al. (2003) recognized the fact that the switch of one rate of decline in CFU count to another (i.e. EBA versus sterilization) is likely to be smooth.

Those authors thus motivate the fitting of a bi-exponential regression model to CFU count when the decline is biphasic. The regression function is defined as:

$$\mathrm{Y}_t = \mathrm{C}_1 \cdot e^{-k_1 \cdot t} + \mathrm{C}_2 \cdot e^{-k_2 \cdot t} + \mathrm{S} \tag{1.11}$$

where Y_t is the CFU count at Day t, C_1 and k_1 are the parameters describing the initial decline of CFU count, and C_2 and k_2 the parameters describing the terminal decline in CFU count ($k_1 > k_2$). S represents the remainder CFU count after the sterilization phase (which cannot be eradicated by the drug administered).

1.5.1.5 Nonlinear Mixed Effects Regression Models

Davies et al. (2006a)

The use of nonlinear mixed effects (NLME) regression models for log(CFU) count from TB trials was first proposed by Davies et al. (2006a). In contrast to conventional fixed effects models, mixed effects models can be associated with improved precision of estimates of random effects relative to their fixed effects counterparts, with more appropriate fixed effects estimates and SEs, and may reduce the bias caused by missing data. Davies et al. (2006a) reanalyzed the data from Brindle et al. (2001) by fitting NLME exponential regression models (both mono- and bi-exponential models) to log(CFU) count over time. The proposed bi-exponential model took the following form, and was fitted using the "nlme" library of the R project (Pinheiro et al., 2014; R Core Team, 2014):

$$\log_{10}(y_t) = \log_{10}(e^{\theta_1} \cdot e^{-t \cdot e^{\theta_2}} + e^{\theta_3} \cdot e^{-t \cdot e^{\theta_4}}) \tag{1.12}$$

where y_t is the CFU count at time t, θ_1, θ_2, θ_3 and θ_4 are the model parameters similarly to those of Equation (1.10). A distribution was assigned to each of the model parameters (i.e. random effects) for imposing correlation between the multiple observations (i.e. log(CFU) counts) observed within the same patient over time. To compare EBA between treatment groups, the model parameters were re-expressed as $\alpha_1 = \theta_1 \log_{10}(e)$ and $\alpha_2 = \theta_3 \log_{10}(e)$ as the respective intercept

terms, and $\lambda_1 = e^{\theta_2} \log_{10}(e)$ and $\lambda_2 = e^{\theta_4} \log_{10}(e)$ as the respective slope terms. The model also included covariates, in a linear format, for the intercept terms. Wald tests were used for statistical inference on the model parameters. Models were compared using the Akaike Information Criterion, likelihood ratio test and residual plots. In addition, the effects of HIV status and cavitation score were tested for the fixed intercept terms α_1 and α_2.

Davies et al. (2006b)

Davies et al. (2006b) performed a simulation study to assess the effect of the optimization of SSCC sampling schemes on sample size requirements, relating to the analysis of sterilization of anti-TB drugs. The simulation study was based on the bi-exponential NLME regression model published by Davies et al. (2006a). The specific aim of this study was to identify sampling schemes which provide the highest precision for estimating the parameter pertaining to sterilization activity, i.e. θ_4. A total of 29 different sampling schemes was investigated which ranged from 6 up to 11 sampling days.

Rustomjee et al. (2008)

Objectives

In an analysis of a 6-month Phase II randomized clinical trial, Rustomjee et al. (2008) fitted exponential NLME regression models for the assessment of the sterilization activity of three anti-TB drugs, i.e. ofloxacin, gatifloxacin and moxifloxacin, in TB patients.

Study Design

The clinical trial involved 217 patients treated for 8 weeks with either one of the following drug combinations: Ethambutol, isoniazid, rifampicin and pyrazinamide

as the control arm (54 patients); gatifloxacin, isoniazid, rifampicin and pyrazinamide as the first test arm (55 patients); moxifloxacin, isoniazid, rifampicin and pyrazinamide as the second test arm (53 patients); ofloxacin, isoniazid, rifampicin and pyrazinamide as the last test arm (55 patients). Following the 8-week treatment period, the patients were treated with a combination therapy of isoniazid and rifampicin for an additional 4 months. Detail on the dosing schedule of this clinical trial is available in the article.

Methodology

For the assessment of the sterilization activities of each of the treatment combinations, 10 overnight sputum samples were collected, relative to the start of treatment, on Day 0, Day 2, Day 7, Day 14, Day 21, Day 28, Day 35, Day 42, Day 49 and Day 56.

The following NLME regression models (mono-exponential, bi-exponential and tri-exponential) were investigated (see Davies et al. (2006a)):

$$\log_{10}(y_t) = \log_{10}(e^{\theta_1} \cdot e^{-t \cdot e^{\theta_2}}) \tag{1.13}$$

$$\log_{10}(y_t) = \log_{10}(e^{\theta_1} \cdot e^{-t \cdot e^{\theta_2}} + e^{\theta_3} \cdot e^{-t \cdot e^{\theta_4}}) \tag{1.14}$$

$$\log_{10}(y_t) = \log_{10}(e^{\theta_1} \cdot e^{-t \cdot e^{\theta_2}} + e^{\theta_3} \cdot e^{-t \cdot e^{\theta_4}} + e^{\theta_5} \cdot e^{-t \cdot e^{\theta_6}}) \tag{1.15}$$

Here y_t represents the CFU count at Day t, θ_1, θ_3 and θ_5 the respective intercept terms (at Day 0) and θ_2, θ_4 and θ_6 the respective slope parameters. A power function was used to model the potential heteroscedasticity of residuals (error terms). The bi-exponential regression model was selected as the most appropriate regression model (Equation (1.14)). A multivariate normal distribution was assumed for the model's random effects, therefore modeling correlation between the multiple observations within the same patient. The parameters of the bi-exponential regression model were estimated through maximum likelihood (ML) and restricted maximum likelihood (REML) methods. The effects of censoring of

log(CFU) count reported below the LLOQ, as well as the inclusion of covariates (such as HIV status), were investigated.

Sloan et al. (2012)

Objectives

Sloan et al. (2012) conducted a longitudinal cohort study for the optimization of SSCC counting for TB studies in patients located in resource-poor settings. Specifically, the pattern of CFU count and rate of sample contamination were compared between 4 different media plate settings. The media plate settings were as follows:

- Plates treated with Middlebrook 7H10 in combination with 10 mg/mL amphotericin (AmB).
- Plates treated with Middlebrook 7H10 in combination with 30 mg/mL AmB.
- Plates treated with Middlebrook 7H11 in combination with 30 mg/mL AmB.
- Plates treated with Middlebrook 7H11 in combination with 10 mg/mL AmB and carbendazim.

Study Design

Overnight sputum samples were collected on Day 0, Day 2, Day 4, Day 7, Day 14, Day 28, Day 49 and Day 56.

Methodology

The mean $\log_{10}$(CFU) count per timepoint were compared between media plate settings by means of a t-test, whereas the contamination rates were compared by use of risk ratios. Multivariate analysis assessing the contribution of patient factors towards contamination rates were assessed by random effects logistic regression.

The NLME regression models described by Davies et al. (2006a) were employed for the assessment of the pattern of log(CFU) count over time.

1.5.2 Time to Positivity

The majority of research papers on the analysis of time to sputum culture conversion in liquid culture includes survival analysis methods such as Kaplan-Meier survival rates and Cox proportional hazards regression models (e.g. Rustomjee et al. (2008)). However, not much literature is available on the regression analysis of TTP data over time. Examples of relevant papers are Diacon et al. (2010, 2012a,c, 2013). In all cases, the analysis of TTP data is similar to the CFU count data. Hence, the aforementioned literature material on TTP data consists of regression analysis on a by-patient basis, similar to the case of CFU data.

1.5.3 Summary and Discussion

The above literature review shows that various articles on the application of linear, bilinear and nonlinear regression models for log(CFU) count have been published. Most literature on the EBA and sterilization activity of anti-TB drugs involved by-patient regression analyses, based on the assumption that log(CFU) count and time are linearly related. Most authors employed basic statistical techniques such as parametric and nonparametric ANOVA for the analysis of log(CFU) count. Often the model-free approach (Equation (1.1)) was used for calculation of $\text{EBA}(t_1 - t_2)$.

In order to account for the biphasic nature of log(CFU) versus time curves, two types of nonlinear regression models have been described in the literature, namely bilinear and bi-exponential regression.

Diacon et al. (2010, 2012a,c, 2013) performed bilinear regression of log(CFU) count and TTP against time on a by-patient basis, with visual identification of the node parameter, and assuming that the node was the same for all patients in a given treatment group (Diacon et al., 2012a, 2013). Thus, the approach of Diacon et al.

(2012a, 2013) did not accommodate between-patient variation in the node. EBA was compared between treatment groups using ANOVA of the resulting by-patient EBA estimates. Clearly it would seem preferable to estimate the node parameter from the data, rather than determine it through visual inspection. In addition, it would seem preferable to fit the model as a bilinear mixed effects regression model to the data of all patients jointly in a given EBA trial.

Jindani et al. (2003) suggested that the switch of one rate of decline in log(CFU) count to another might be smooth (rather than abrupt, as would be implied with a bilinear regression model). Modeling such a smooth transition, Gillespie et al. (2002) and Jindani et al. (2003) used bi-exponential regression of CFU count against time. However, in bi-exponential regression models, the initial rate of decline in CFU count necessarily is greater than the terminal rate. Thus, bi-exponential regression models do not seem adequate for treatments (and individual profiles) which are associated with terminal rates of decline that are faster than initial rates of decline. Such treatments have in fact been described recently (Diacon et al., 2012a). Furthermore, Gillespie et al. (2002) introduced an iterative approach for exclusion of outliers in CFU count. It would seem preferable to model such outliers using robust regression techniques as an alternative to excluding these outliers from the analysis.

As an alternative to (linear and nonlinear) modeling of log(CFU) count against time on a by-patient basis, Hafner et al. (1997), Davies et al. (2006a), Davies et al. (2006b), Rustomjee et al. (2008) and Sloan et al. (2012) used mixed effects regression models in the form of repeated measures linear and mixed effects bi-exponential or multi-exponential regression models, assuming normal random effects. In particular, Davies et al. (2006a), Davies et al. (2006b) and Rustomjee et al. (2008) regressed log(CFU) count, observed over 56 days of treatment, against the logarithm of a bi-exponential function as a mixed effects regression model. The bi-exponential mixed effects regression model can fit data beyond 14 days of treatment, e.g. for 56-day "SSCC" trials (Rustomjee et al., 2008). The trial discussed by Rustomjee et al. (2008) shows a clear distinction between the EBA and longer term sterilizing activity for each of the treatment regimens: More specifically, per treatment group, the mean log(CFU) count over time suggests

that the initial slope is substantially larger than the terminal slope. However, an attempt to fit such a model to data beyond the scope of 14-day EBA trials results in convergence issues when the terminal slopes are greater than the initial slopes. Furthermore, with mixed effects regression models, it would seem preferable to assume distributions for random effects other than the normal distribution for purpose of sensitivity testing. Regarding statistical inference for model parameters, it would seem preferable to calculate exact 95% CIs as an alternative to approximate 95% CIs (calculated by the "nlme" library of the R project (Pinheiro et al., 2014; R Core Team, 2014)).

Existing literature on the regression of TTP data over time is limited to (bilinear) by-patient analyses (Diacon et al., 2010, 2012a,c, 2013), and thus suggests a more thorough investigation is required.

1.6 Key Problem Statement and Contributions

The observations stated in the above sections indicate that nonlinear regression models for log(CFU) versus time data published in the literature might require some modification and generalization. In particular, this thesis proposes a new class of biphasic nonlinear regression models for log(CFU) count that comprises linear and bilinear regression models as special cases. The new regression models are biphasic, but allow for a smooth transition between the two rates of decline in log(CFU) count. The regression models approximate bi-exponential regression models, but are more flexible in the sense that they allow for terminal rates of decline to be greater than initial rates of decline. The models are implemented as Bayesian NLME regression models, fitted jointly to the data of all patients from various trials. Statistical inference about the mean EBA of TB treatments is based on the Bayesian NLME regression model.

Further contributions made by the research contained in this thesis are summarized in the "preface" chapter (see Page xxi).

1.7 List of Associated Research Outputs

A list of research outputs resulting from this thesis, authored or coauthored by the author of this thesis, is provided below. The statistical contents of the below-mentioned research outputs are discussed in this thesis in detail.

Paper in Statistical Journal (Peer Reviewed)

Burger, D. A. and Schall, R. (2014a). A Bayesian non-linear mixed effects regression model for the characterisation of early bactericidal activity of tuberculosis drugs. *Journal of Biopharmaceutical Statistics,* in press, published online. URL: `http:// www.tandfonline.com/doi/abs/10.1080/10543406.2014.971170#.VGOTH_mUe VM`.

Papers in Medical Journals (Peer Reviewed)

Dawson, R., Diacon, A. H., Everitt, D., Van Niekerk, C., Donald, P. R., Burger, D. A., Schall, R., Spigelman, M., Conradie, A., Eisenach, K., Venter, A., Ive, P., Page-Shipp, L., Variava, E., Reither, K., Elias, N., Pym, A Von Groote-Bidlingmaier, F., and Mendel, C. M. (2015). Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *The Lancet,* in press, published online.

Diacon, A. H., Dawson, R., Von Groote-Bidlingmaier, F., Symons, G., Venter, A., Donald, P. R., Van Niekerk, C., Everitt, D., Hutchings, J., Burger, D. A., Schall, R., and Mendel, C. M. (2015). Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. *American Journal of Respiratory and Critical Care Medicine,* in press, published online.

Statistical Technical Report

Burger, D. A. and Schall, R. (2014b). A Bayesian non-linear mixed effects regression model for the characterisation of early bactericidal activity of tuberculosis drugs. Technical Report 433, Department of Mathematical Statistics and Actuarial Science, Faculty of Natural and Agricultural Sciences, University of the Free State. **URL:** `http://natagri.ufs.ac.za/dl/Userfiles/Documents/00003/3802_eng.pdf`.

Chapter 2

Mixed Effects Regression Models for Colony Forming Unit Count

2.1 Introduction

Mixed effects regression models are regression models that contain both fixed and random effects, and are flexible in modeling repeated measures data, repeated either in time or space. In clinical research, the term "repeated measures" usually refers to measurements made repeatedly over time on the same patient. Typically, the random effects represent patient-specific effects, whereas the fixed effects represent the population-level effects of the model. In most situations it is inappropriate to treat repeated measures data coming from the same patient as uncorrelated. Mixed effects regression models allow the modeling of correlation among measurements made on the same patient, either by incorporating random effects, random coefficients or specification of covariance patterns into the regression model. Mixed effects models are also appealing in the sense that they allow one to fit the repeated measures data of all patients in a clinical trial in a single model, such that the model parameters can vary between patients (hence, the applicable regression can be tailored for each patient) (Lindstrom and Bates, 1990). Furthermore, mixed effects regression models appropriately accommodate missing

(when missing at random) and unbalanced data which are regularly encountered in repeated measures modeling.

Most mixed effects regression models used in practice are linear and assume that the residual terms are normally distributed (Brown and Prescott, 2006). However, as mentioned in Chapter 1, CFU counts typically follow a bilinear or nonlinear pattern over time. Thus, CFU data in general require the use of NLME regression modeling.

2.2 General Mixed Effects Regression Model

One way of modeling repeated measures data, and specifically log(CFU) count over time, is to design a regression model that explains the relationship between the outcome measurement (i.e. log(CFU) count) and time. That is, a quantitative "time" effect is included as a covariate in the regression model, resulting in a so-called random coefficients model.

The following sections describe a generalized mixed effects regression model for modeling log(CFU) counts in a general format, and describe estimation of and inference on model parameters from a Bayesian perspective.

2.2.1 Mean-Variance Relationship

After log-transformation of CFU data from previous trials (e.g. Diacon et al. (2012a)), the variance of CFU data over time appears stable, so that one promising approach to modeling CFU count over time is to regress log(CFU) data against time. The observation of constant variance on the log-scale suggests that the mean-variance relationship of the distribution of CFU count on the original scale is characterized by a constant coefficient of variation (CV). Constant variance of CFU data on the logarithmic scale is confirmed by the extensive empirical study reported in Section 4.2.

2.2.2 Model Specification

This section provides an overview of the general mixed effects regression model for cases when censoring of CFU count is disregarded. An extension which incorporates censored CFU counts into the likelihood is also provided.

2.2.2.1 General Model

In the application of TB trials, the following general mixed effects regression model, also known as the general random coefficients model, can be assumed for the log(CFU) counts over time (the model being fitted jointly to the data of all patients from a given trial):

$$\log(y_{ijk}) = f(t_{ijk}, \boldsymbol{\phi_{ij}}) + \varepsilon_{ijk} \tag{2.1}$$

where $\log(y_{ijk})$ represents the log(CFU) count for patient $i = 1, \ldots, N_j$ in treatment group $j = 1, \ldots, J$ at timepoint $k = 1, \ldots, K_{ij}$, and $t_{ijk} \geq 0$ is the corresponding measurement time. Here, N_j denotes the number of patients assigned to treatment group j, and T_j the total number of timepoints across all patients assigned to treatment group j. Let $\sum_{j=1}^{J} N_j = N$ represent the total number of patients in a given trial. Furthermore, the function f describes the relationship between t_{ijk} and the $r \times 1$ vector of model parameters, $\boldsymbol{\phi_{ij}}$. The random error terms for modeling the within-patient variation of log(CFU) counts, ε_{ijk}, are assumed to be independent and identically distributed (*i.i.d.*) with mean 0 and constant variance across all measurements within each treatment group.

The vector of parameters is assumed to vary between patients as follows:

$$\boldsymbol{\phi_{ij}} = \boldsymbol{\phi_j} + \boldsymbol{\varphi_{ij}} \tag{2.2}$$

where the $\boldsymbol{\varphi_{ij}}$ (or $\boldsymbol{\phi_{ij}}$) represent $r \times 1$ vectors of random effects, and $\boldsymbol{\phi_j}$ represent the associated vectors of fixed effects. The fixed effects represent the average effect for each treatment group. Eventually, the fixed effects allow one to make inferences on the average EBA or sterilization activities for each of the treatment

groups. Moreover, since the fixed effects are specified in such a way as to allow for differences between treatment groups, the extent to which treatments differ in respect to the average parameters of interest can be assessed. The random effects, in the other hand, allow for separate regression curves to be fitted for each patient (since the model parameters are allowed to vary between patients). The specification of a random coefficients model generally shrinks the estimates of the random effects (hence, regression estimates per patient) towards the "average" estimates (or estimates of the fixed effects), thus avoiding outlier estimates of the random effects which might arise from incomplete data (Brown and Prescott, 2006).

The distributions of ε_{ijk} are assumed independent of the distributions of $\boldsymbol{\varphi_{ij}}$.

In Equation (2.2), the distributions specified for the random effects, $\boldsymbol{\varphi_{ij}}$, should preferably be symmetrical around 0, such as the normal distribution. For random coefficients models, the multivariate normal distribution is commonly used to model the dependency (or correlation) among all or a subset of the various random effects in $\boldsymbol{\varphi_{ij}}$. The truncated normal distribution can also be used to describe certain elements of $\boldsymbol{\phi_{ij}}$, should the parameter space of the applicable elements of $\boldsymbol{\phi_{ij}}$ be bounded. Another way to account for random variation around the fixed effects $\boldsymbol{\phi_j}$ is to assume a distribution directly on the $\boldsymbol{\phi_{ij}}$ such that $\mathrm{E}(\boldsymbol{\phi_{ij}}) = \mathrm{E}(\boldsymbol{\phi_j})$.

Without loss of generality, assume that vectors $\boldsymbol{\phi_{ij}}$ in Equation (2.2) can be partitioned as follows:

$$\boldsymbol{\phi_{ij}} = \begin{bmatrix} \boldsymbol{\phi_{ij}^{(1)}} \\ \boldsymbol{\phi_{ij}^{(2)}} \end{bmatrix} = \begin{bmatrix} \boldsymbol{\phi_{j}^{(1)}} \\ \boldsymbol{\phi_{j}^{(2)}} \end{bmatrix} + \begin{bmatrix} \boldsymbol{\varphi_{ij}^{(1)}} \\ \boldsymbol{\varphi_{ij}^{(2)}} \end{bmatrix} \tag{2.3}$$

where sets $(\boldsymbol{\phi_{ij}^{(1)}}, \boldsymbol{\phi_{j}^{(1)}}, \boldsymbol{\varphi_{ij}^{(1)}})$ and $(\boldsymbol{\phi_{ij}^{(2)}}, \boldsymbol{\phi_{j}^{(2)}}, \boldsymbol{\varphi_{ij}^{(2)}})$ represent the first and second subset of vectors, with size $m_1 \times 1$ and $m_2 \times 1$, from $\boldsymbol{\phi_{ij}}$, $\boldsymbol{\phi_j}$ and $\boldsymbol{\varphi_{ij}}$, respectively (also provided that $m_1 + m_2 = r$).

Assume $\boldsymbol{\phi_{ij}^{(1)}}$ follow multivariate distributions g with mean $\boldsymbol{\phi_{j}^{(1)}}$ and unstructured $m_1 \times m_1$ covariance matrices Ψ_j, so that:

$$\boldsymbol{\phi_{ij}^{(1)}} \sim g(\boldsymbol{\phi_{j}^{(1)}}, \Psi_j) \tag{2.4}$$

The diagonal entries of covariance matrices Ψ_j in Equation (2.4) reflect the magnitude of the between-patient variation among the random coefficients of $\boldsymbol{\phi_{ij}^{(1)}}$, whereas the remainder entries refer to the covariance between the random coefficients.

Further assume $\phi_{ijz}^{(2)}$, $\phi_{jz}^{(2)}$ and ψ_{jz} are the z^{th} element of $\boldsymbol{\phi_{ij}^{(2)}}$, $\boldsymbol{\phi_{j}^{(2)}}$ and $\boldsymbol{\psi_j}$, respectively, where $z = 1, \ldots, m_2$. Accordingly, assume that $\phi_{ijz}^{(2)}$ follow univariate distributions h_z with mean $\phi_{jz}^{(2)}$ and variance or scale parameters ψ_{jz}, so that:

$$\phi_{ijz}^{(2)} \sim h_z(\phi_{jz}^{(2)}, \psi_{jz}) \tag{2.5}$$

Without loss of generality, the residuals ε_{ijk} are assumed to follow normal *i.i.d.* distributions with mean 0 and variance $\sigma_{\varepsilon j}^2$ as follows:

$$\varepsilon_{ijk}|\sigma_{\varepsilon j}^2 \sim N(0, \sigma_{\varepsilon j}^2) \tag{2.6}$$

Accordingly, the likelihood of $\boldsymbol{\phi_{ij}^{(1)}}$, $\boldsymbol{\phi_{j}^{(1)}}$, Ψ_j, $\boldsymbol{\phi_{ij}^{(2)}}$, $\boldsymbol{\phi_{j}^{(2)}}$, $\boldsymbol{\psi_j}$ and $\sigma_{\varepsilon j}^2$ for patient i assigned to treatment group j can be written as follows:

$$\begin{aligned} &L(\boldsymbol{\phi_{ij}^{(1)}}, \boldsymbol{\phi_{j}^{(1)}}, \Psi_j, \boldsymbol{\phi_{ij}^{(2)}}, \boldsymbol{\phi_{j}^{(2)}}, \boldsymbol{\psi_j}, \sigma_{\varepsilon j}^2 | \boldsymbol{y_{ij}}) \\ &= \left(\prod_{k=1}^{K_{ij}} P(y_{ijk}|\boldsymbol{\phi_{ij}^{(1)}}, \boldsymbol{\phi_{ij}^{(2)}}, \sigma_{\varepsilon j}^2) \right) \cdot P_g(\boldsymbol{\phi_{ij}^{(1)}}|\boldsymbol{\phi_{j}^{(1)}}, \Psi_j) \cdot \prod_{z=1}^{m_2} P_{h_z}(\phi_{ijz}^{(2)}|\phi_{jz}^{(2)}, \psi_{jz}) \end{aligned} \tag{2.7}$$

where $P(y_{ijk}|\boldsymbol{\phi_{ij}^{(1)}}, \boldsymbol{\phi_{ij}^{(2)}}, \sigma_{\varepsilon j}^2)$, $P_g(\boldsymbol{\phi_{ij}^{(1)}}|\boldsymbol{\phi_{j}^{(1)}}, \Psi_j)$ and $P_{h_z}(\phi_{ijz}^{(2)}|\phi_{jz}^{(2)}, \psi_{jz})$ denote the probability density function of $\log(y_{ijk})$, $\boldsymbol{\phi_{ij}^{(1)}}$ and $\phi_{ijz}^{(2)}$, respectively, and $\boldsymbol{y_{ij}}$ denote $K_{ij} \times 1$ vectors containing $\big(\log[y_{ij1}], \log[y_{ij2}], \ldots, \log[y_{ijK_{ij}}]\big)'$.

Let $\boldsymbol{\Theta} = (\Theta_1, \Theta_2, \ldots, \Theta_p)'$ denote the complete set of p parameters of the model in Equation (2.1) for all $i = 1, \ldots, N$, $j = 1, \ldots, J$ and $k = 1, \ldots, K_{ij}$. Using Equation (2.7), the likelihood of $\boldsymbol{\Theta}$ can be calculated accordingly. One should note that patients are only assigned to a single treatment group for all t_{ijk}. The notation $i \in \{j\}$ is used to assign only the treatment group indices (j) for which the treatment group is applicable to a given patient (i), and therefore, forbid

irrelevant/non-existing data from the likelihood:

$$L(\boldsymbol{\Theta}|\boldsymbol{y}) = \prod_{i=1}^{N}\prod_{\substack{j=1\\ i\in\{j\}}}^{J} L(\boldsymbol{\phi_{ij}^{(1)}}, \boldsymbol{\phi_{j}^{(1)}}, \Psi_j, \boldsymbol{\phi_{ij}^{(2)}}, \boldsymbol{\phi_{j}^{(2)}}, \boldsymbol{\psi_j}, \sigma^2_{\varepsilon j}|\boldsymbol{y_{ij}}) \tag{2.8}$$

$$= (2\cdot\pi)^{-\frac{1}{2}\sum_{i=1}^{N}\sum_{j=1,i\in\{j\}}^{J} K_{ij}} \cdot \left(\prod_{j=1}^{J}\left(\sigma^2_{\varepsilon j}\right)^{-\frac{1}{2}T_j}\right) \cdot \exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\sum_{k=1}^{K_{ij}} A_{ijk}\right) \cdot$$

$$\prod_{i=1}^{N}\prod_{\substack{j=1\\ i\in\{j\}}}^{J}\left(P_g(\boldsymbol{\phi_{ij}^{(1)}}|\boldsymbol{\phi_{j}^{(1)}}, \Psi_j)\cdot\prod_{z=1}^{m_2} P_{h_z}(\phi^{(2)}_{ijz}|\phi^{(2)}_{jz}, \psi_{jz})\right)$$

where $\boldsymbol{y}$ denotes the $\sum_{i=1}^{N}\sum_{j=1,i\in\{j\}}^{J} K_{ij} \times 1$ vector containing $\boldsymbol{y_{ij}}$ for all $i = 1,\ldots,N$ and $j(i \in \{j\}) = 1,\ldots,J$. The quantities A_{ijk} corresponding to the contribution which the $\log(y_{ijk})$ provide to the likelihood (i.e. the log(CFU) count observed for patient i in treatment group j at timepoint k) are defined as follows:

$$A_{ijk} = \left(\frac{\log(y_{ijk}) - f(t_{ijk}, \boldsymbol{\phi_{ij}})}{\sigma_{\varepsilon j}}\right)^2 \tag{2.9}$$

2.2.2.2 Model Incorporating Censoring

A subset of CFU counts might be reported as zero or "no count" values. Genuine zero counts will typically occur when, for a given patient profile, CFU counts are observed over time to decline to near zero values, just prior to observing one or more zero counts. Thus, genuine zero counts will typically occur towards the end of a CFU versus time profile. When regressing log(CFU) count against time using nonlinear regression models, the log(CFU) counts corresponding to either zero count, or counts reported below the LLOQ, can be specified as a left censored value of d (formally, log(CFU) $< d$) (Rustomjee et al., 2008).

Often when mixed effects regression models are fitted, zero counts are imputed with the LLOQ, i.e. d. However, such imputation can lead to biased parameter estimates, even with modest values of d (Vock et al., 2011). The regression

model in Equation (2.1) should preferably incorporate the modeling of left censored log(CFU) counts.

For simplicity, the notation will now be slightly modified: The indices i, j and k of the model in Section 2.2.2.1 will be ignored, thus focusing only on defining regression functions per patient, writing $f(t_{ijk}, \boldsymbol{\phi_{ij}}) = f(t, \boldsymbol{\phi})$. The regression functions obtained can easily be extended to those of the full model in Section 2.2.2.1. Let $\log(y[t])$ denote the log(CFU) count at time t, so that a model can be devised as follows: $\log(y[t]) = f(t, \boldsymbol{\phi}) + \varepsilon(t)$ where $\varepsilon(t)$ is some additive error term at time t. Similarly, let $\log(\mu[t])$ and σ_ε^2 denote the mean and variance of log(CFU) count at time t, respectively, so that $\mathrm{E}(\log(y[t])) = \log(\mu[t]) = f(t, \boldsymbol{\phi})$ and $\mathrm{Var}(\log(y[t])) = \mathrm{Var}(\varepsilon[t]) = \sigma_\varepsilon^2$.

Let F_N denote the cumulative distribution function of the standard normal distribution. When $\varepsilon(t) \sim N(0, \sigma_\varepsilon^2)$, the density function of $\log(y[t])$ can be extended as follows:

$$P(\log(y[t])) = \left(F_N \left[\frac{d - \log(\mu[t])}{\sigma_{\varepsilon j}} \right] \right)^p \cdot \left(\frac{1}{\sqrt{2 \cdot \pi} \cdot \sigma_{\varepsilon j}} \cdot e^{-\frac{1}{2}\left(\frac{\log(y[t]) - \log(\mu[t])}{\sigma_{\varepsilon j}} \right)^2} \right)^{1-p} \tag{2.10}$$

where $p = 1$ if $\log(y[t]) = d$ and $p = 0$ otherwise.

The contribution of $\log(y[t])$ to the likelihood of Equation (2.8), whether $\log(y(t))$ is censored at d or uncensored, can be altered according to Equation (2.10).

The right censoring of CFU counts reported above the upper limit of quantification (ULOQ), i.e. $\log(\mathrm{CFU}) > d$, is analogous to left censoring.

2.2.3 Bayesian Estimation and Inference

2.2.3.1 General Considerations

The regression parameters of the model in Equation (2.1) can in principle be estimated by maximizing the likelihood function of Equation (2.8). A wide variety

of classical techniques for maximizing this likelihood function is available, and literature on this topic can be found in Brown and Prescott (2006) and Vonesh (2012). The Bayesian approach is an alternative to the classical methods. The Bayesian method involves the derivation of the posterior distribution of model parameters based on specified prior distributions on the corresponding model parameters. Subsequently, conditional on the observed data of a given analysis, the posterior distribution of the model parameters is computed.

Specifically, according the Bayes's theorem, the joint posterior distribution of the model parameters in Equation (2.1) can be expressed as follows:

$$P(\boldsymbol{\Theta}|\boldsymbol{y}) = \frac{L(\boldsymbol{\Theta}|\boldsymbol{y}) \cdot P(\boldsymbol{\Theta})}{\int L(\boldsymbol{\Theta}|\boldsymbol{y}) \cdot P(\boldsymbol{\Theta}) \mathrm{d}\boldsymbol{\Theta}} \tag{2.11}$$

$P(\boldsymbol{\Theta})$ represents the prior distribution on $\boldsymbol{\Theta}$, $L(\boldsymbol{\Theta}|\boldsymbol{y})$ the likelihood as in Equation (2.8), and $\int L(\boldsymbol{\Theta}|\boldsymbol{y}) \cdot P(\boldsymbol{\Theta}) \mathrm{d}\boldsymbol{\Theta}$ is the proportionality constant of the posterior distribution. The posterior distribution can be utilized for estimation and inference on the model parameters $\boldsymbol{\Theta}$. More specifically, the marginal posterior distribution of each of the model parameters is used for Bayesian estimation and inference on $\boldsymbol{\Theta}$.

The marginal posterior distribution of a parameter in question is calculated by integrating the joint posterior distribution over the remainder parameters. Let Θ_l denote the l^{th} parameter of $\boldsymbol{\Theta}$, and $\boldsymbol{\Theta}_{[l]}$ the set of parameters in $\boldsymbol{\Theta}$ with the l^{th} parameter removed, i.e. $\boldsymbol{\Theta}_{[l]} = (\Theta_1, \Theta_2, \ldots, \Theta_{l-1}, \Theta_{l+1}, \ldots, \Theta_p)'$. The marginal posterior distribution of Θ_l is then obtained as follows:

$$\begin{aligned} P(\Theta_l|\boldsymbol{y}) &= \int P(\boldsymbol{\Theta}|\boldsymbol{y}) \mathrm{d}\boldsymbol{\Theta}_{[l]} \\ &= \frac{\int L(\boldsymbol{\Theta}|\boldsymbol{y}) \cdot P(\boldsymbol{\Theta}) \mathrm{d}\boldsymbol{\Theta}_{[l]}}{\int L(\boldsymbol{\Theta}|\boldsymbol{y}) \cdot P(\boldsymbol{\Theta}) \mathrm{d}\boldsymbol{\Theta}} \end{aligned} \tag{2.12}$$

Should Θ_l represent a location parameter (i.e. fixed and random effects), the mean of the marginal posterior distribution of Θ_l can accordingly be used to serve as an estimator of Θ_l (i.e. the estimator which minimizes the associated squared error loss function). For variance components (i.e. if Θ_l represents a variance parameter,

e.g. Ψ_j), the median of the marginal posterior distribution of Θ_l might be a more appropriate choice of an estimator of Θ_l than the mean (i.e. the estimator which minimizes the associated absolute error loss function) (Box and Tiao, 1973). Given a significance level α_s, the $100 \cdot (1 - \alpha_s)\%$ Bayesian credibility interval (BCI) of Θ_l, which is analogous to the $100 \cdot (1 - \alpha_s)\%$ CI of Θ_l in classical inference, can be calculated from the cumulative probability density of the marginal posterior distribution of Θ_l.

As depicted in Equation (2.12), the calculation of the marginal posterior distribution of $\Theta_l|\boldsymbol{y}$ generally requires high dimensional integration, which may seem intractable. The Markov Chain Monte Carlo (MCMC) Gibbs sampling algorithm (Gelfand and Smith, 1990; Gilks et al., 1996) can, however, be employed to draw samples from the joint posterior distribution of $\boldsymbol{\Theta}|\boldsymbol{y}$ (Equation (2.11)), and as a consequence, samples from the marginal posterior distribution of $\Theta_l|\boldsymbol{y}$ (Equation (2.12)) can be obtained. This sampling technique is based on drawing from the full conditional posterior distribution of each model parameter, conditional on the latest values of the remaining parameters in the model. The algorithm for the Gibbs sampler can be summarized as follows (Ntzoufras, 2009):

1. Set initial values for $\boldsymbol{\Theta}$, i.e. $\boldsymbol{\Theta}^{(0)}$.
2. Repeat the following steps for $t = 1, \ldots, T$ iterations:
   (a) Set $\boldsymbol{\Theta} = \boldsymbol{\Theta}^{(t-1)}$.
   (b) Sample Θ_l from $P\left(\Theta_l|\boldsymbol{\Theta}_{[l]}, \boldsymbol{y}\right)$ (i.e. the conditional distribution of Θ_l given $\boldsymbol{\Theta}_{[l]}$ and $\boldsymbol{y}$) for $l = 1, \ldots, p$.
   (c) Set $\boldsymbol{\Theta}^{(t)} = \boldsymbol{\Theta}$.

Provided that convergence has been reached at the r^{th} iteration, $\boldsymbol{\Theta}^{(r)}$ represents a valid sample from the joint posterior distribution of $\boldsymbol{\Theta}|\boldsymbol{y}$ for all $r \leq t \leq T$. Samples drawn from the full conditional posterior distributions have been shown to approximate samples from each model parameter's unconditional joint posterior distribution once convergence has been reached. The full conditional posterior distribution of each of the parameters in Equation (2.11) should therefore be derived

to enable the implementation of the Gibbs sampler. The conditional posterior distributions of the model parameters are derived from the joint posterior distribution by ignoring terms in Equation (2.11) that do not include the relevant model parameter. Random sampling from conditional posterior distributions which are conjugate to their respective prior distributions is convenient. Conversely, calculations are more difficult in the absence of conjugacy (as such conditional posterior densities are usually of unfamiliar form). Sampling from unfamiliar densities requires more advanced sampling techniques, e.g. the slice sampler which is convenient for densities based on a restricted parameter range (e.g. in the application of the truncated normal distribution) (Neal, 2003). In practice, software such as WinBUGS and OpenBUGS, which is efficient in implementing MCMC procedures, can be employed to carry out the Gibbs sampling procedure (Lunn et al., 2009).

The main difference between Bayesian and classical ML estimation is that the posterior density in a Bayesian setup is fully evaluated, whereas with ML estimation, parameter values (and their corresponding SEs) which maximize the likelihood are reported (Farrel and Ludwig, 2008). In Bayesian inference, the SEs are calculated directly from the posterior distribution, and therefore, the problem of bias does not arise in a Bayesian framework (Brown and Prescott, 2006). In cases when the sample sizes are large and the prior distributions are "objective", Bayesian inference usually yields results similar to those by classical methods such as ML estimation (SAS Institute Inc., 2008).

One important advantage of Bayesian inference is that it does not rely on asymptotic approximations, as classical inference methods do for complex models (SAS Institute Inc., 2008). Bayesian methods are therefore attractive for inference in complex models such as NLME regression modeling. Furthermore, classical inferential methods applied to mixed effects regression models might yield estimates of variance components that are negative. When performing Bayesian analyses instead, such undesirable estimates can be avoided by the specification of prior distributions for the variance components covering only parameter spaces lying above 0 (Brown and Prescott, 2006). Furthermore, Bayesian inference adheres to the likelihood principle, as opposed to some classical inference methods which violate the likelihood principle (Press, 1989). The main criticism of the Bayesian

framework concerns the selection of prior distributions, and care should be taken in this regard to avoid misleading results (Robert, 2007). The prior distributions should preferably be specified to assure vagueness with regard to prior belief on the model parameters (i.e. the specification of objective prior distributions). However, Robert (2007) has highlighted that Bayesian hierarchical models (such as Bayesian mixed effects regression models) are less sensitive to the choice of prior distributions (unlike models with no hierarchical structure), and thus may lift the burden of the misspecification of prior distributions to some extent.

2.2.3.2 Model Selection

Alternative NLME regression models can be explored via various Bayesian model selection tools, and may be fitted to assess:

- Alternative shapes of the log(CFU) versus time profiles, e.g. assuming a linear, bilinear or biphasic relationship between log(CFU) count and time.
- The sensitivity of results to the choice of prior distributions.
- Alternative distributions for random effects and residuals (error terms).

Two methods for discriminating between various regression models can be considered: The deviance information criterion (DIC) (Spiegelhalter et al., 2002) and Bayes factors (Kass and Raftery, 1995), both of which can take model uncertainty into account (Ward, 2008).

Deviance Information Criterion

The DIC is a model adequacy and goodness of fit measure, and is defined for Model M as follows:

$$\mathrm{DIC}(M) = 2\overline{\mathrm{D}(\boldsymbol{\theta_m}, M)} - \mathrm{D}(\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}, M) = \mathrm{D}(\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}, M) + 2p_m \tag{2.13}$$

where $\boldsymbol{\theta_m}$ is a $d_m \times 1$ vector of model parameters, $\boldsymbol{y}$ is an $n \times 1$ vector of observed data, $\mathrm{D}(\boldsymbol{\theta_m}, M) = -2\log(f(\boldsymbol{y}|\boldsymbol{\theta_m}, M))$ is the conventional deviance measure (i.e. minus twice the log-likelihood), $\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}$ and $\overline{\mathrm{D}(\boldsymbol{\theta_m}, M)}$ are the mean of the posterior distribution of $\boldsymbol{\theta_m}$ and $\mathrm{D}(\boldsymbol{\theta_m}, M)$, respectively, and $p_m = \overline{\mathrm{D}(\boldsymbol{\theta_m}, M)} - \mathrm{D}(\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}, M)$ is the number of "effective" parameters.

The quantity $\mathrm{DIC}(M)$ is therefore a measure which takes both goodness of fit and complexity of Model M into account, and is appropriate for assessment of the predictability of random effects in Model M (Spiegelhalter et al., 2003). The model with the smallest DIC is considered to fit the data best. However, the DIC measure may be unreliable in cases where $\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}$ is an unreliable estimator of $\boldsymbol{\theta_m}$ (Ntzoufras, 2009).

Bayes Factors

When comparing two models, say Model M_0 and Model M_1, based on the posterior probability of each of the models given the data, the Bayes factor in favor of M_0 is defined as follows:

$$B_{01} = \frac{f(\boldsymbol{y}|M_0)}{f(\boldsymbol{y}|M_1)} \tag{2.14}$$

where $\boldsymbol{y}$ is an $n \times 1$ vector of observed data, and $f(\boldsymbol{y}|M_0)$ and $f(\boldsymbol{y}|M_1)$ are the marginal likelihoods of $\boldsymbol{y}$ under Model M_0 and Model M_1, respectively.

Equivalently:

$$\log(B_{01}) = \log(f[\boldsymbol{y}|M_0]) - \log(f[\boldsymbol{y}|M_1]) \tag{2.15}$$

Unlike the DIC, Bayes factors do not explicitly include a term that penalizes model complexity, but rather incorporate the latter in the marginal likelihood of a given model automatically (Ward, 2008). Furthermore, the DIC compares models conditional on their model parameters, whereas the Bayes factors compare models on a marginal basis.

In the case of NLME regression modeling, the marginal likelihoods in Equation (2.14) need to be approximated. Approximation techniques for marginal

likelihoods include the Laplace-Metropolis approximation (Raftery, 1996; Lewis and Raftery, 1997), and the harmonic mean (Newton and Raftery, 1994), importance (Newton and Raftery, 1994), bridge (Meng and Wong, 1996) and Chib's (Chib, 1995) sampling estimators. It should be noted that in some cases the harmonic mean sampling estimator has infinite variance (which does not adhere to the central limit theorem) (Wolpert and Schmidler, 2012) and preferably should be avoided.

The Laplace-Metropolis approximation, in its general form, for $\log(f(\boldsymbol{y}|M))$ is given by the following expression (Ntzoufras, 2009):

$$\begin{aligned}\log(\hat{f}(\boldsymbol{y}|M)) =& \frac{1}{2} d_m \log(2\pi) + \frac{1}{2}\log|R_{\boldsymbol{\theta_m}}| + \sum_{j=1}^{d_m}\log(s_j) \\ &+ \sum_{i=1}^{n}\log(f[y_i|\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}, M]) + \sum_{j=1}^{d_m}\log(f[\bar{\theta}_{mj}|M])\end{aligned} \tag{2.16}$$

where $\bar{\theta}_{mj}$ and s_j are the mean and standard deviation (SD), respectively, of the posterior distribution of θ_{mj}, and $|R_{\boldsymbol{\theta_m}}|$ is the determinant of the $d_m \times d_m$ correlation matrix of the posterior distribution of $\boldsymbol{\theta_m}$, $f(y_i|\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}, M)$ is the likelihood of the i^{th} observation, conditional on $\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}$, and $f(\bar{\theta}_{mj}|M)$ is the prior probability density of θ_{mj} (j^{th} model parameter) evaluated at $\bar{\theta}_{mj}$.

The model with the largest log-marginal likelihood, i.e. $\log(\hat{f}(\boldsymbol{y}|M))$, is considered to fit the data more appropriately. The Laplace-Metropolis approximation in Equation (2.16) is based on asymptotic theory of the normal distribution, and works well for symmetric posterior distributions of $\boldsymbol{\theta_m}$ (Ntzoufras, 2009).

In mixed effects models, the calculation of the Laplace-Metropolis marginal likelihood requires that the random effects included in each patient's likelihood function, i.e. $f(y_i|\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}, M)$, are integrated out. This marginal likelihood (after integrating out the random effects) is referred to as the compound Laplace-Metropolis marginal likelihood (Lewis and Raftery, 1997). Here, $|R_{\boldsymbol{\theta_m}}|$ and s_j are associated with fixed effects and none of the variance hyperparameters of random effects,

whereas both fixed effects and variance hyperparameters of random effects are taken into consideration for $f(\bar{\theta}_{mj}|M)$.

2.2.3.3 Model Checking

Model checking can include the assessment of the predictive performance of the regression model using the posterior predictive distribution of replicated data $\boldsymbol{y_f}$. The goodness of fit between replicated and observed data can be assessed accordingly (Ntzoufras, 2009). The posterior predictive distribution of $\boldsymbol{y_f}$ is given by the following expression:

$$f(\boldsymbol{y_f}|\boldsymbol{y}) = \int f(\boldsymbol{y_f}, \boldsymbol{\theta}|\boldsymbol{y}) d\boldsymbol{\theta} = \int f(\boldsymbol{y_f}|\boldsymbol{\theta}) f(\boldsymbol{\theta}|\boldsymbol{y}) d\boldsymbol{\theta} \tag{2.17}$$

where $\boldsymbol{y_f}$, $\boldsymbol{y}$ and $\boldsymbol{\theta}$ represent a $f \times 1$, $n \times 1$ and $d \times 1$ vector of replicated and observed data, and model parameters, respectively.

The aforementioned approach has been criticized because of its double use of the data, and as a result, Geisser and Eddy (1979) proposed the use of the leave-one-out cross-validation predictive distribution instead, namely:

$$f(y_i|\boldsymbol{y}_{[i]}) = \int f(y_i|\boldsymbol{\theta}) f(\boldsymbol{\theta}|\boldsymbol{y}_{[i]}) d\boldsymbol{\theta} \tag{2.18}$$

where $\boldsymbol{y}_{[i]}$ represents the vector $\boldsymbol{y}$ with the i^{th} observation (i.e. y_i) omitted.

The quantity $f(y_i|\boldsymbol{y}_{[i]})$ in Equation (2.18) is also known as the conditional posterior ordinate (CPO), and can be estimated by the following:

$$\widehat{\text{CPO}}_i = \left(\frac{1}{L} \sum_{l=1}^{L} \frac{1}{f(y_i|\boldsymbol{\theta}^{(l)})} \right)^{-1} \tag{2.19}$$

where $\boldsymbol{\theta}^{(l)}$ represents the vector of posterior MCMC samples from $\boldsymbol{\theta}$ at iteration l. The $\widehat{\text{CPO}}_i$ estimate can be interpreted as the harmonic mean of the probability

distribution of y_i for each $\boldsymbol{\theta}^{(l)}$, where $l = 1, 2, \ldots, L$ following the simulation burn-in period.

A large number of small $\widehat{\text{CPO}}_i$ estimates would indicate a poor fit of the candidate model. Such $\widehat{\text{CPO}}_i$ estimates can be used to identify possible outliers in the data. Conversely, the reciprocal of $\widehat{\text{CPO}}_i$, or $\widehat{\text{ICPO}}_i$, can be used to assess model fit. Estimates of $\widehat{\text{ICPO}}_i > 40$ and $\widehat{\text{ICPO}}_i > 70$ highlight possible or extreme outliers in the data, respectively (Ntzoufras, 2009).

2.3 Regression Functions

Now that a formulation of the general mixed effects regression model for modeling log(CFU) counts has been given (see Section 2.2.2.1), the underlying regression functions (having a common structure across all patients), $f(t_{ijk}, \boldsymbol{\phi_{ij}})$, which appropriately describe log(CFU) count over time, should be selected. The simplified notation used in Section 2.2.2.2 will be used from here onwards, such as $f(t_{ijk}, \boldsymbol{\phi_{ij}}) = f(t, \boldsymbol{\phi})$.

If it is assumed that the rate of change (decrease) in expected CFU count at time t is proportional to the expected value at time t, $\mu(t)$, the following well-known differential equation is obtained:

$$\frac{\mathrm{d}\mu(t)}{\mathrm{d}t} = -\lambda(t) \cdot \mu(t) \tag{2.20}$$

Here $\lambda(t) > 0$ is the proportionality function and characterizes the rate of decrease. From Equation (2.20) it follows that:

$$\frac{\mathrm{d}\mu(t)}{\mu(t)} = -\lambda(t)\mathrm{d}t \tag{2.21}$$

Integrating both sides of Equation (2.21) results in:

$$\int \frac{1}{\mu(t)}\mathrm{d}\mu(t) = \mathrm{C} - \int \lambda(t)\mathrm{d}t \tag{2.22}$$

with solution:

$$\log(\mu[t]) = \mathrm{C} - \int \lambda(t)\mathrm{d}t \tag{2.23}$$

where C is some constant, obtained after integration.

To include a parameter describing the intercept of the regression function in Equation (2.23) by a single parameter α, assume the condition $\log(\mu[0]) = \alpha$ and solve for C:

$$\mathrm{C} = \alpha + \int \lambda(0)\mathrm{d}t \tag{2.24}$$

Replacing C in Equation (2.23) with Equation (2.24) results in the following regression function:

$$\log(\mu[t]) = \alpha + \int \lambda(0)\mathrm{d}t - \int \lambda(t)\mathrm{d}t \tag{2.25}$$

In the following sections various functions are discussed which might appropriately describe $\lambda(t)$ in the application of regression modeling of CFU count over time. The regression model with constant rate of change (mono-exponential or log-linear regression model) is described first, and then generalized to various other regression models incorporating two rates of change (initial and late), and to a regression model that allows for a smooth transition from the first to the second phase.

2.3.1 Linear Regression Function

In Equation (2.25), assuming $\lambda(t)$ is constant for all t:

$$\lambda(t) = \lambda \tag{2.26}$$

the following is obtained:

$$\log(\mu[t]) = \alpha - \lambda \cdot t \tag{2.27}$$

Equivalently to Equation (2.26), one can write:

$$\mu(t) = e^{\alpha} \cdot e^{-\lambda t} \tag{2.28}$$

where α and λ can be interpreted as the intercept and slope (or rather, parameter characterizing the rate of decline), respectively, of the regression function.

Figure 2.1 shows an example of the expected log(CFU) count and its corresponding rate of decline from a linear regression function over time, i.e. plot of Equation (2.26) and Equation (2.27), of a patient from a typical 14-day EBA study. For Figure 2.1, the expected log(CFU) count in Equation (2.26) is assumed to be declining constantly over time, i.e. $\lambda > 0$. For this example, the regression parameters are set at $\alpha = 7$ and $\lambda = 0.1$.

Based on Equation (2.28), one can postulate the following multiplicative mono-exponential regression model for $y(t)$, namely:

$$y(t) = e^{\alpha} \cdot e^{-\lambda t} \cdot \ e^{\varepsilon(t)} \tag{2.29}$$

where $e^{\varepsilon(t)}$ is a multiplicative error term at time t. However, conventionally the CFU counts $y(t)$ are transformed logarithmically, which leads to the log-linear regression model:

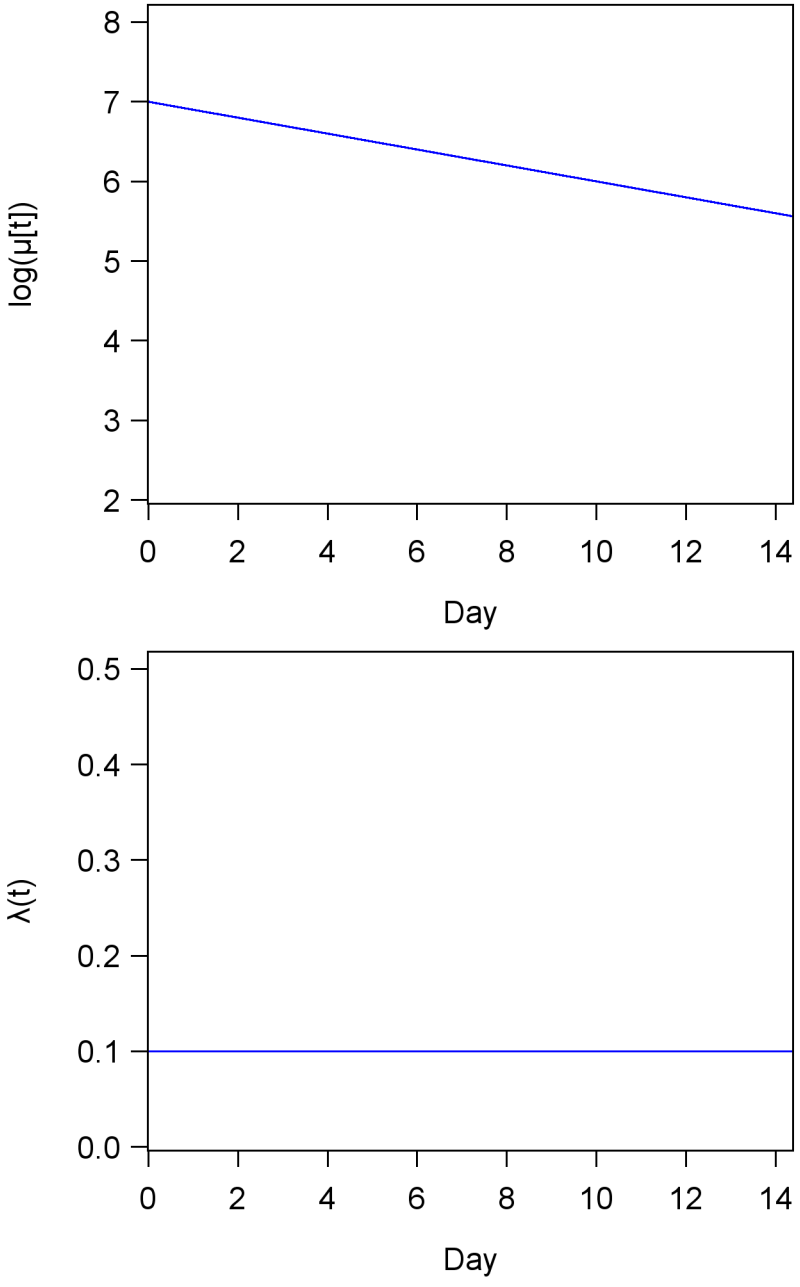
$$\log(y[t]) = \alpha - \lambda \cdot t + \varepsilon(t) \tag{2.30}$$

In summary, the assumption of a constant rate of change in CFU count over time leads to the mono-exponential regression model in Equation (2.29), and after logarithmic transformation, the simple log-linear regression model (single slope) of log(CFU) count against time in Equation (2.30). The linear regression model implies that $f(t, \boldsymbol{\phi})$ in Section 2.3 can be written as

$$f(t, \boldsymbol{\phi}) = \alpha - \lambda \cdot t$$

where $\boldsymbol{\phi} = (\alpha, \lambda)'$. This regression model is referred to as the linear mixed effects regression model when fitted to CFU data of all patients jointly.

Figure 2.1: Example Plot of Expected log(CFU) Count ($\log[\mu\{t\}]$) and Corresponding Rate of Change ($\lambda[t]$) Over Time from Linear Regression Function



2.3.2 Bilinear and Nonlinear Regression Functions

As mentioned earlier, previous analyses of CFU count have suggested that profiles of log(CFU) count over time follow bilinear or nonlinear patterns over time. In this case, the rate of change in CFU count itself changes over time. The regression model in Equation (2.25) is therefore assumed in this regard.

2.3.2.1 Conventional Bilinear Regression Function

Bilinear regression modeling of log(CFU) count against time, with slopes λ_1 and λ_2, is equivalent to the assumption that, from time 0 up to some time κ, the rate of change is λ_1, and after time κ, the rate of change is λ_2 (therefore implying an "instant" change in the rate of decline of log(CFU) count at time κ). Under the bilinear regression model, the rate of change as a function of time is a step function, with change point at time κ.

When $\lambda(t)$ (see Equation (2.25)) is a step function, the following is obtained:

$$\lambda(t) = \begin{cases} \lambda_1 & t \leq \kappa \\ \lambda_2 & t > \kappa \end{cases} \tag{2.31}$$

Figure 2.2 and Figure 2.3 show examples of the rate of decline in expected log(CFU) count over time, as described by a step function, i.e. plot of Equation (2.31), of a patient from a typical 14-day EBA study. Figure 2.2 depicts a situation where the rate of decline from time 0 up to time κ is smaller than the rate of decline after time κ, i.e. $\lambda_1 < \lambda_2$. For this example, the regression parameters are set at $\lambda_1 = 0.1 < \lambda_2 = 0.45$, and $\kappa = 7$. Figure 2.3 depicts a situation where the rate of decline from time 0 up to time κ is larger than the rate of decline after time κ, i.e. $\lambda_1 > \lambda_2$. For this example, the values of the slopes in Figure 2.3 are reversed (as opposed to Figure 2.2), i.e. $\lambda_1 = 0.45 > \lambda_2 = 0.1$.

Figure 2.2: Example Plot of Rate of Change in Expected log(CFU) Count ($\lambda[t]$) Over Time Modeled by Step Function: $\lambda_1 < \lambda_2$

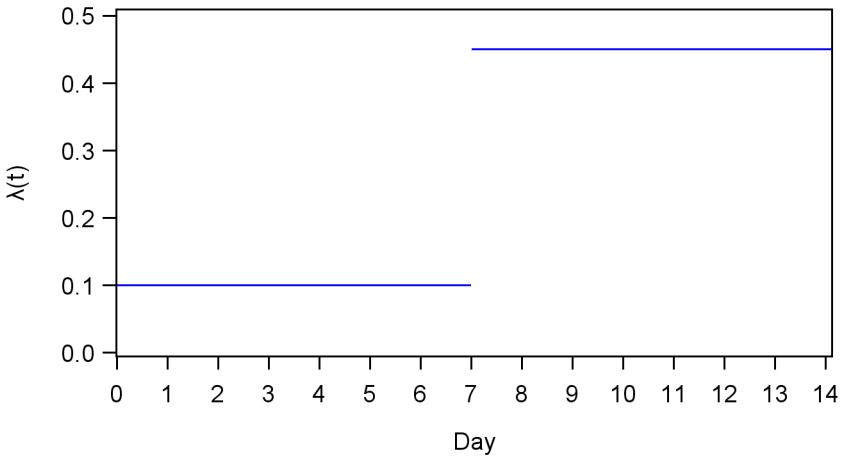
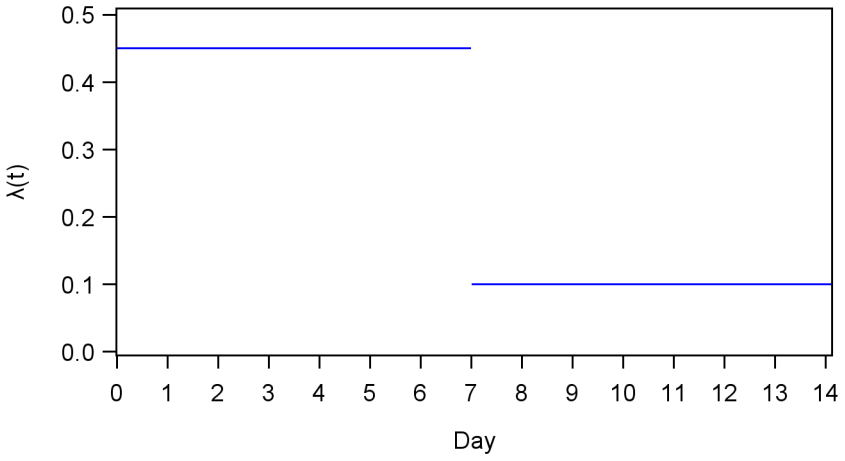


Figure 2.3: Example Plot of Rate of Change in Expected log(CFU) Count ($\lambda[t]$) Over Time Modeled by Step Function: $\lambda_1 > \lambda_2$



Substituting Equation (2.31) in Equation (2.25):

$$\log(\mu[t]) = \begin{cases} \alpha - \int_0^t \lambda_1 \mathrm{d}t & t \leq \kappa \\ \alpha - \int_0^\kappa \lambda_1 \mathrm{d}t - \int_\kappa^t \lambda_2 \mathrm{d}t & t > \kappa \end{cases} \tag{2.32}$$

Completing the integration leads to the following conventional bilinear regression model:

$$\log(\mu[t]) = \begin{cases} \alpha - \lambda_1 \cdot t & t \leq \kappa \\ \alpha + (\lambda_2 - \lambda_1) \cdot \kappa - \lambda_2 \cdot t & t > \kappa \end{cases} \tag{2.33}$$

Here, α and κ are the intercept and node (or inflection point) parameter, respectively, and the slope λ_1 characterizes the linear decline on or before the node ($t \leq \kappa$), while the slope λ_2 characterizes the linear decline after the node ($t > \kappa$).

The bilinear regression function reduces to the conventional linear regression function (see Equation (2.27)) when $\lambda_1 = \lambda_2$.

Figure 2.4 and Figure 2.5 show examples of bi-linear regression functions of log(CFU) count over time, i.e. plot of Equation (2.31) and Equation (2.33), in analogy to information contained in Figure 2.2 and Figure 2.3, also provided that $\alpha = 7$.

Finally, it is noted that the regression model in Equation (2.33) can be parameterized as follows:

$$\beta_1 = \frac{\lambda_1 + \lambda_2}{2}$$
$$\beta_2 = \frac{\lambda_2 - \lambda_1}{2}$$

so that Equation (2.33) becomes:

$$\log(\mu[t]) = \begin{cases} \alpha - (\beta_1 - \beta_2) \cdot t & t \leq \kappa \\ \alpha + 2 \cdot \beta_2 \cdot \kappa - (\beta_1 + \beta_2) \cdot t & t > \kappa \end{cases} \tag{2.34}$$

The parameters β_1 and β_2 are the average of and half the difference between the two rate constants λ_1 and λ_2, respectively.

Figure 2.4: Example Plot of Expected log(CFU) Count ($\log[\mu\{t\}]$) and Corresponding Rate of Change ($\lambda[t]$) Over Time from Bilinear Regression Function: $\lambda_1 < \lambda_2$

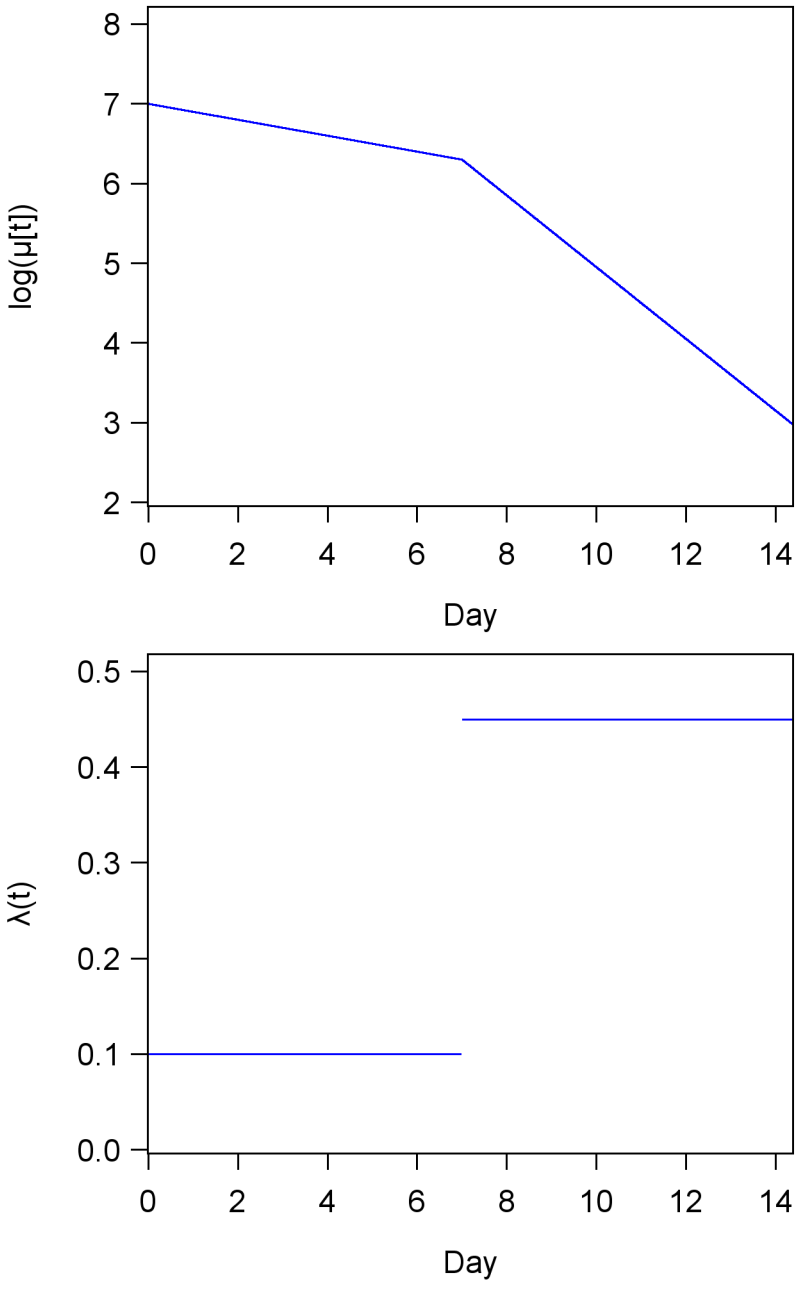
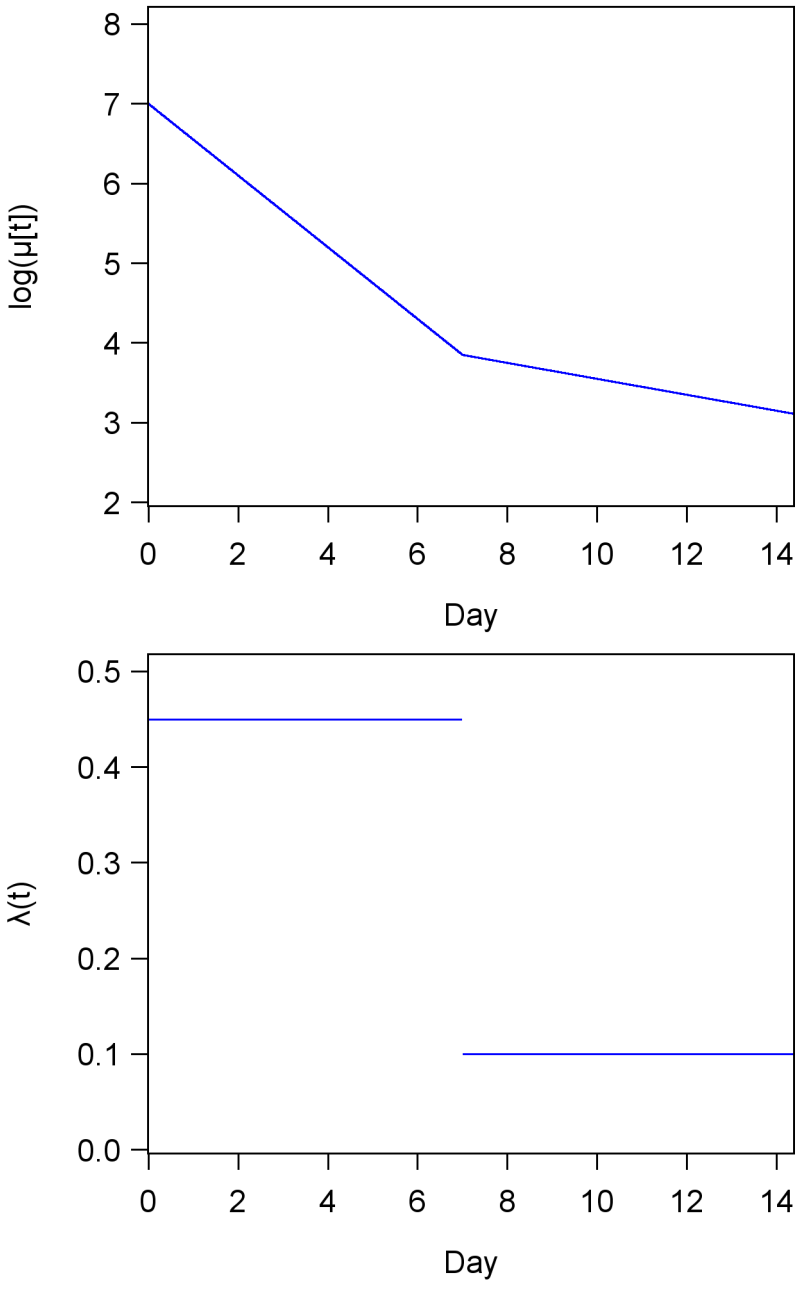


Figure 2.5: Example Plot of Expected log(CFU) Count ($\log[\mu\{t\}]$) and Corresponding Rate of Change ($\lambda[t]$) Over Time from Bilinear Regression Function: $\lambda_1 > \lambda_2$



Based on Equation (2.34), a bilinear regression model for $y(t)$ is obtained, namely:

$$\log(y[t]) = \begin{cases} \alpha - (\beta_1 - \beta_2) \cdot t + \varepsilon(t) & t \leq \kappa \\ \alpha + 2 \cdot \beta_2 \cdot \kappa - (\beta_1 + \beta_2) \cdot t + \varepsilon(t) & t > \kappa \end{cases} \tag{2.35}$$

where $\varepsilon(t)$ is an additive error term at time t.

In summary, the bilinear regression model in Equation (2.35) implies that $f(t, \boldsymbol{\phi})$ in Section 2.3 can be written as

$$f(t, \boldsymbol{\phi}) = \begin{cases} \alpha - (\beta_1 - \beta_2) \cdot t & t \leq \kappa \\ \alpha + 2 \cdot \beta_2 \cdot \kappa - (\beta_1 + \beta_2) \cdot t & t > \kappa \end{cases}$$

where $\boldsymbol{\phi} = (\alpha, \beta_1, \beta_2, \kappa)'$. This regression model is referred to as the conventional bilinear mixed effects regression model when fitted to CFU data of all patients jointly.

2.3.2.2 Nonlinear Regression Functions

As has been pointed out by Jindani et al. (2003), the switch from one rate of decline in log(CFU) count to another might be smooth, rather than abrupt as is implied with by the bilinear regression model in Equation (2.35). In order to model a smooth transition, one can use a monotonic function that interpolates between the early rate of decline, λ_1, and the late rate of decline, λ_2. A class of such functions is formed by linear transformations of cumulative distribution functions (Seber and Wild, 1989). Various other regression functions derived from functions which provide smooth modeling of the step function in Equation (2.31) are described in the next few sections. It will be noted that the bi-exponential regression function, as used for modeling of log(CFU) count as by Davies et al. (2006a), Davies et al. (2006b), Rustomjee et al. (2008) and Sloan et al. (2012), is based on a smooth version of the aforementioned step function.

Differential Hyperbolic Tangent Regression Function

When $\lambda(t)$ (see Equation (2.25)) follows a hyperbolic tangent function, one has:

$$\lambda(t) = \frac{\lambda_1 + \lambda_2}{2} + \frac{\lambda_2 - \lambda_1}{2} \cdot \frac{e^{\frac{t-\kappa}{\gamma}} - e^{-\frac{t-\kappa}{\gamma}}}{e^{\frac{t-\kappa}{\gamma}} + e^{-\frac{t-\kappa}{\gamma}}} \tag{2.36}$$

where $\kappa \geq 0$ and $\gamma > 0$.

The hyperbolic tangent function in Equation (2.36) is essentially a smooth version of the step function in Equation (2.31). For small t, the function $\lambda(t)$ tends to λ_1, i.e., $\lim_{t\to 0} \lambda(t) = \lambda_1$, and similarly, for large t, the function $\lambda(t)$ tends to λ_2, i.e., $\lim_{t\to\infty} \lambda(t) = \lambda_2$. Thus, when assuming $\lambda_1 < \lambda_2$, the parameters λ_1 and λ_2 are the minimum and maximum values of $\lambda(t)$, respectively. *Vice versa*, when assuming $\lambda_1 > \lambda_2$, the parameters λ_1 and λ_2 are the maximum and minimum values of $\lambda(t)$, respectively. Furthermore, $\lambda(\kappa) = (\lambda_1 + \lambda_2)/2$, so that κ can be viewed the node at which transition within $\lambda(t)$ occurs. Lastly, the parameter γ governs the "smoothness" or the "speed" of the transition from rate λ_1 to rate λ_2. As $\gamma \to 0$, the switch from λ_1 to λ_2 is rapid, whereas the switch slows down as γ moves further away from 0.

With $\lambda(t)$ as in Equation (2.36), the following regression model for $\log(\mu[t])$ is obtained by calculating the integral in Equation (2.25):

$$\log(\mu[t]) = \alpha - \frac{\lambda_1 + \lambda_2}{2} \cdot t - \frac{\lambda_2 - \lambda_1}{2} \cdot \gamma \cdot \log\left(\frac{e^{\frac{t-\kappa}{\gamma}} + e^{-\frac{t-\kappa}{\gamma}}}{e^{\frac{\kappa}{\gamma}} + e^{-\frac{\kappa}{\gamma}}}\right) \tag{2.37}$$

For the regression function in Equation (2.37), α is the intercept, κ the node parameter, γ the "smoothness" parameter, whereas λ_1 and λ_2 are the respective slope parameters.

Note that, for small t (and small γ relative to κ), the term $e^{\frac{t-\kappa}{\gamma}}$ tends to zero, while the term $e^{-\frac{t-\kappa}{\gamma}}$ becomes large. Thus, for small t, $\log(\mu[t])$ becomes:

$$\begin{aligned}\log(\mu[t]) &\approx \alpha - \frac{\lambda_1+\lambda_2}{2}\cdot t - \frac{\lambda_2-\lambda_1}{2}\cdot\gamma\cdot\log\left(\frac{e^{-\frac{t-\kappa}{\gamma}}}{e^{\frac{\kappa}{\gamma}}+e^{-\frac{\kappa}{\gamma}}}\right)\\ &\approx \alpha - \frac{\lambda_1+\lambda_2}{2}\cdot t + \frac{\lambda_2-\lambda_1}{2}\cdot\gamma\cdot\left(\frac{t-\kappa}{\gamma}+\log\left(e^{\frac{\kappa}{\gamma}}+e^{-\frac{\kappa}{\gamma}}\right)\right)\\ &\approx \left(\alpha - \frac{\lambda_2-\lambda_1}{2}\cdot\left(\kappa-\gamma\cdot\log\left[e^{\frac{\kappa}{\gamma}}+e^{-\frac{\kappa}{\gamma}}\right]\right)\right) - \lambda_1\cdot t\end{aligned}$$

Therefore, for small t ($t \leq \kappa$), $\log(\mu[t])$ declines linearly with slope $-\lambda_1$.

Vice versa, for large t, the term $e^{\frac{t-\kappa}{\gamma}}$ becomes large, while the term $e^{-\frac{t-\kappa}{\gamma}}$ tends to 0. Thus, for large t, $\log(\mu[t])$ becomes:

$$\begin{aligned}\log(\mu[t]) &\approx \alpha - \frac{\lambda_1+\lambda_2}{2}\cdot t - \frac{\lambda_2-\lambda_1}{2}\cdot\gamma\cdot\log\left(\frac{e^{\frac{t-\kappa}{\gamma}}}{e^{\frac{\kappa}{\gamma}}+e^{-\frac{\kappa}{\gamma}}}\right)\\ &\approx \alpha - \frac{\lambda_1+\lambda_2}{2}\cdot t - \frac{\lambda_2-\lambda_1}{2}\cdot\gamma\cdot\left(\frac{t-\kappa}{\gamma}-\log\left(e^{\frac{\kappa}{\gamma}}+e^{-\frac{\kappa}{\gamma}}\right)\right)\\ &\approx \left(\alpha + \frac{\lambda_2-\lambda_1}{2}\cdot\left(\kappa+\gamma\cdot\log\left[e^{\frac{\kappa}{\gamma}}+e^{-\frac{\kappa}{\gamma}}\right]\right)\right) - \lambda_2\cdot t\end{aligned}$$

Therefore, for large t ($t \geq \kappa$), $\log(\mu[t])$ declines linearly with slope $-\lambda_2$.

From hereafter, the regression function in Equation (2.37) will be referred to as the differential hyperbolic tangent regression function.

Similar to the bilinear regression function, the differential hyperbolic tangent regression function reduces to the conventional linear regression function when $\lambda_1 = \lambda_2$. Furthermore, the differential hyperbolic tangent regression function (see Equation (2.37)) is a "smooth" version of the bilinear regression model (see Equation (2.33)). In fact, the regression function in Equation (2.33) is a special case of the regression function in Equation (2.37) when $\gamma \to 0$. Importantly, for small t (when $\lambda_1 > \lambda_2 > 0$), the variable $\mu(t)$ (i.e. CFU count on the original scale) is approximated by an exponential function $C_1 \cdot e^{-\lambda_1 \cdot t}$,

where $C_1 = \exp\left(\alpha - \frac{\lambda_2-\lambda_1}{2} \cdot \left[\kappa - \gamma \cdot \log\left\{e^{\frac{\kappa}{\gamma}} + e^{-\frac{\kappa}{\gamma}}\right\}\right]\right)$, and for large t, the variable $\mu(t)$ is approximated by an exponential function $C_2 \cdot e^{-\lambda_2 \cdot t}$, where $C_2 = \exp\left(\alpha + \frac{\lambda_2-\lambda_1}{2} \cdot \left[\kappa + \gamma \cdot \log\left\{e^{\frac{\kappa}{\gamma}} + e^{-\frac{\kappa}{\gamma}}\right\}\right]\right)$. In that sense, both Equation (2.33) and Equation (2.37) approximate bi-exponential regression functions.

Figure 2.6 and Figure 2.7 show examples of the expected log(CFU) count and its corresponding rate of decline from a differential hyperbolic tangent regression function over time, i.e. plot of Equation (2.36) and Equation (2.37), of a patient from a typical 14-day EBA study. Figure 2.6 depicts a situation where the rate of decline from time 0 up to time κ is smaller than the rate of decline after time κ, i.e. $\lambda_1 < \lambda_2$. For this example, the regression parameters $\alpha = 7$, $\lambda_1 = 0.1 < \lambda_2 = 0.45$, and $\kappa = 7$ are kept fixed, but showed for different values of γ, i.e. $\gamma \, \epsilon \, \{0.1, 1, 2, 4\}$. This figure shows how the rate of change changes faster for values of γ closer to 0. In Figure 2.7, the rate of decline from time 0 up to time κ is larger than the rate of decline after time κ, i.e. $\lambda_1 > \lambda_2$. For this example, the values of the slopes in Figure 2.7 are reversed (as opposed to Figure 2.6), i.e. $\lambda_1 = 0.45 > \lambda_2 = 0.1$.

When β_1 and β_2 are the average of and half the difference between the two rate constants λ_1 and λ_2, respectively (analogous to Equation (2.34)), then Equation (2.37) becomes:

$$\log(\mu[t]) = \alpha - \beta_1 \cdot t - \beta_2 \cdot \gamma \cdot \log\left(\frac{e^{\frac{t-\kappa}{\gamma}} + e^{-\frac{t-\kappa}{\gamma}}}{e^{\frac{\kappa}{\gamma}} + e^{-\frac{\kappa}{\gamma}}}\right) \tag{2.38}$$

Thus one has the following nonlinear regression model for $\log(y[t])$:

$$\log(y[t]) = \alpha - \beta_1 \cdot t - \beta_2 \cdot \gamma \cdot \log\left(\frac{e^{\frac{t-\kappa}{\gamma}} + e^{-\frac{t-\kappa}{\gamma}}}{e^{\frac{\kappa}{\gamma}} + e^{-\frac{\kappa}{\gamma}}}\right) + \varepsilon(t) \tag{2.39}$$

where $\varepsilon(t)$ is an additive error term at time t.

In summary, the differential hyperbolic tangent regression model in Equation (2.39) implies that $f(t, \boldsymbol{\phi})$ in Section 2.3 can be written as

$$f(t, \boldsymbol{\phi}) = \alpha - \beta_1 \cdot t - \beta_2 \cdot \gamma \cdot \log\left(\frac{e^{\frac{t-\kappa}{\gamma}} + e^{-\frac{t-\kappa}{\gamma}}}{e^{\frac{\kappa}{\gamma}} + e^{-\frac{\kappa}{\gamma}}}\right)$$

Figure 2.6: Example Plot of Expected log(CFU) Count ($\log[\mu\{t\}]$) and Corresponding Rate of Change ($\lambda[t]$) Over Time from Differential Hyperbolic Tangent Regression Function: $\lambda_1 < \lambda_2$

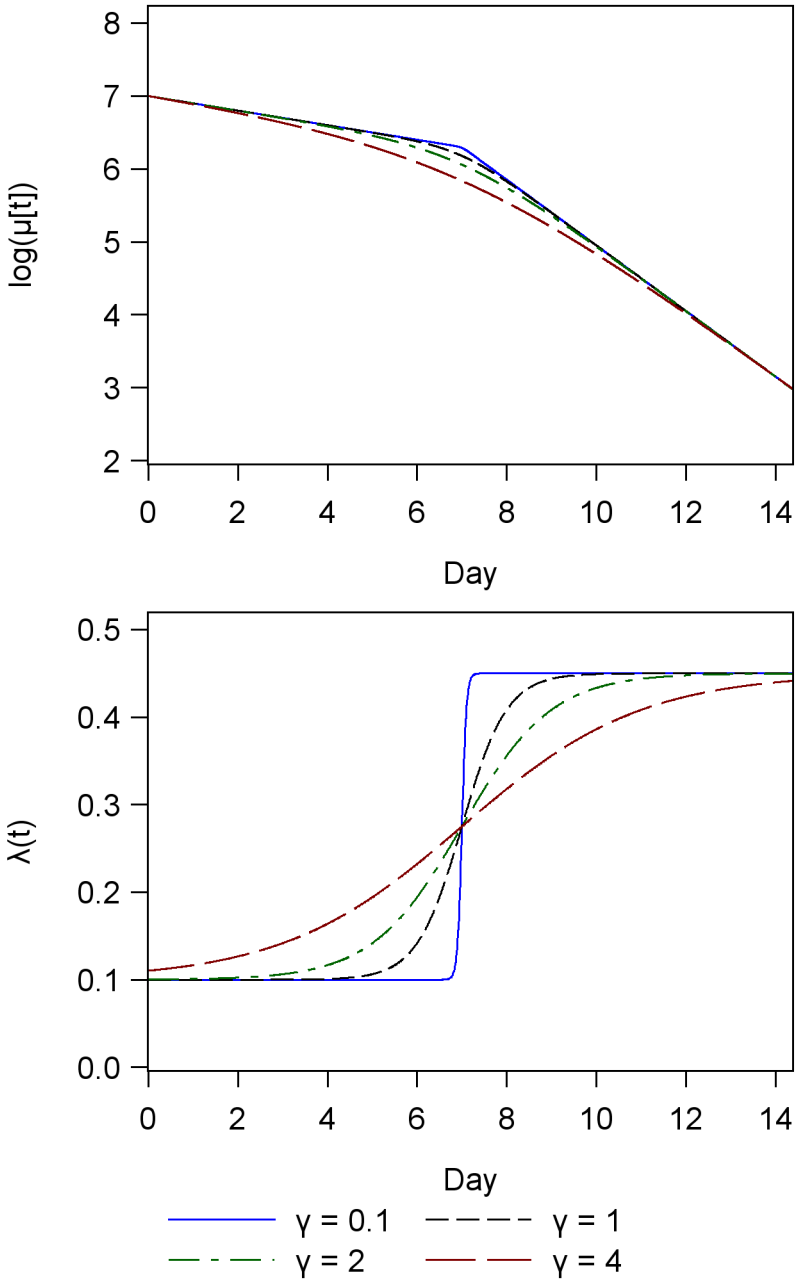
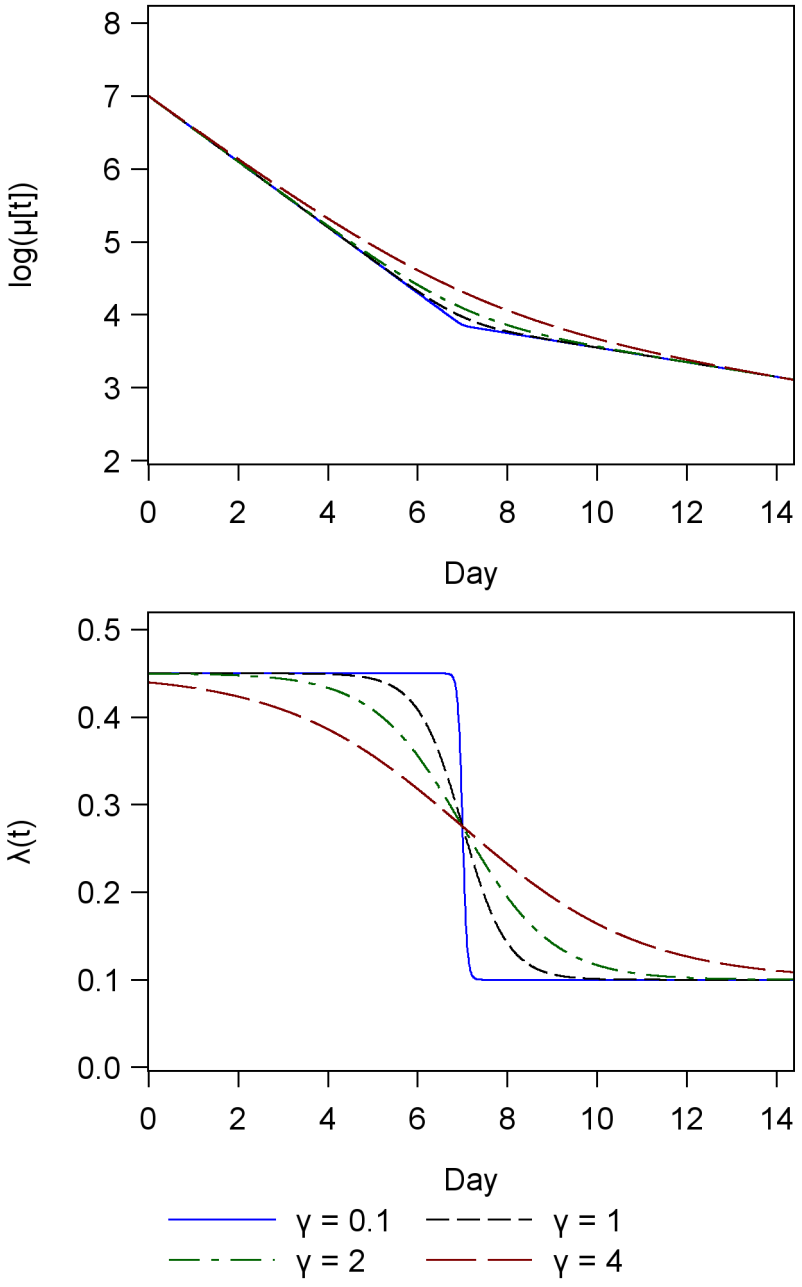


Figure 2.7: Example Plot of Expected log(CFU) Count ($\log[\mu\{t\}]$) and Corresponding Rate of Change ($\lambda[t]$) Over Time from Differential Hyperbolic Tangent Regression Function: $\lambda_1 > \lambda_2$



where $\boldsymbol{\phi} = (\alpha, \beta_1, \beta_2, \kappa, \gamma)'$. This regression model is referred to as an NLME regression model when fitted to CFU data of all patients jointly.

Bi-Exponential Regression Function

A model that has been used in literature for CFU data is the bi-exponential regression function (Davies et al., 2006a,b; Rustomjee et al., 2008; Sloan et al., 2012) for $\mu(t)$, or, after logarithmic transformation:

$$\log(\mu[t]) = \log\left(e^{\theta_1} \cdot e^{-\lambda_1 \cdot t} + e^{\theta_2} \cdot e^{-\lambda_2 \cdot t}\right) \tag{2.40}$$

where it is assumed that $\lambda_1 = e^{\theta_3}$ and $\lambda_2 = e^{\theta_4}$. The parameters θ_1 and θ_2 control the intercept term of the regression function, whereas λ_1 and λ_2 are parameters governing the rate of decline during the initial and terminal phase of the observation period, respectively. The first and second slope are expressed as the exponents of θ_3 and θ_4, respectively, to ensure numerical stability when estimated from CFU data over time (Rustomjee et al., 2008). Such parameterization of the bi-exponential regression function does not allow for increasing CFU versus time profiles.

Differentiating Equation (2.40) with respect to t, one can write the corresponding $\lambda(t)$ (Equation (2.25)) as follows:

$$\lambda(t) = \frac{\lambda_1 \cdot e^{\theta_1} \cdot e^{-\lambda_1 \cdot t} + \lambda_2 \cdot e^{\theta_2} \cdot e^{-\lambda_2 \cdot t}}{e^{\theta_1} \cdot e^{-\lambda_1 \cdot t} + e^{\theta_2} \cdot e^{-\lambda_2 \cdot t}} \tag{2.41}$$

The regression function in Equation (2.40) can be written as:

$$\begin{aligned} \log(\mu[t]) &= \log\left(\left[e^{\theta_1} \cdot e^{-\lambda_1 \cdot t}\right]\left[1 + e^{\theta_2 - \theta_1} \cdot e^{-(\lambda_2 - \lambda_1) \cdot t}\right]\right) \\ &= (\theta_1 - \lambda_1 \cdot t) + \log\left(1 + e^{\theta_2 - \theta_1} \cdot e^{-(\lambda_2 - \lambda_1) \cdot t}\right) \end{aligned}$$

Without loss of generality, assume that $\lambda_1 > \lambda_2$. In that case, for large t, the term $e^{\theta_2-\theta_1} \cdot e^{-(\lambda_2-\lambda_1)\cdot t}$ becomes much larger than 1 so that:

$$\log(\mu[t]) \approx (\theta_1 - \lambda_1 \cdot t) + \log\left(e^{\theta_2-\theta_1} \cdot e^{-(\lambda_2-\lambda_1)\cdot t}\right) = \theta_2 - \lambda_2 \cdot t \tag{2.42}$$

Equation (2.42) implies that, with the conventional bi-exponential regression function, the terminal slope (i.e. λ_2) is always smaller than the initial slope (i.e. λ_1). The bi-exponential regression function, therefore, is suitable only for situations when CFU count initially decreases fast, followed by a slower rate of decrease. The conventional bi-exponential regression function cannot accommodate an initially slow rate of decrease, followed by a faster rate of decrease in the terminal phase.

Similar to the previously discussed regression functions, the bi-exponential regression function also reduces to the conventional linear regression function when $\theta_1 = \theta_2$ and $\lambda_1 = \lambda_2$.

Figure 2.8 shows an example of the expected log(CFU) count and its corresponding rate of decline from a bi-exponential regression function over time, i.e. plot of Equation (2.40) and Equation (2.41), of a patient from a 56-day "SSCC" study. For this example, the regression parameters $\theta_1 = 7$, $\lambda_1 = 0.4$, and $\theta_2 = 5$ are kept fixed, but showed for different values of λ_2, i.e. $\lambda_2 \in \{0.07, 0.06, 0.05, 0.03\}$.

Thus one has the following nonlinear regression model for $\log(y[t])$:

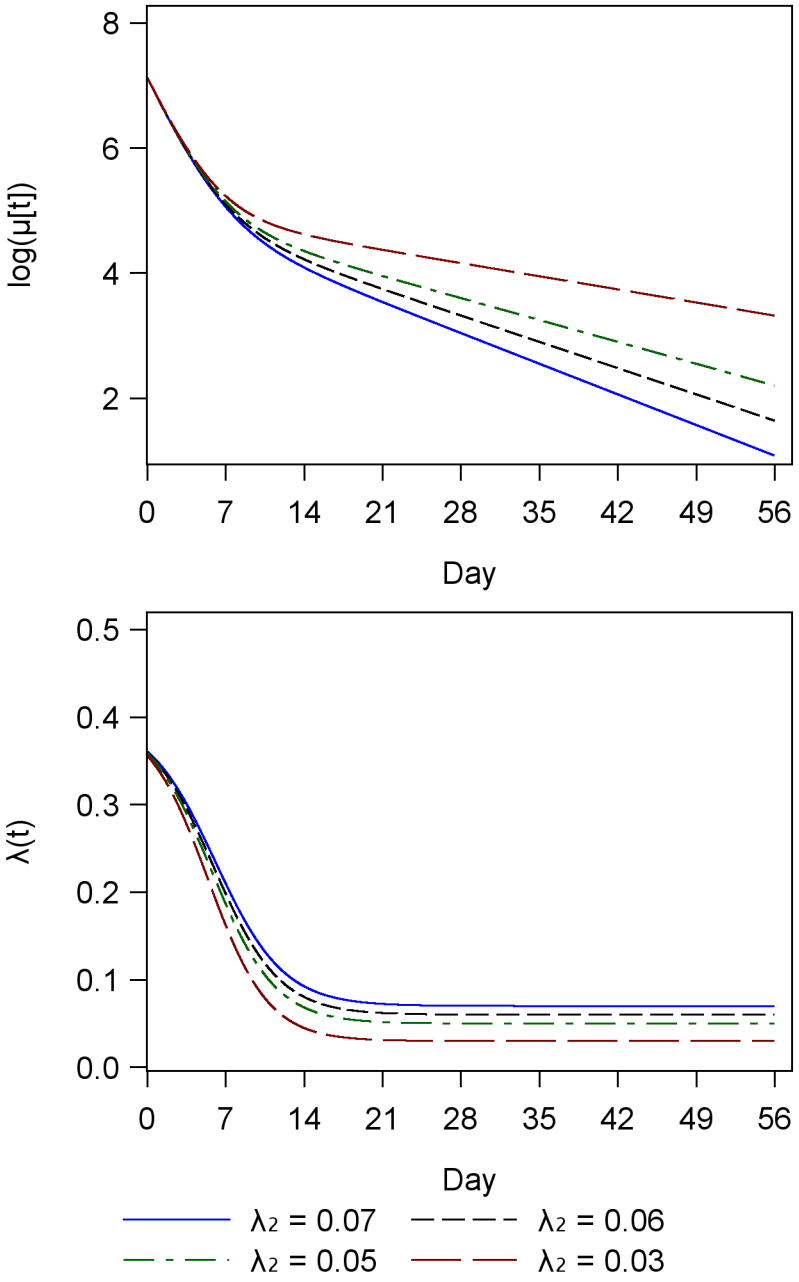
$$\log(y[t]) = \log\left(e^{\theta_1} \cdot e^{-\lambda_1\cdot t} + e^{\theta_2} \cdot e^{-\lambda_2\cdot t}\right) + \varepsilon(t) \tag{2.43}$$

where $\varepsilon(t)$ is an additive error term at time t.

In summary, the bi-exponential regression model in Equation (2.43) implies that $f(t, \boldsymbol{\phi})$ in Section 2.3 can be written as

$$f(t, \boldsymbol{\phi}) = \log\left(e^{\theta_1} \cdot e^{-\lambda_1\cdot t} + e^{\theta_2} \cdot e^{-\lambda_2\cdot t}\right)$$

Figure 2.8: Example Plot of Expected log(CFU) Count ($\log[\mu\{t\}]$) and Corresponding Rate of Change ($\lambda[t]$) Over Time from Bi-Exponential Regression Function



where $\boldsymbol{\phi} = (\theta_1, \lambda_1, \theta_2, \lambda_2)'$. This regression model is referred to as an NLME regression model when fitted to CFU data of all patients jointly.

Other "Bi-Linear" Regression Functions as Limiting Case

Regression functions made up of two intersecting line segments as a limiting case have been proposed by various authors. Among others, the following "bilinear" regression functions have been proposed:

A regression function adapted from that proposed by Ratkowsky (1983), which is a reparameterized version of the regression function suggested by Griffiths and Miller (1973):

$$\log(\mu[t]) = \theta_1 - \theta_2 \cdot (t - \theta_4) + \theta_3 \sqrt{(t - \theta_4)^2 + \theta_5^2} \tag{2.44}$$

where $\theta_1 + \theta_2 \cdot \theta_4 + \theta_3 \cdot \sqrt{\theta_4^2 + \theta_5^2}$ is the intercept and $\theta_2 - 2 \cdot \theta_3$ and $\theta_2 + 2 \cdot \theta_3$ the respective regression slopes (or parameters characterizing the rate of decline) of the regression function, and θ_4 is the node at which the slope transitions from one rate of decline to another. The parameter θ_5 governs the "speed" at which transition from one slope to another occurs.

The following regression function proposed by Bacon and Watts (1971) uses the hyperbolic tangent function as the transition function between line segments, and also results in a smooth "bilinear" regression function as a limiting case:

$$\log(\mu[t]) = \theta_1 - \theta_2 \cdot (t - \theta_4) + \theta_3 \cdot (t - \theta_4) \cdot \frac{e^{\frac{t-\theta_4}{\theta_5}} - e^{-\frac{t-\theta_4}{\theta_5}}}{e^{\frac{t-\theta_4}{\theta_5}} + e^{-\frac{t-\theta_4}{\theta_5}}} \tag{2.45}$$

where

$$\theta_1 + \theta_2 \cdot \theta_4 - \theta_3 \cdot \theta_4 \cdot \frac{e^{\frac{\theta_4}{\theta_5}} - e^{-\frac{\theta_4}{\theta_5}}}{e^{\frac{\theta_4}{\theta_5}} + e^{-\frac{\theta_4}{\theta_5}}}$$

is the intercept and $\theta_2 - \theta_3$ and $\theta_2 + \theta_3$ the respective regression slopes (or parameters characterizing the rate of decline) of the regression function, and θ_4 is

the node at witch the slope transitions from one rate of decline to another. The parameter θ_5 governs the "speed" at which transition from one slope to another occurs.

The regression function proposed by Grossman et al. (1999) was used to model the persistency in milk lactation, and is written as follows:

$$\log(\mu[t]) = \theta_1 - \theta_2 \cdot t - \theta_5 \cdot (\theta_3 - \theta_2) \cdot \log\left(\frac{e^{\frac{t}{\theta_5}} + e^{\frac{\theta_4}{\theta_5}}}{1 + e^{\frac{\theta_4}{\theta_5}}}\right) \tag{2.46}$$

where θ_1 is the intercept and θ_2 and θ_3 the respective regression slopes (or parameters characterizing the rate of decline) of the regression function, and θ_4 is the node at witch the slope transitions from one rate of decline to another. The parameter θ_5 governs the "speed" at which transition from one slope to another occurs.

One can therefore note that the regression functions in Equation (2.44), Equation (2.45) and Equation (2.46) are similar to the differential hyperbolic tangent regression function in Equation (2.38).

2.3.3 Summary

From the previous sections, the following regression functions have been suggested for $f(t, \boldsymbol{\phi})$ in Section 2.3:

- Linear regression function (Equation (2.27)).
- Conventional bilinear regression function (Equation (2.34)).
- Differential hyperbolic tangent regression function (Equation (2.38)).
- Bi-exponential regression function (Equation (2.40)).

Among the various suggested regression functions, the differential hyperbolic tangent regression function seems to be most flexible since this function:

- Reduces to the linear regression function when $\lambda_1 = \lambda_2$.
- Contains the smooth bilinear regression function as a special case ($\gamma \to 0$).
- Is more flexible than the conventional bi-exponential regression as the latter cannot produce regression curves where the initial rate of decrease is slower than the terminal rate.

Chapter 3

Statistical Methods: Colony Forming Unit Count

3.1 Introduction

This chapter presents statistical methods for the assessment of CFU data. Regression models presented in Section 2.3 can be fitted to CFU data either on a by-patient basis, or fitted to the data of all patients jointly as mixed effects regression models (see Section 2.2).

3.2 General Considerations

When fitting regression models to CFU data, the following three important aspects, namely the identification of censored data, handling of sparse data profiles of individual patients, and outliers in the data should be considered (Burger and Schall, 2014b):

- **Data or "analysis variable"**: Provided that two CFU plate counts, denoted by CFU_1 and CFU_2, are associated with a given sputum sample from two different plates, the CFU count is calculated as follows:

$$CFU = \frac{1}{2}(CFU_1 + CFU_2) \times 20 \times 10^{\text{dilution}} \tag{3.1}$$

  In the above formula, the factor "$20 \times 10^{\text{dilution}}$" compensates for the dilution of the specimens during the culture process, converting the result back to the actual CFU count per mL. Then $\log(CFU)$ is given by:

$$\log(CFU) = \log_{10}(CFU) \tag{3.2}$$

- **Censored data**: CFU counts of zero must be identified and confirmed to be "genuine", i.e. genuine zero counts must be distinguished from missing CFU values, or from contaminated or otherwise invalid data. Genuine zero counts are valid data and should preferably be included in the analysis as censored observations (see Section 2.2.2.2) (Rustomjee et al., 2008). Here, zero CFU counts will be specified as a left censored value of 1, i.e. $\log_{10}(CFU) < 1$. Rationale: The smallest possible CFU count above zero is 1 for the count from one of the two plates and zero for the count from the other plate, with zero dilution, leading to a calculated log(CFU) count of:

$$\log(CFU) = \log_{10}([\{0+1\}/2] \times 20 \times 10^0) = \log_{10}(10) = 1$$

  CFUs which are too numerous to count should be right censored at the corresponding ULOQ, e.g. $\log_{10}(CFU) > d$.

- **Sparse data**: When the data for a given patient is sparse, several problems might occur when fitting the regression model to the data of individual patients.
  - Over-fit of the regression model: It might be inappropriate to fit two slope parameters when there are only 4 or 5 data points.
  - Slope parameters cannot be identified: When data are available only either in the early part or in late part of the study period, it might not be possible to identify and estimate both slope parameters.

  - The node cannot be identified: If the data in the middle of the study period are missing, the node parameter cannot be identified (which can imply that the slope parameters cannot be identified).
  - Convergence problems when trying to fit the regression model.

- **Outliers**: Outliers in CFU count might be present in the data due to erroneous sampling or reporting of the data, or such values might be true observations, but of extreme nature. As suggested by Gillespie et al. (2002), when individual fitting of the regression function to log(CFU) count is of concern, it is important to exclude implausible data points, i.e. data points causing irregularities in the pattern of an individual patient's CFU count over time (i.e. those not adhering to an expected longitudinal biologic pattern). Such outliers may produce unreliable parameter estimates, which may subsequently jeopardize the validity of the statistical inference of EBA.

Statistical inferences based on regression modeling of CFU count over time need be robust to the aspects listed above.

3.3 By-Patient Fit of Regression Models

The analysis strategy for CFU count should preferably be pragmatic and robust. As is done in most TB trials (see Section 1.5), by-patient regression modeling is the relatively simple fit of appropriate regression models to the data of individual patients.

The regression models discussed in Section 2.3 can be fitted to CFU data on an individual (or "by-patient") basis:

$$\log(y[t]) = f(t, \boldsymbol{\phi}) + \varepsilon(t) \tag{3.3}$$

where $f(t, \boldsymbol{\phi})$ is the appropriate base function, and $\varepsilon(t) \sim N(0, \sigma_\varepsilon^2)$ is an additive error term at time t. (For a summary of various base functions, see Section 2.3.3.)

As previously noted in the literature review of Chapter 1, log(CFU) count is usually calculated using the logarithm to the base of 10 (see Section 1.5). The regression models in Section 2.3 could therefore be adjusted so that $\log_{10}(y) = \log(y)/\log(10)$. This leads to the re-specification of the regression models as follows:

$$\log_{10}(y[t]) = \frac{f(t, \boldsymbol{\phi}) + \varepsilon(t)}{\log(10)} \tag{3.4}$$

Such adjustment as in Equation (3.4) is not taken into account since the "log(10)" counterpart is absorbed into the model parameters and error terms (in effect, the regression model is merely multiplied by a constant term).

From the individual regression fits, the relevant model parameters, per patient, can be estimated, together with their SEs. Similarly, relevant patient-specific EBA values from these regression fits to the data of each patient can be calculated. Both the patient-specific model parameters, and the patient-specific EBA values can then be compared between treatment groups using standard techniques such as ANOVA or analysis of covariance (ANCOVA). The ANOVA or ANCOVA should preferably allow for different variances across treatment groups. In this way, treatments can be compared and the significance of between-treatment differences in EBA values can be assessed.

The nonlinear regression models can be fitted, for each patient separately, to the log(CFU) versus time data using the SAS® procedure NLMIXED (SAS Institute Inc., 2008) via ML estimation. Basic SAS® code for fitting the differential hyperbolic tangent regression model (Equation (2.39)) to the data of individual patients of a typical 14-day EBA study is presented in Section B.1 (Appendix B). When the data contain censored values, the database should include an indicator variable, called "censor" (say), which take on a value 0 for non-censored data and a value of 1 for censored data. The dependent variable, log(CFU) count contains the calculated log(CFU) count value for non-censored data, and the value log(CFU) = 1 for left censored data. When fitting the nonlinear regression model above, the node parameter κ needs to be restricted to a suitable time range, in order to avoid over-fit of the first few and last few observations. The appropriate time range to which the node parameter is restricted depends on the length and intensity of

sputum sampling, and might be informed by a-priori knowledge on when the node is expected to occur for a particular drug. For a 14-day data profile with daily sputum samples, the node might be restricted to the range $L_\kappa = 2$ to $U_\kappa = 11$ days. Another rationale behind the choice for $L_\kappa = 2$ is that isoniazid (contained in Rifafour) is expected to eradicate most of the TB bacteria within the first two or three days of treatment (Gumbo et al., 2007) (hence the node of transition between the respective rates of decline is restricted to be on or after Day 2). The "smoothness" parameter γ is restricted to the range $L_\gamma = 0.1$ to $U_\gamma = 2$, in order to allow for smooth transition between a few successive data points. The SAS® code includes example statements for the calculation of ML estimates of $\text{EBA}(t_1 - t_2)$, and in accordance with Equation (1.2), are calculated by to the following formula:

$$\text{EBA}(t_1 - t_2) = \hat{\beta}_1 + \hat{\beta}_2 \cdot \hat{\gamma} \cdot \log \left(\frac{e^{\frac{t_2 - \hat{\kappa}}{\hat{\gamma}}} + e^{-\frac{t_2 - \hat{\kappa}}{\hat{\gamma}}}}{e^{\frac{t_1 - \hat{\kappa}}{\hat{\gamma}}} + e^{-\frac{t_1 - \hat{\kappa}}{\hat{\gamma}}}} \right)^{(t_2 - t_1)} \tag{3.5}$$

where $\hat{\beta}_1$. $\hat{\beta}_2$, $\hat{\kappa}$ and $\hat{\gamma}$ represent the ML estimates of β_1, β_2, κ and γ, respectively.

Patients with sparse data, or outliers in log(CFU) count (see Section 3.2), might have to be excluded in the case when regression models are fitted to data on a by-patient basis.

3.4 Bayesian Mixed Effects Regression Models

This section proposes (hierarchical) Bayesian mixed effects regression models for log(CFU) versus time, fitted jointly to the data of all patients from a given trial. The Bayesian implementation of the general mixed effects regression model in Section 2.2, based on each of the regression functions outlined in Section 2.3, is discussed here in detail. Table 3.1 provides a summary of the mixed effects regression models for log(CFU) count that are discussed in the subsections below. The models with normally distributed residuals and random coefficients are considered primary, whereas the remainder models are regarded as sensitivity analyses.

Table 3.1: Bayesian Mixed Effects Regression Models for log(CFU) Counts

			Bayesian Specification			
			Distributions			
Regression Function	**No.**	**Implementation**	**Residuals**	**Random Coefficients**	**Prior for Covariance Matrix**	**Page**
Differential hyperbolic tangent	1.1	Primary	Normal	Normal	"Default"	Page 77
	1.2	Sensitivity	Normal	Normal, fixed smoothness	"Default"	Page 90
	1.3	Sensitivity	Normal	Normal	"Frequentist"	Page 91
	1.4	Sensitivity	Skew normal	Normal	"Default"	Page 92
	1.5	Sensitivity	Student t	Normal	"Default"	Page 95
	1.6	Sensitivity	Student t	Normal	"Frequentist"	Page 96
	1.7	Sensitivity	Student t	Student t	"Default"	Page 97
	1.8	Sensitivity	Student t	Skew normal	"Default"	Page 98
	1.9	Sensitivity	Skew Student t	Normal	"Default	Page 101
Linear	2.1	Primary	Normal	Normal	"Default"	Page 103
	2.2	Sensitivity	Student t	Normal	"Default"	Page 104
Conventional bilinear	3.1	Primary	Normal	Normal	"Default"	Page 104
	3.2	Sensitivity	Student t	Normal	"Default"	Page 105
Bi-Exponential	4.1	Primary	Normal	Normal	"Frequentist"	Page 106
	4.2	Sensitivity	Student t	Normal	"Frequentist"	Page 107

Note: Covariance matrix (applicable to random coefficients): Choice of R_j for the Wishart distribution.

3.4.1 Differential Hyperbolic Tangent Regression Model

The subsections below provide full specifications, including random effects and prior distributions, of the primary Bayesian differential hyperbolic tangent NLME regression model: That is, the mixed effects regression model for which the underlying regression function is the differential hyperbolic tangent regression function (Equation (2.38)).

Section 3.4.1.7 provides detail on alternative Bayesian specifications of the primary model (Model 1.1) with the aim of assessing the sensitivity of results to alternative specifications.

3.4.1.1 Model Specification

Model 1.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Based on Equation (2.38), one can postulate the following NLME regression model:

$$\log(y_{ijk}) = \alpha_{ij} - \beta_{1ij} \cdot t_{ijk} - \beta_{2ij} \cdot \gamma_{ij} \cdot \log\left(\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right) + \varepsilon_{ijk} \quad (3.6)$$

where $\log(y_{ijk})$ represents the log(CFU) count for patient $i = 1, \ldots, N_j$ in treatment group $j = 1, \ldots, J$ at timepoint $k = 1, \ldots, K_{ij}$, and $t_{ijk} \geq 0$ is the corresponding measurement time. Here, N_j denotes the number of patients in treatment group j, and T_j the total number of timepoints across all patients in treatment group j. Let $\sum_{j=1}^{J} N_j = N$ represent the total number of patients in a given trial (see Section 2.2.2.1).

The parameters of the regression model in Equation (3.6) are analogous to those of the "by-patient" regression model in Equation (2.39).

3.4.1.2 Random Effects

The residuals ε_{ijk} are assumed to follow *i.i.d.* normal distributions (see Section 2.2.2.1), independent of α_{ij}, β_{1ij}, β_{2ij}, κ_{ij} and γ_{ij}, as follows:

$$\varepsilon_{ijk}|\sigma^2_{\varepsilon_j} \sim N(0, \sigma^2_{\varepsilon_j}) \tag{3.7}$$

where $\sigma^2_{\varepsilon_j}$ are the corresponding residual variances.

Censoring of log(CFU) count with the Bayesian NLME regression model is analogous to that of "by-patient" regression modeling (see Equation (2.10)).

The terms α_{ij}, β_{1ij}, β_{2ij}, κ_{ij} and γ_{ij} in the regression model presented in Equation (3.6) are the sums of the fixed effects and associated random coefficients, namely:

$$\boldsymbol{\mu_{ij}} = \begin{bmatrix} \alpha_{ij} \\ \beta_{1ij} \\ \beta_{2ij} \end{bmatrix} = \begin{bmatrix} \alpha_j \\ \beta_{1j} \\ \beta_{2j} \end{bmatrix} + \begin{bmatrix} u_{0ij} \\ u_{1ij} \\ u_{2ij} \end{bmatrix}$$

and

$$\begin{bmatrix} \kappa_{ij} \\ \gamma_{ij} \end{bmatrix} = \begin{bmatrix} \kappa_j \\ \gamma_j \end{bmatrix} + \begin{bmatrix} u_{3ij} \\ u_{4ij} \end{bmatrix}$$

where $\boldsymbol{\mu_{ij}} = (\alpha_{ij}, \beta_{1ij}, \beta_{2ij})'$ (or $[u_{0ij}, u_{1ij}, u_{2ij}]'$) and $\boldsymbol{\mu_j} = (\alpha_j, \beta_{1j}, \beta_{2j})'$ are respectively the vectors of random and mean intercepts and slopes, and respectively, $(\kappa_{ij}, \gamma_{ij})'$ (or $[u_{3ij}, u_{4ij}]'$) and $(\kappa_j, \gamma_j)'$ are the vectors of random and mean nodes and smoothness parameters.

For the uncensored case, the likelihood for $\boldsymbol{\mu_{ij}}$, κ_{ij}, γ_{ij} and $\sigma^2_{\varepsilon j}$ is written as:

$$L\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \sigma^2_{\varepsilon j}, k = 1, \ldots, K_{ij} | \boldsymbol{y_{ij}}\right) \propto \left(\prod_{k=1}^{K_{ij}} \left(\sigma^2_{\varepsilon_j}\right)^{-\frac{1}{2}}\right) \cdot \exp\left(-\frac{1}{2}\sum_{k=1}^{K_{ij}} A_{ijk}\right) \tag{3.8}$$

where $\boldsymbol{y_{ij}}$ denote $K_{ij} \times 1$ vectors containing $\left(\log[y_{ij1}], \log[y_{ij2}], \ldots, \log[y_{ijK_{ij}}]\right)'$. The quantities A_{ijk} are defined as follows:

$$\mathrm{A}_{ijk} = \left(\frac{\log(y_{ijk}) - \left(\alpha_{ij} - \beta_{1ij} \cdot t_{ijk} - \beta_{2ij} \cdot \gamma_{ij} \cdot \log \left[\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}} \right] \right)}{\sigma_{\varepsilon_j}} \right)^2 \tag{3.9}$$

In Equation (3.6), the random vectors $\boldsymbol{\mu_{ij}}$ are assumed independent across patients (i.e. independent across indices i and j), with tri-variate normal distributions as:

$$\boldsymbol{\mu_{ij}} | \boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j} \sim N_3(\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}) \tag{3.10}$$

$\Omega_{\boldsymbol{\mu}j}$ are the associated covariance matrices, namely:

$$\Omega_{\boldsymbol{\mu}j} = \begin{bmatrix} \sigma^2_{\alpha_j} & \sigma_{\alpha_j\beta_{1j}} & \sigma_{\alpha_j\beta_{2j}} \\ \sigma_{\alpha_j\beta_{1j}} & \sigma^2_{\beta_{1j}} & \sigma_{\beta_{1j}\beta_{2j}} \\ \sigma_{\alpha_j\beta_{2j}} & \sigma_{\beta_{1j}\beta_{2j}} & \sigma^2_{\beta_{2j}} \end{bmatrix}$$

where $\sigma^2_{\alpha_j} = \mathrm{Var}_j(\alpha_{ij})$, $\sigma^2_{\beta_{1j}} = \mathrm{Var}_j(\beta_{1ij})$, $\sigma^2_{\beta_{2j}} = \mathrm{Var}_j(\beta_{2ij})$, $\sigma_{\alpha_j\beta_{1j}} = \mathrm{Cov}_j(\alpha_{ij}, \beta_{1ij})$, $\sigma_{\alpha_j\beta_{2j}} = \mathrm{Cov}_j(\alpha_{ij}, \beta_{2ij})$ and $\sigma_{\beta_{1j}\beta_{2j}} = \mathrm{Cov}_j(\beta_{1ij}, \beta_{2ij})$.

The density function of $\boldsymbol{\mu_{ij}} | \boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}$ is written as:

$$P\left(\boldsymbol{\mu_{ij}} | \boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}\right) \propto |\Omega_{\boldsymbol{\mu}j}|^{-\frac{1}{2}} \cdot \exp\left(-\frac{1}{2} \left(\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}\right)' \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \left(\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}\right) \right) \tag{3.11}$$

Furthermore, the parameters κ_{ij} and γ_{ij} are assumed to follow *i.i.d.* truncated normal distributions, independent of $\boldsymbol{\mu_{ij}}$, as:

$$\kappa_{ij} | \kappa_j, \sigma^2_{\kappa_j} \sim TN(\kappa_j, \sigma^2_{\kappa_j}) \cdot I(L_\kappa \leq \kappa_{ij} \leq U_\kappa) \tag{3.12}$$

$$\gamma_{ij} | \gamma_j, \sigma^2_{\gamma_j} \sim TN(\gamma_j, \sigma^2_{\gamma_j}) \cdot I(L_\gamma \leq \gamma_{ij} \leq U_\gamma) \tag{3.13}$$

In Equation (3.12) and Equation (3.13), $I(x)$ denotes an indicator function taking the value 1 if x is true, and 0 otherwise, and L_κ, U_κ, L_γ and U_γ are pre-specified lower bound and upper bound for the parameters κ_{ij} and γ_{ij}, respectively.

The density functions of $\kappa_{ij}|\kappa_j, \sigma^2_{\kappa_j}$ and $\gamma_{ij}|\gamma_j, \sigma^2_{\gamma_j}$ are written as:

$$P\left(\kappa_{ij}|\kappa_j, \sigma^2_{\kappa_j}\right) \propto \frac{\left(\sigma^2_{\kappa_j}\right)^{-\frac{1}{2}} \cdot I(L_\kappa \leq \kappa_{ij} \leq U_\kappa)}{F_N\left(\frac{U_\kappa - \kappa_j}{\sigma_{\kappa_j}}\right) - F_N\left(\frac{L_\kappa - \kappa_j}{\sigma_{\kappa_j}}\right)} \cdot \exp\left(-\frac{1}{2}\left[\frac{\kappa_{ij} - \kappa_j}{\sigma_{\kappa_j}}\right]^2\right) \tag{3.14}$$

$$P\left(\gamma_{ij}|\gamma_j, \sigma^2_{\gamma_j}\right) \propto \frac{\left(\sigma^2_{\gamma_j}\right)^{-\frac{1}{2}} \cdot I(L_\gamma \leq \gamma_{ij} \leq U_\gamma)}{F_N\left(\frac{U_\gamma - \gamma_j}{\sigma_{\gamma_j}}\right) - F_N\left(\frac{L_\gamma - \gamma_j}{\sigma_{\gamma_j}}\right)} \cdot \exp\left(-\frac{1}{2}\left[\frac{\gamma_{ij} - \gamma_j}{\sigma_{\gamma_j}}\right]^2\right) \tag{3.15}$$

3.4.1.3 Prior Distributions

In order to complete the Bayesian specification of the model in Equation (3.6), proper prior distributions are assigned to all unknown parameters. The values of the hyper parameters are chosen in such a way to assure vagueness with regard to prior belief on the parameters.

Prior Distributions for $\boldsymbol{\mu_j}$ and $\boldsymbol{\Omega_{\mu j}}$

Firstly, tri-variate normal and Wishart prior distributions are specified, respectively, for $\boldsymbol{\mu_j}$ and $\Omega^{-1}_{\boldsymbol{\mu j}}$, namely:

$$\boldsymbol{\mu_j} \sim N_3(\mathbf{0}, 10^4 \times I_3) \tag{3.16}$$

$$\Omega^{-1}_{\boldsymbol{\mu j}} \sim W_3(3, 3 \times R_j) \tag{3.17}$$

where $\mathbf{0} = (0, 0, 0)'$ and I_3 denotes a 3×3 identity matrix. The R_j represent 3×3 inverse scale matrices from the corresponding Wishart distribution.

The density functions of $\boldsymbol{\mu_j}$ and $\Omega^{-1}_{\boldsymbol{\mu j}}$ are written as:

$$P\left(\boldsymbol{\mu_j}\right) \propto \exp\left(-\frac{1}{2}\boldsymbol{\mu_j}' \cdot \frac{1}{10^4} \cdot \boldsymbol{\mu_j}\right) \tag{3.18}$$

$$P\left(\Omega^{-1}_{\boldsymbol{\mu j}}\right) \propto |\Omega^{-1}_{\boldsymbol{\mu j}}|^{-\frac{1}{2}} \cdot \text{etr}\left(-\frac{3}{2} \cdot R_j \cdot \Omega^{-1}_{\boldsymbol{\mu j}}\right) \tag{3.19}$$

Choice of $\boldsymbol{R_j}$

The choice of an appropriate prior distribution for the covariance matrix of the vectors of random intercepts and slopes $\boldsymbol{\mu_{ij}}$, i.e. $\Omega_{\boldsymbol{\mu j}}$ is challenging. In the application of mixed effects regression models for CFU data, the true variability between (random) slopes can be quite small (close to zero). It is known that inferences for close-to-zero variance components can be sensitive to the specification of "too" vague prior distributions (Gelman, 2006). That is, inferences may be sensitive to large values of R_j. Such prior misspecification can produce variance component estimates that are biased upwards, and as a result, cause the coverage of the 95% BCIs of the corresponding fixed effects to be too high ($> 95\%$) (Lambert et al., 2005).

The methodology by Kass and Natarajan (2006), here referred to as the "default" Wishart prior, for choosing R_j, is adapted for the primary model. This methodology relates to the choice of R_j in the application of generalized linear mixed effects regression, and is derived from the data directly (hence, the resulting posterior distribution does make double use of the data). The inverse scale matrix R_j is derived by selecting the weight which the mean of the "shrinkage" prior, i.e. $\mathbf{0}$, should contribute towards its posterior (where "shrinkage" represents $\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}$). Under the assumption that the node and smoothness parameters are fixed at $\kappa_p = (U_\kappa + L_\kappa)/2$ and $\gamma_p = (U_\gamma + L_\gamma)/2$, respectively (which are the prior mean for κ_j and γ_j, respectively (see below)), the regression model (Equation (3.6)) reduces

to a linear mixed effects regression model, for which R_j are derived as follows:

$$R_j = c \cdot \left(\frac{1}{N_j \cdot \tilde{\sigma}^2_{\varepsilon j}} \sum_{i=1}^{N_j} Z'_{ij} \cdot Z_{ij} \right)^{-1} \tag{3.20}$$

where $\tilde{\sigma}^2_{\varepsilon j}$ are the ML estimates of $\sigma^2_{\varepsilon_j}$ when assuming the regression model is homogeneous across all patients, i.e. disregarding random effects such that $\alpha_{ij} = \alpha_j$ (or $u_{0ij} = 0$), $\beta_{1ij} = \beta_{1j}$ (or $u_{1ij} = 0$) and $\beta_{2ij} = \beta_{2j}$ (or $u_{2ij} = 0$). The matrices Z_{ij} are defined as follows:

$$Z_{ij} = \begin{bmatrix} 1 & -t_{ij1} & -\gamma_p \cdot \ln\left(\frac{e^{\frac{t_{ij1}-\kappa_p}{\gamma_p}} + e^{-\frac{t_{ij1}-\kappa_p}{\gamma_p}}}{e^{\frac{\kappa_p}{\gamma_p}} + e^{-\frac{\kappa_p}{\gamma_p}}} \right) \\ \vdots & \vdots & \vdots \\ 1 & -t_{ijk} & -\gamma_p \cdot \ln\left(\frac{e^{\frac{t_{ijk}-\kappa_p}{\gamma_p}} + e^{-\frac{t_{ijk}-\kappa_p}{\gamma_p}}}{e^{\frac{\kappa_p}{\gamma_p}} + e^{-\frac{\kappa_p}{\gamma_p}}} \right) \\ \vdots & \vdots & \vdots \\ 1 & -t_{ijK_{ij}} & -\gamma_p \cdot \ln\left(\frac{e^{\frac{t_{ijK_{ij}}-\kappa_p}{\gamma_p}} + e^{-\frac{t_{ijK_{ij}}-\kappa_p}{\gamma_p}}}{e^{\frac{\kappa_p}{\gamma_p}} + e^{-\frac{\kappa_p}{\gamma_p}}} \right) \end{bmatrix}$$

For the "default" Wishart prior, $c = 2.5$ is used which causes the mean of the 'shrinkage" prior, i.e. $\mathbf{0}$, to have little contribution towards its posterior. The choice of $c = 2.5$ is equivalent to setting the interval between the lowest and highest possible values for the relative contribution matrix of the mean of the "shrinkage" prior (to its posterior) to 28.6%. The methodology of Kass and Natarajan (2006) relates to conventional linear mixed effects regression modeling, and does not take censoring of log(CFU) count into account. With the calculation of "default" Wishart priors throughout this thesis, "zero" CFU counts were imputed with 0.01, or equivalently, $\log_{10}(\text{CFU}) = -2$ (hence assuming near complete eradication of TB mycobacteria).

Section B.2.1 (Appendix B) provides SAS® example code for determining R_j.

Prior Distributions for κ_j, γ_j, $\sigma^2_{\kappa j}$ and $\sigma^2_{\gamma j}$

The parameters κ_j, γ_j, $\sigma^2_{\kappa j}$ and $\sigma^2_{\gamma j}$ are assumed to follow uniform prior distributions, namely:

$$\kappa_j \sim U(L_\kappa, U_\kappa) \tag{3.21}$$

$$\gamma_j \sim U(L_\gamma, U_\gamma) \tag{3.22}$$

$$\sigma^2_{\kappa j} \sim U(L_{\sigma^2_{\kappa_j}}, U_{\sigma^2_{\kappa_j}}) \tag{3.23}$$

$$\sigma^2_{\gamma j} \sim U(L_{\sigma^2_{\gamma_j}}, U_{\sigma^2_{\gamma_j}}), \tag{3.24}$$

where $L_{\sigma^2_\kappa}$, $U_{\sigma^2_\kappa}$, $L_{\sigma^2_\gamma}$, $U_{\sigma^2_\gamma}$ are the pre-specified lower bound and upper bound for parameters $\sigma^2_{\kappa j}$ and $\sigma^2_{\gamma j}$, respectively.

The density functions of κ_j, γ_j, $\sigma^2_{\kappa_j}$ and $\sigma^2_{\gamma_j}$ are written as:

$$P(\kappa_j) \propto I(L_\kappa \leq \kappa_j \leq U_\kappa) \tag{3.25}$$

$$P(\gamma_j) \propto I(L_\gamma \leq \gamma_j \leq U_\gamma) \tag{3.26}$$

$$P\left(\sigma^2_{\kappa_j}\right) \propto I(L_{\sigma^2_\kappa} \leq \sigma^2_{\kappa_j} \leq U_{\sigma^2_\kappa}) \tag{3.27}$$

$$P\left(\sigma^2_{\gamma_j}\right) \propto I(L_{\sigma^2_\gamma} \leq \sigma^2_{\gamma_j} \leq U_{\sigma^2_\gamma}) \tag{3.28}$$

Prior Distributions for $\sigma^2_{\varepsilon j}$

Finally, the variances $\sigma^{-2}_{\varepsilon_j}$ are assumed to follow gamma distributions:

$$\sigma^{-2}_{\varepsilon_j} \sim G(10^{-4}, 10^{-4}) \tag{3.29}$$

The gamma distribution in Equation (3.29) provides an approximately uniform distribution over the applicable parameter space, but with higher density mass for values closer to zero (Lambert et al., 2005).

The density function of $\sigma_{\varepsilon j}^{-2}$ is written as:

$$P\left(\sigma_{\varepsilon j}^{-2}\right) \propto \left(\sigma_{\varepsilon j}^{-2}\right)^{\left(10^{-4}-1\right)} \cdot \exp\left(-10^{-4} \cdot \sigma_{\varepsilon j}^{-2}\right) \tag{3.30}$$

Hyper Parameters

For a typical 14-day EBA study, the hyper parameters of the distributions can be chosen as follows: $L_\kappa = 2$, $U_\kappa = 11$ (to avoid over-fit of the first few and last few observations over time), $L_\gamma = 0.1$, $U_\gamma = 2$ (allowing for smooth transition between a few successive data points), $L_{\sigma_\kappa^2} = 0.01$, $U_{\sigma_\kappa^2} = 30$, $L_{\sigma_\gamma^2} = 0.01$ and $U_{\sigma_\gamma^2} = 5$ (providing weakly informative prior distributions for the scale parameters $\sigma_{\kappa_j}^2$ and $\sigma_{\gamma_j}^2$).

For a typical 8-week "SSCC" study, the regression model should preferably be fitted with the times t_{ijk} expressed in weeks for the prevention of numerical overflow. Accordingly, L_κ, U_κ, $L_{\sigma_\kappa^2}$ and $U_{\sigma_\kappa^2}$ should also be expressed in weeks.

3.4.1.4 Conditional and Joint Posterior Distributions

Software

The OpenBUGS software can be used to implement the MCMC Gibbs sampling algorithm to draw samples from the joint posterior distribution of the model parameters (Gelfand and Smith, 1990; Gilks et al., 1996; Lunn et al., 2009). OpenBUGS can be downloaded for free from URL `http://www.openbugs.net/w/Downloads`.

The OpenBUGS software can be called remotely from SAS®, and accordingly, posterior MCMC samples can be exported back to SAS® for further computation.

Page 262 of Section B.3.1 (Appendix B) provides OpenBUGS example code for the implementation of the primary model (Model 1.1) for a typical 14-day EBA study.

Posterior Distributions

The resulting joint posterior distribution of all quantities of the preceding regression model is obtained by forming the product of all likelihoods and prior distributions, and is provided in Appendix A for cases where all log(CFU) counts are treated as uncensored. The MCMC Gibbs sampling algorithm discussed in Section 2.2.3 can be used to draw samples from the joint posterior distribution of the model parameters. The conditional posterior distributions of the model parameters are derived from the joint posterior distribution by ignoring terms that do not include the relevant model parameter. The derivations for the latter are provided in Appendix A.

Due to the high dimensional nature of NLME regression models, by-patient parameter estimates, obtained from regression fits (see Section 3.3) for each patient individually (using SAS® procedure NLMIXED), should ideally be used as starting values for the random effects. The posterior samples could be thinned to reduce the autocorrelation among posterior samples (Ntzoufras, 2009). Graphical convergence diagnostics, such as iteration and autocorrelation plots (Ntzoufras, 2009), and the Brooks-Gelman-Rubin statistic (Brooks and Gelman, 1998) for two parallel MCMC chains, could be used to monitor convergence of posterior samples. Dispersed starting values for the second MCMC chain should preferably be provided to ensure convergence of the two respective MCMC chains (Ntzoufras, 2009).

Bactericidal Activity

Posterior distributions for quantities $\lambda_{1j} = \beta_{1j} - \beta_{2j}$, $\lambda_{2j} = \beta_{1j} + \beta_{2j}$, $\sigma^2_{\lambda_{1j}} = \sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} - 2 \cdot \sigma_{\beta_{1j}\beta_{2j}}$, $\sigma^2_{\lambda_{2j}} = \sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} + 2 \cdot \sigma_{\beta_{1j}\beta_{2j}}$ can be obtained using the posterior MCMC output of the Gibbs sampling algorithm of the joint posterior distribution of the regression model parameters.

Similarly, the mean EBA$(t_1 - t_2)$ for treatment group j, i.e. EBA$_j(t_1 - t_2)$, can be obtained as:

$$\text{EBA}_j(t_1 - t_2) = \beta_{1j} + \beta_{2j} \cdot \gamma_j \cdot \log \left(\frac{e^{\frac{t_2 - \kappa_j}{\gamma_j}} + e^{-\frac{t_2 - \kappa_j}{\gamma_j}}}{e^{\frac{t_1 - \kappa_j}{\gamma_j}} + e^{-\frac{t_1 - \kappa_j}{\gamma_j}}} \right)^{t_2 - t_1} \tag{3.31}$$

The between-treatment differences in EBA values can similarly be calculated: That is, EBA$_j(t_1 - t_2) -$ EBA$_{j'}(t_1 - t_2)$. Here, the EBA values come from different treatment groups (i.e. $j \neq j^{'}$).

Posterior distributions for EBA$_{ij}(t_1 - t_2)$, i.e. EBA quantities for patient i in treatment group j, can be obtained similarly.

Mean Profiles Over Time

The posterior distribution for the mean log(CFU) count for treatment group j at timepoint k and corresponding measurement time t_k can similarly be obtained as:

$$\alpha_j - \beta_{1j} \cdot t_k - \beta_{2j} \cdot \gamma_j \cdot \log \left(\frac{e^{\frac{t_k - \kappa_j}{\gamma_j}} + e^{-\frac{t_k - \kappa_j}{\gamma_j}}}{e^{\frac{\kappa_j}{\gamma_j}} + e^{-\frac{\kappa_j}{\gamma_j}}} \right) \tag{3.32}$$

Mean Percentage Reduction

The time at which the percentage change from baseline in mean log(CFU) count for treatment group j reaches 50% can be calculated as the quantity v_{50j} which satisfies the following equation:

$$\frac{1}{\alpha_j} \cdot \left(\beta_{1j} \cdot v_{50j} + \beta_{2j} \cdot \gamma_j \cdot \log \left[\frac{e^{\frac{v_{50j} - \kappa_j}{\gamma_j}} + e^{-\frac{v_{50j} - \kappa_j}{\gamma_j}}}{e^{\frac{\kappa_j}{\gamma_j}} + e^{-\frac{\kappa_j}{\gamma_j}}} \right] \right) = 0.5 \tag{3.33}$$

In Equation (3.33), v_{50j} can be sampled directly from the posterior MCMC samples, provided that the regression function for treatment group j is decreasing monotonically over time. That is, in order for the posterior distribution of v_{50j} to

exist, the posterior distribution of λ_{1j} and λ_{2j} should completely lie above zero (i.e. in order for v_{50j} to exist, a treatment regimen should be associated with strong bactericidal activity and the study should provide the statistical power to detect such significant slopes).

Correlation Coefficients

It might be of scientific interest to establish whether patients with higher bacterial load at Day 0 (i.e. α_{ij}) are associated with higher initial and terminal rates of decline in log(CFU) count (i.e. λ_{1ij} and λ_{2ij}, respectively) and similarly, to establish whether higher rates of decline during the initial phase (i.e. λ_{1ij}) are associated with higher terminal rates of decline (i.e. λ_{2ij}), or *vice versa*. That is, posterior samples of correlation coefficients between random effects, i.e. $\rho_{\alpha_j\lambda_{1j}}$, $\rho_{\alpha_j\lambda_{2j}}$ and $\rho_{\lambda_{1j}\lambda_{2j}}$, can be obtained, e.g.:

$$\rho_{\alpha_j\lambda_{1j}} = \frac{\mathrm{Cov}_j\left(\alpha_{ij}, \lambda_{1ij}\right)}{\sqrt{\mathrm{Var}_j\left(\alpha_{ij}\right) \cdot \mathrm{Var}_j\left(\lambda_{1ij}\right)}} = \frac{\sigma_{\alpha_j\beta_{1j}} - \sigma_{\alpha_j\beta_{2j}}}{\sqrt{\sigma^2_{\alpha_j} \cdot \left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} - 2 \cdot \sigma_{\beta_{1j}\beta_{2j}}\right)}} \tag{3.34}$$

$$\rho_{\alpha_j\lambda_{2j}} = \frac{\mathrm{Cov}_j\left(\alpha_{ij}, \lambda_{2ij}\right)}{\sqrt{\mathrm{Var}_j\left(\alpha_{ij}\right) \cdot \mathrm{Var}_j\left(\lambda_{2ij}\right)}} = \frac{\sigma_{\alpha_j\beta_{1j}} + \sigma_{\alpha_j\beta_{2j}}}{\sqrt{\sigma^2_{\alpha_j} \cdot \left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} + 2 \cdot \sigma_{\beta_{1j}\beta_{2j}}\right)}} \tag{3.35}$$

$$\begin{aligned}\rho_{\lambda_{1j}\lambda_{2j}} &= \frac{\mathrm{Cov}_j\left(\lambda_{1ij}, \lambda_{2ij}\right)}{\sqrt{\mathrm{Var}_j\left(\lambda_{1ij}\right) \cdot \mathrm{Var}_j\left(\lambda_{2ij}\right)}} \\ &= \frac{\sigma^2_{\beta_{1j}} - \sigma^2_{\beta_{2j}}}{\sqrt{\left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} - 2 \cdot \sigma_{\beta_{1j}\beta_{2j}}\right) \cdot \left(\sigma^2_{\beta_{1j}} + \sigma^2_{\beta_{2j}} + 2 \cdot \sigma_{\beta_{1j}\beta_{2j}}\right)}}\end{aligned} \tag{3.36}$$

3.4.1.5 Posterior Predictive Distributions

A basic question of interest about the nature of the regression of log(CFU) count against time associated with a certain treatment is whether or not the decline in log(CFU) count is simply linear, or bilinear (more generally, biphasic).

In terms of Equation (2.38) the question about the biphasic nature of the regression can be answered by statistical inference on the parameter β_2. Specifically, if $\beta_2 = 0$,

then Equation (2.38) reduces to a simple linear model; if $\beta_2 > 0$, then the regression model is biphasic where the terminal rate of decline is larger than the initial rate; if $\beta_2 < 0$, then the regression model is biphasic where the terminal rate of decline is smaller than the initial rate. In the most simple approach, a statistically significant slope β_2 could be interpreted as evidence for the fact that the decline of log(CFU) count is "bilinear" or "biphasic". However, estimates of the parameter β_2 may exhibit substantial individual variation across patients, even for patients receiving the same treatment. Thus, for a certain treatment, the nature of the regression of log(CFU) count against time is characterized not only by the mean slope β_2 for the treatment, but also by its variability across different patients within the treatment group. More generally, the nature of the regression of log(CFU) count against time is characterized by the *distribution* of the slope β_2 among patients receiving a certain treatment. It seems, therefore, that mixed effects regression models are best suited to investigate the question about the nature of the decline in log(CFU) count (mono- versus biphasic).

In particular, the posterior predictive distribution of relevant intercepts and slopes of the Bayesian NLME regression model can provide insight into the nature of the EBA of TB treatments; specifically, the posterior predictive distributions of β_{2j} allow one to judge whether treatments are associated with mono-linear or biphasic decline of log(CFU) count (depending on whether a future β_{2j} is likely to be close to or substantially different from zero), and whether log(CFU) count initially decreases fast, followed by a slower rate of decrease (if a future β_{2j} is likely to be negative, i.e. $\beta_{2j} < 0$), or *vice versa* (if a future β_{2j} is likely to be positive, i.e. $\beta_{2j} > 0$).

The quantity $\boldsymbol{\mu_{fj}}$, where the subscript f stands for "future patient", is defined as:

$$\boldsymbol{\mu_{fj}} = \begin{bmatrix} \alpha_{fj} \\ \beta_{1fj} \\ \beta_{2fj} \end{bmatrix} = \begin{bmatrix} \alpha_j \\ \beta_{1j} \\ \beta_{2j} \end{bmatrix} + \begin{bmatrix} u_{0fj} \\ u_{1fj} \\ u_{2fj} \end{bmatrix} = \boldsymbol{\mu_j} + \begin{bmatrix} u_{0fj} \\ u_{1fj} \\ u_{2fj} \end{bmatrix}$$

By specification of the regression model, the distribution of $\boldsymbol{\mu_{fj}}$, conditional on $\boldsymbol{\mu_j}$ and $\Omega_{\boldsymbol{\mu}j}$, is tri-variate normal $\boldsymbol{\mu_{fj}}|\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j} \sim N_3(\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j})$ with probability density

function $\phi\left(\boldsymbol{\mu_{fj}} \mid \boldsymbol{\mu_j}, \Omega_{\mu j}\right)$. Thus the probability density function of the posterior predictive distribution of $\boldsymbol{\mu_{fj}}|\boldsymbol{y}$ is given by:

$$f\left(\boldsymbol{\mu_{fj}}|\boldsymbol{y}\right) = \mathrm{d}\phi\left(\boldsymbol{\mu_{fj}} \mid \boldsymbol{\mu_j}, \Omega_{\mu j}\right) p\left(\boldsymbol{\mu_j}, \Omega_{\mu j}|\boldsymbol{y}\right)\ d\left(\boldsymbol{\mu_j}, \Omega_{\mu j}\right)$$

where $p\left(\boldsymbol{\mu_j}, \Omega_{\mu j}|\boldsymbol{y}\right)$ is the joint posterior distribution of $\boldsymbol{\mu_j}$ and $\Omega_{\mu j}$. Therefore, the posterior predictive distribution of $\boldsymbol{\mu_{fj}}$ can be simulated as follows:

1. Draw a random copy $\left(\boldsymbol{\mu_j^*}, \Omega_{\boldsymbol{\mu j}}^*\right)$ of $\left(\boldsymbol{\mu_j}, \Omega_{\mu j}\right)$ from the joint posterior distribution of $\left(\boldsymbol{\mu_j}, \Omega_{\mu j}\right)$.
2. Draw a random copy $\boldsymbol{\mu_{fj}^*}$ of $\boldsymbol{\mu_{fj}}$ from the tri-variate normal $N_3\left(\boldsymbol{\mu_j^*}, \Omega_{\boldsymbol{\mu j}}^*\right)$ distribution.

The simulation of the posterior predictive distribution of the future regression slope β_{2fj} can be implemented in a straightforward manner using the posterior MCMC samples of the Gibbs sampling algorithm of the joint posterior distribution of the regression model parameters.

3.4.1.6 SAS® Procedure NLMIXED

Fits of the mixed model, when the fitting algorithm of the SAS® procedure NLMIXED converges, are generally good and, consistent with this observation, the resulting estimates of the random coefficients seem appropriate. Nevertheless, it is preferred to fit the model as a Bayesian NLME regression model (compared to "frequentist" methods using the SAS® procedure NLMIXED) for the following reasons:

- The fitting algorithm for the mixed model, as implemented through the SAS® procedure NLMIXED, only works with the FIRO method, which implies that censored data cannot be handled (a property of the SAS® procedure).
- Random effects associated with the parameters γ_j cannot be fitted since otherwise the problem becomes too large.

- The mixed model can be fitted to the data of one treatment at a time. However, for between-treatment comparisons the mixed model has to be fitted to the data of at least two treatments jointly, specifying different covariance structures $\Omega_{\boldsymbol{\mu}j}$ for the random coefficients of the different treatments. This makes the problem very large.
- Although the estimates of the random coefficients are usually plausible, the ML estimates of their variances, as obtained from the SAS® procedure NLMIXED, do not always seem reliable.
- Statistical inference based on the mixed model, such as between-treatment comparisons of mean EBA parameters, is approximate (i.e. relies on asymptotic arguments). The quality of the approximation for relatively small sample sizes such as those found with EBA studies is doubtful.

3.4.1.7 Sensitivity Analyses

In order to check the primary model (Model 1.1), and to assess the aspects listed in Section 2.2.3.2, the primary model (Model 1.1) with alternative Bayesian specifications can be fitted.

Model 1.2: **Residuals: Normal**
Random Coefficients: Normal, Fixed Smoothness
Prior for Covariance Matrix: "Default" Wishart

The specification of the primary model (Model 1.1) with (random) "smoothness" parameters γ_{ij} may result in an over-complex model, and a model which treats γ_{ij} as fixed effects instead (per treatment group) may fit the data adequately (hence a trade-off between model complexity and model adequacy). That is, when $u_{4ij} = 0$ (or equivalently, $\gamma_{ij} = \gamma_j$), the model in Equation (3.6) becomes:

$$\log(y_{ijk}) = \alpha_{ij} - \beta_{1ij} \cdot t_{ijk} - \beta_{2ij} \cdot \gamma_j \cdot \log\left(\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_j}} + e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_j}}}{e^{\frac{\kappa_{ij}}{\gamma_j}} + e^{-\frac{\kappa_{ij}}{\gamma_j}}}\right) + \varepsilon_{ijk} \quad (3.37)$$

The remainder model assumptions are equivalent to those of the primary model (Model 1.1).

Page 282 of Section B.3.1 (Appendix B) provides OpenBUGS example code for the implementation of the sensitivity model (Model 1.2) for a typical 14-day EBA study.

Model 1.3: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

To assess the sensitivity of results to the choice of R_j (see Equation (3.17)), one can fit the primary model (Model 1.1) as a linear mixed effects regression model under the assumption that the node and smoothness parameters (i.e. κ_{ij}, κ_j, γ_{ij} and γ_j) are fixed at $(U_\kappa + L_\kappa)/2$ and $(U_\gamma + L_\gamma)/2$, respectively. Accordingly, one can calculate the "frequentist" estimates for $\Omega_{\boldsymbol{\mu}j}$, using the SAS® procedure NLMIXED via ML estimation, to serve as R_j. Here, the censoring of "zero" CFU count should preferably be incorporated to avoid underestimation of the variances in random slopes. Fitting such a full model using the SAS® procedure NLMIXED may result in convergence issues. One could attempt to simplify the model by disregarding the random intercepts (therefore assuming that all patients have the same bacterial load at baseline (Day 0)), and accordingly, use the variance and covariance estimates of random slopes for determining R_j. Similarly, one can fit the model allowing for both random intercepts and slopes, but for simplicity purposes, pooling together the data of all treatment groups (thus removing the "treatment" effect for the fixed effects). The resulting estimate for the variance of random intercepts can accordingly be used for determining R_j.

Basic SAS® example code for calculating R_j is presented in Section B.2.2 (Appendix B).

Model 1.4: Residuals: Skew Normal
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

The primary model (Model 1.1) can incorporate the assumption that the residuals follow *i.i.d.* skew normal distributions (i.e. instead of conventional normal distributions), i.e.:

$$\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, \delta_j \sim SN(0, \sigma^2_{\varepsilon_j}, \delta_j) \tag{3.38}$$

where $\sigma^2_{\varepsilon j}$ and δ_j are scale and skewness parameters, respectively, from the corresponding skew normal distribution.

The density function of $\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, \delta_j$, using a slightly different parameterization defined by Sahu et al. (2003), is written as:

$$P\left(\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, \delta_j\right) = 2\cdot\left(\sigma^2_{\varepsilon_j} + \delta_j^2\right)^{-\frac{1}{2}} \cdot f_N\left(\frac{\varepsilon_{ijk} + \sqrt{\frac{2}{\pi}}\cdot\delta_j}{\sqrt{\sigma^2_{\varepsilon_j} + \delta_j^2}}\right) \cdot F_N\left(\frac{\delta_j}{\sigma_{\varepsilon_j}} \cdot \frac{\varepsilon_{ijk} + \sqrt{\frac{2}{\pi}}\cdot\delta_j}{\sqrt{\sigma^2_{\varepsilon_j} + \delta_j^2}}\right) \tag{3.39}$$

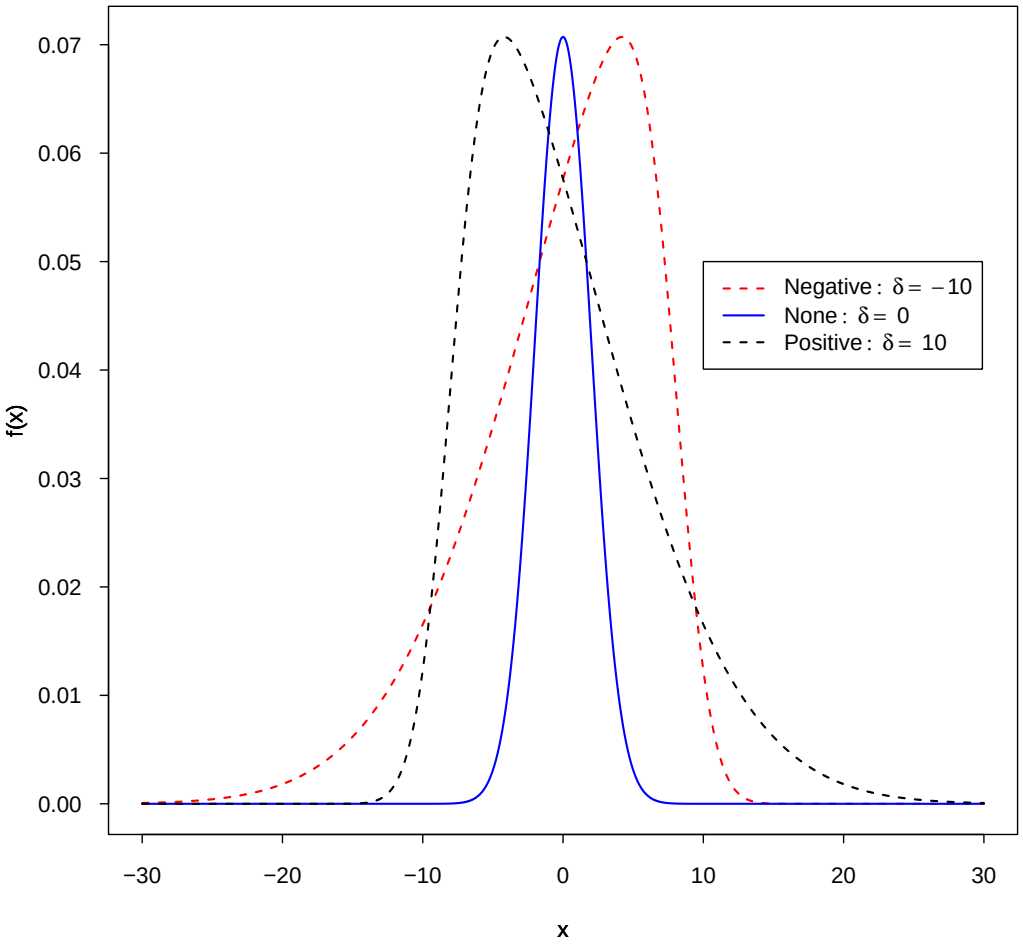
where f_N and F_N respectively denote the density and cumulative distribution function of the standard normal distribution.

Say $X|\theta, \sigma^2, \delta$ follows a skew normal distribution with mean θ, scale parameter σ^2 and skewness parameter δ, i.e. $X \sim SN(\theta, \sigma^2, \delta)$. Figure 3.1 shows examples of the distribution of $X|\theta, \sigma^2, \delta$, i.e. $f(x)$ versus x, where the mean and scale parameters are kept fixed at $\theta = 0$ and $\sigma^2 = 4$, respectively, but shown for different values of skewness, i.e. $\delta \,\epsilon\, \{-10, 0, 10\}$. The conventional normal distribution is a special case of the skew normal distribution when $\delta = 0$, i.e. $X \sim N(\theta, \sigma^2)$. The skew normal distribution is negatively skewed for $\delta < 0$, and positively skewed for $\delta > 0$.

The scale parameters follow gamma prior distributions, namely $\sigma^{-2}_{\varepsilon_j} \sim G(10^{-4}, 10^{-4})$ (see Equation (3.29)), and the skewness parameters follow normal prior distributions, namely:

$$\delta_j \sim N(0, 10^4) \tag{3.40}$$

Figure 3.1: Example Plot of Skew Normal Distribution



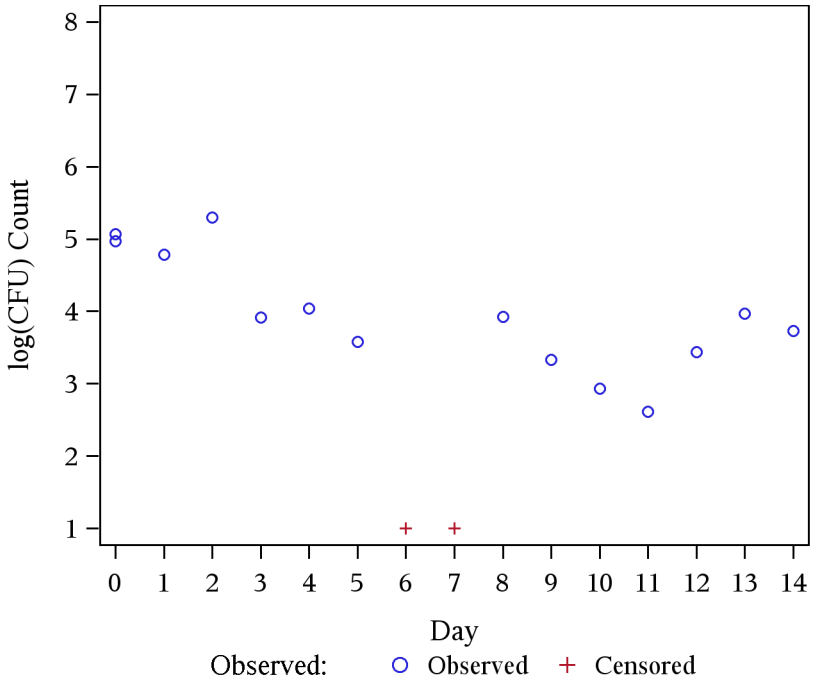
The density function of δ_j is written as:

$$P\left(\delta_j\right) \propto \exp\left(-\frac{1}{2} \cdot \frac{\delta_j^2}{10^4}\right) \tag{3.41}$$

Visual CFU counting processes may lead to compromised data for a variety of reasons (see Van Zyl-Smit et al. (2011)) (see Section 3.2). Therefore, some log(CFU) versus time profiles may be erratic (Gillespie et al., 2002). Figure 3.2 shows an example of a log(CFU) versus time profile with potentially compromised data. Such data may accordingly yield skewness in the distribution of the residuals of model fits. In this particular example, no logical product of a sequential pattern of zero counts over time is visible (see Day 6 and Day 7). The specification of

the skew normal distribution can accommodate such skewed residuals (depending on its skewness parameter δ_j) which, in this regard, is more flexible than the conventional normal distribution.

Figure 3.2: log(CFU) Versus Time Profile Containing Potentially Compromised Data



The skew normal distribution can be specified as a mixture of the following random variables (Sahu et al., 2003):

$$X|\theta, \sigma^2, \delta, \xi \sim N\left(\theta - \left[\sqrt{\frac{2}{\pi}} - \xi\right] \cdot \delta, \sigma^2\right) \tag{3.42}$$

$$\xi \sim TN\,(0,1)\,I(0,\infty) \tag{3.43}$$

Accordingly, the nuisance parameter ξ of the specified mixture distribution (Equation (3.42) and Equation (3.43)) integrated out results in the skew normal distribution:

$$P\left(X|\theta, \sigma^2, \delta\right) = \int P\left(X|\theta, \sigma^2, \delta, \xi\right) \cdot P\left(\xi\right) \mathrm{d}\xi \tag{3.44}$$

In that sense, the Gibbs sampling algorithm with skew normally distributed residuals can be implemented in a straight forward manner as its conjugacy of model parameters (conditional posterior distributions versus prior distributions) is similar to the model with normally distributed residuals.

The remainder model assumptions are equivalent to those of the primary model (Model 1.1).

Page 287 of Section B.3.1 (Appendix B) provides OpenBUGS example code for the implementation of the sensitivity model (Model 1.4) for a typical 14-day EBA study.

Model 1.5: Residuals: Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

The primary model (Model 1.1) can incorporate the assumption that the residuals follow *i.i.d.* Student t distributions (i.e. instead of normal distributions), i.e.:

$$\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, v_j \sim T(0, \sigma^2_{\varepsilon_j}, v_j) \tag{3.45}$$

where $\sigma^2_{\varepsilon j}$ and v_j are scale parameters and degrees of freedom, respectively, from the corresponding Student t distribution.

The density function of $\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, v_j$ is written as:

$$P\left(\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, v_j\right) \propto \frac{\Gamma\left(\frac{v_j+1}{2}\right)}{\Gamma\left(\frac{v_j}{2}\right) \cdot \sqrt{v_j \cdot \sigma^2_{\varepsilon_j}}} \cdot \left(1 + \frac{\varepsilon^2_{ijk}}{v_j \cdot \sigma^2_{\varepsilon j}}\right)^{-\frac{v_j+1}{2}} \tag{3.46}$$

where $\Gamma(.)$ denotes the gamma function. The scale parameters follow gamma prior distributions, namely $\sigma^{-2}_{\varepsilon_j} \sim G(10^{-4}, 10^{-4})$ (see Equation (3.29)), and the degrees of freedom follow uniform prior distributions, namely:

$$v_j \sim U(2, 100) \tag{3.47}$$

The density function of v_j is written as:

$$P(v_j) \propto I(2 \leq v_j \leq 100) \tag{3.48}$$

The specification of the Student t distribution can accommodate heavily tailed residuals (depending on its degrees of freedom v_j) in CFU count (see Gillespie et al. (2002)) which, in this regard, is more flexible than the normal distribution.

The Student t distribution can be specified as a mixture of a normal distribution with mean zero and unknown variance, and an inverse gamma distribution assumed for the unknown variance which parameters are a function of $\sigma^2_{\varepsilon_j}$ and v_j. Accordingly, the unknown variance of the specified mixture distribution integrated out results in the Student t distribution (Prince, 2012) in Equation (3.45). In that sense, the Gibbs sampling algorithm with Student t distributed residuals can be implemented in a straight forward manner as its conjugacy of model parameters (conditional posterior distributions versus prior distributions) is similar to the model with normally distributed residuals. The specification of the Student t distribution as a mixture of random variables is implemented automatically in OpenBUGS.

The remainder model assumptions are equivalent to those of the primary model (Model 1.1).

Page 292 of Section B.3.1 (Appendix B) provides OpenBUGS example code for the implementation of the sensitivity model (Model 1.5) for a typical 14-day EBA study.

Model 1.6: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

The sensitivity of results to the choice of R_j in Model 1.5 can be assessed using the "frequentist" approach specified for Model 1.3.

Model 1.7: Residuals: Student t
Random Coefficients: Student t
Prior for Covariance Matrix: "Default" Wishart

The primary model (Model 1.5) can incorporate the assumption that the vectors of random intercepts and slopes follow *i.i.d.* tri-variate Student t distributions (i.e. instead of tri-variate normal distributions), i.e.:

$$\boldsymbol{\mu_{ij}}|\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}, w_j \sim T_3(\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}, w_j) \tag{3.49}$$

where $\boldsymbol{\mu_j}$ are the vectors of mean intercepts and slopes, and $\Omega_{\boldsymbol{\mu}j}$ and w_j are scale matrices and degrees of freedom, respectively, from the corresponding tri-variate Student t distribution.

The density function of $\boldsymbol{\mu_{ij}}|\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}, w_j$ is written as:

$$\begin{aligned} &P(\boldsymbol{\mu_{ij}}|\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}, w_j) \\ &\propto \frac{\Gamma_3\left(\frac{w_j+3}{2}\right)}{\Gamma_3\left(\frac{w_j}{2}\right) \cdot w_j^{\frac{3}{2}}} \cdot |\Omega_{\boldsymbol{\mu}j}|^{-\frac{1}{2}} \cdot \left(1 + \frac{1}{w_j}\left(\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}\right)' \cdot \Omega_{\boldsymbol{\mu}j}^{-1} \cdot \left(\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}\right)\right)^{-\frac{w_j+3}{2}} \end{aligned} \tag{3.50}$$

where $\Gamma_3(.)$ denotes the tri-variate gamma function.

The scale matrices follow tri-variate Wishart prior distributions, namely $\Omega_{\boldsymbol{\mu}j}^{-1} \sim W_3(3, 3 \times R_j)$ (see Equation (3.17)), and the degrees of freedom follow uniform prior distributions, namely:

$$w_j \sim U(2, 100) \tag{3.51}$$

The density function of w_j is written as:

$$P(w_j) \propto I(2 \leq w_j \leq 100) \tag{3.52}$$

The tri-variate Student t distribution can accommodate heavily tailed intercepts and slopes (depending on its degrees of freedom w_j) which, in this regard, is more

flexible than the tri-variate normal distribution. In general, the specification of the Student t distribution for both random effects (intercepts and slopes) and residuals may provide a more robust modeling approach for outliers in any of the latter components of the given model.

Similar to the univariate Student t distribution, the tri-variate Student t distribution can be specified as a mixture of a tri-variate normal distribution with mean $\boldsymbol{\mu_j}$ and unknown covariance matrix, and an inverse Wishart distribution assumed for the unknown covariance matrix which parameters are a function of $\Omega_{\boldsymbol{\mu j}}$ and w_j. Accordingly, the unknown covariance matrix of the specified mixture distribution integrated out results in the tri-variate Student t distribution (Zhu et al., 2008) in Equation (3.49). In that sense, the Gibbs sampling algorithm with tri-variate Student t distributed (random) intercepts and slopes can be implemented in a straight forward manner as its conjugacy of model parameters (conditional posterior distributions versus prior distributions) is similar to the model which random intercepts and slopes are assumed to follow tri-variate normal distributions. The specification of the tri-variate Student t distribution as a mixture of random variables is implemented automatically in OpenBUGS.

The remainder model assumptions are equivalent to those of Model 1.5.

Page 296 of Section B.3.1 (Appendix B) provides OpenBUGS example code for the implementation of the sensitivity model (Model 1.7) for a typical 14-day EBA study.

Model 1.8: Residuals: Student t
Random Coefficients: Skew Normal
Prior for Covariance Matrix: "Default" Wishart

The primary model (Model 1.5) can incorporate the assumption that the vectors of random intercepts and slopes follow *i.i.d.* skew tri-variate normal distributions (i.e. instead of conventional tri-variate normal distributions), i.e.:

$$\boldsymbol{\mu_{ij}}|\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu j}}, \boldsymbol{\delta_j} \sim SN_3(\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu j}}, \boldsymbol{\delta_j}) \tag{3.53}$$

where $\boldsymbol{\mu_j}$ are the vectors of mean intercepts and slopes, and $\Omega_{\boldsymbol{\mu}j}$ and $\boldsymbol{\delta_j} = \left(\delta_{\alpha_j}, \delta_{\beta_{1j}}, \delta_{\beta_{2j}}\right)'$ are scale matrices and skewness vectors, respectively, from the corresponding skew tri-variate normal distribution.

The density function of $\boldsymbol{\mu_{ij}}|\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}, \boldsymbol{\delta_j}$, using a slightly different parameterization defined by Sahu et al. (2003), is written as:

$$\begin{aligned} & P\left(\boldsymbol{\mu_{ij}}|\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}, \boldsymbol{\delta_j}\right) \\ =& 2^3 |\Omega_{\boldsymbol{\mu}j} + \Delta_j^2|^{-\frac{1}{2}} f_{N_3}\left(\left(\Omega_{\boldsymbol{\mu}j} + \Delta_j^2\right)^{-\frac{1}{2}}\left[\boldsymbol{\mu_{ij}} - \left\{\boldsymbol{\mu_j} - \sqrt{\frac{2}{\pi}}\boldsymbol{\delta_j}\right\}\right]\right) \cdot \\ & P\left(\boldsymbol{Q_{ij}} \leq \mathbf{0}\right) \end{aligned} \tag{3.54}$$

where f_{N_3} denotes the density function of the standard tri-variate normal distribution, $P\left(\boldsymbol{Q_{ij}} < \mathbf{0}\right)$ the cumulative distribution function, evaluated at $\mathbf{0}$, of the tri-variate normal distribution with mean and covariance matrix of $\Delta_j \cdot \left(\Omega_{\boldsymbol{\mu}j} + \Delta_j^2\right)^{-1} \cdot \left(\boldsymbol{\mu_{ij}} - \left[\boldsymbol{\mu_j} - \sqrt{\frac{2}{\pi}}\boldsymbol{\delta_j}\right]\right)$ and $I_3 - \Delta_j \cdot \left(\Omega_{\boldsymbol{\mu}j} + \Delta_j^2\right)^{-1} \cdot \Delta_j$, respectively. Here, $\Delta_j = \text{diag}\left(\delta_{\alpha_j}, \delta_{\beta_{1j}}, \delta_{\beta_{2j}}\right)$ are matrices with diagonal entries $\delta_{\alpha_j}, \delta_{\beta_{1j}}, \delta_{\beta_{2j}}$, for which the remainder entries are set to 0.

The scale matrices follow tri-variate Wishart prior distributions, namely $\Omega_{\boldsymbol{\mu}j}^{-1} \sim W_3(3, 3 \times R_j)$ (see Equation (3.17)), and the skewness vectors tri-variate normal prior distributions, namely:

$$\boldsymbol{\delta_j} \sim N_3(\mathbf{0}, 10^4 \times I_3) \tag{3.55}$$

The density function of $\boldsymbol{\delta_j}$ is written as:

$$P\left(\boldsymbol{\delta_j}\right) \propto \exp\left(-\frac{1}{2}\boldsymbol{\delta_j}' \cdot \frac{1}{10^4} \cdot \boldsymbol{\delta_j}\right) \tag{3.56}$$

Some treatment regimens occasionally exhibit remarkable decline in log(CFU) count over time in a subset of patients, and as a result, may cause skewness in the distribution of random slopes. The specification of the skew tri-variate normal distribution can accommodate skewed random intercepts and slopes (depending on

its skewness vector $\boldsymbol{\delta_j}$) which, in this regard, is more flexible than the conventional tri-variate normal distribution.

Say $\boldsymbol{X}|\boldsymbol{\theta}, \Sigma, \boldsymbol{\delta}$ follows a skew tri-variate normal distribution with mean $\boldsymbol{\theta}$, scale matrix Σ and skewness vector $\boldsymbol{\delta}$, i.e. $\boldsymbol{X} \sim SN(\boldsymbol{\theta}, \Sigma, \boldsymbol{\delta})$. The skew tri-variate normal distribution can be specified as a mixture of the following random variables (Sahu et al., 2003):

$$\boldsymbol{X}|\boldsymbol{\theta}, \Sigma, \boldsymbol{\delta}, \boldsymbol{\xi} \sim N\left(\boldsymbol{\theta} - \left[\sqrt{\frac{2}{\pi}} \cdot \boldsymbol{\delta} - \Delta \cdot \boldsymbol{\xi}\right], \Sigma\right) \tag{3.57}$$

$$\boldsymbol{\xi} \sim TN_3\left(\mathbf{0}, I_3\right) I(\mathbf{0}, \boldsymbol{\infty}) \tag{3.58}$$

where $\Delta = \text{diag}\left(\delta_1, \delta_2, \delta_3\right)$, and $TN_3(\mathbf{0}, I_3)I(\mathbf{0}, \boldsymbol{\infty})$ denotes a tri-variate standard normal distribution truncated over the parameter space $\mathbf{0}$ to $\boldsymbol{\infty}$. Accordingly, the nuisance vector $\boldsymbol{\xi}$ of the specified mixture distribution (Equation (3.57) and Equation (3.58)) integrated out results in the skew tri-variate normal distribution:

$$P\left(\boldsymbol{X}|\boldsymbol{\theta}, \Sigma, \boldsymbol{\delta}\right) = \int P\left(\boldsymbol{X}|\boldsymbol{\theta}, \Sigma, \boldsymbol{\delta}, \boldsymbol{\xi}\right) \cdot P\left(\boldsymbol{\xi}\right) \mathrm{d}\boldsymbol{\xi} \tag{3.59}$$

In that sense, the Gibbs sampling algorithm with skew tri-variate normal (random) intercepts and slopes can be implemented in a straight forward manner as its conjugacy of model parameters (conditional posterior distributions versus prior distributions) is similar to the model which random intercepts and slopes are assumed to follow tri-variate normal distributions.

The remainder model assumptions are equivalent to those of Model 1.5.

Page 300 of Section B.3.1 (Appendix B) provides OpenBUGS example code for the implementation of the sensitivity model (Model 1.8) for a typical 14-day EBA study.

Model 1.9: Residuals: Skew Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

The primary model (Model 1.1) can incorporate the assumption that the residuals follow *i.i.d.* skew Student t distributions (i.e. instead of normal distributions), i.e.:

$$\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, \delta_j, v_j \sim ST(0, \sigma^2_{\varepsilon_j}, \delta_j, v_j) \tag{3.60}$$

where $\sigma^2_{\varepsilon j}$, δ_j and v_j are scale and skewness parameters, and degrees of freedom, respectively, from the corresponding skew Student t distribution.

The density function of $\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, \delta_j, v_j$, using a slightly different parameterization defined by Sahu et al. (2003), is written as:

$$\begin{aligned} & P\left(\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, \delta_j, v_j\right) \\ =& 2\left(\sigma^2_{\varepsilon_j} + \delta_j^2\right)^{-\frac{1}{2}} \frac{\Gamma\left(\frac{v_j+1}{2}\right)}{\Gamma\left(\frac{v_j}{2}\right)\sqrt{v_j\pi}} \left(1 + \frac{\left[\varepsilon_{ijk} + \left(\frac{v_j}{\pi}\right)^{\frac{1}{2}} \frac{\Gamma\left(\frac{v_j-1}{2}\right)}{\Gamma\left(\frac{v_j}{2}\right)}\delta_j\right]^2}{v_j\left(\sigma^2_{\varepsilon_j} + \delta_j^2\right)}\right)^{-\frac{v_j+1}{2}} \cdot \\ & P\left(Q_{ijk} \leq \frac{\delta_j\sqrt{v_j+1}\left[\varepsilon_{ijk} + \left(\frac{v_j}{\pi}\right)^{\frac{1}{2}} \frac{\Gamma\left(\frac{v_j-1}{2}\right)}{\Gamma\left(\frac{v_j}{2}\right)}\delta_j\right]}{\sigma_{\varepsilon_j}\sqrt{\sigma^2_{\varepsilon_j} + \delta_j^2}\sqrt{v_j + \left[\varepsilon_{ijk} + \left(\frac{v_j}{\pi}\right)^{\frac{1}{2}} \frac{\Gamma\left(\frac{v_j-1}{2}\right)}{\Gamma\left(\frac{v_j}{2}\right)}\delta_j\right]^2\left(\sigma^2_{\varepsilon_j} + \delta_j^2\right)^{-1}}}\right) \end{aligned} \tag{3.61}$$

where $P\left(Q_{ijk} \leq x\right)$ denotes the cumulative distribution function, evaluated at x, of the Student t distribution with mean, scale parameter and degrees of freedom of 0, 1 and $v_j + 1$, respectively.

The scale and skewness parameters, and degrees of freedom, follow gamma, normal and uniform prior distributions, namely $\sigma^{-2}_{\varepsilon_j} \sim G(10^{-4}, 10^{-4})$ (see Equation (3.29)), $\delta_j \sim N(0, 10^4)$ (see Equation (3.40)) and $v_j \sim U(2, 100)$ (see Equation (3.47)).

Say $X|\theta, \sigma^2, \delta, v$ follows a skew Student t distribution with mean θ, scale parameter σ^2, skewness parameter δ and degrees of freedom v, i.e. $X \sim ST(\theta, \sigma^2, \delta, v)$. The skew Student t distribution can be specified as a mixture of the following random variables (Sahu et al., 2003):

$$X|\theta, \sigma^2, \delta, v, \xi_1, \xi_2 \sim N\left(\theta - \left[\left(\frac{v}{\pi}\right)^{\frac{1}{2}} \frac{\Gamma\left(\frac{v-1}{2}\right)}{\Gamma\left(\frac{v}{2}\right)} - \xi_1\right] \cdot \delta, \frac{\sigma^2}{\xi_2}\right) \tag{3.62}$$

$$\xi_1|\xi_2 \sim TN\left(0, \frac{1}{\xi_2}\right) I(0, \infty) \tag{3.63}$$

$$\xi_2^{-1} \sim G\left(\frac{v}{2}, \frac{v}{2}\right) \tag{3.64}$$

Accordingly, the nuisance parameters ξ_1 and ξ_2 of the specified mixture distribution (Equation (3.62), Equation (3.63) and Equation (3.64)) integrated out results in the skew Student t distribution:

$$P\left(X|\theta, \sigma^2, \delta, v\right) = \int P\left(X|\theta, \sigma^2, \delta, v, \xi_1, \xi_2\right) \cdot P\left(\xi_1|\xi_2\right) P\left(\xi_2^{-1}\right) \mathrm{d}\left(\xi_1, \xi_2\right) \tag{3.65}$$

In that sense, the Gibbs sampling algorithm with skew Student t distributed residuals can be implemented in a straight forward manner as its conjugacy of model parameters (conditional posterior distributions versus prior distributions) is similar to the model with normally distributed residuals.

The remainder model assumptions are equivalent to those of the primary model (Model 1.1).

Page 307 of Section B.3.1 (Appendix B) provides OpenBUGS example code for the implementation of the sensitivity model (Model 1.9) for a typical 14-day EBA study.

3.4.2 Other Regression Models

The subsections below provide detail of the primary and sensitivity Bayesian linear, conventional bilinear and bi-exponential mixed effects regression models: That

is, the mixed effects regression models for which the underlying regression functions are the linear, conventional bilinear and bi-exponential regression functions, respectively (Equation (2.27), Equation (2.34) and Equation (2.40), respectively).

3.4.2.1 Linear Regression Model

Model 2.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Based on Equation (2.27), one can postulate the following linear mixed effects regression model:

$$\log(y_{ijk}) = \alpha_{ij} - \lambda_{ij} \cdot t_{ijk} + \varepsilon_{ijk} \tag{3.66}$$

Here, the notation is similar to that used for Model 1.1.

The parameters of the regression model in Equation (3.66) are analogous to those of the "by-patient" regression function in Equation (2.27), and the specification of its random effects and prior distributions are similar to those of Model 1.1. Here, the main difference is that bivariate (instead of tri-variate) normal and Wishart distributions are specified for the random and fixed effects.

The matrices Z_{ij} associated with the vectors of random intercepts and slopes (see Equation (3.20)) are required for appropriate specification of priors for covariance matrices $\Omega_{\boldsymbol{\mu}j}$ ("default" Wishart). These matrices are defined as follows:

$$Z_{ij} = \begin{bmatrix} 1 & -t_{ij1} \\ \vdots & \vdots \\ 1 & -t_{ijk} \\ \vdots & \vdots \\ 1 & -t_{ijK_{ij}} \end{bmatrix}$$

Page 313 of Section B.3.2 (Appendix B) provides OpenBUGS example code for the implementation of the primary model (Model 2.1) for a typical 14-day EBA study.

Model 2.2: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Similar to Model 1.5, the primary model (Model 2.1) can incorporate the assumption that the residuals follow *i.i.d.* Student t distributions (i.e. instead of normal distributions).

Page 317 of Section B.3.2 (Appendix B) provides OpenBUGS example code for the implementation of the primary model (Model 2.2) for a typical 14-day EBA study.

3.4.2.2 Conventional Bilinear Regression Model

Model 3.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Based on Equation (2.34), one can postulate the following bilinear mixed effects regression model:

$$\log(y_{ijk}) = \alpha_{ij} - \beta_{1ij} \cdot t_{ijk} + (-1)^{J_{ijk}+1} \cdot \beta_{2ij} \cdot t_{ijk} + 2\,(J_{ijk} - 1) \cdot \beta_{2ij} \cdot \kappa_{ij} + \varepsilon_{ijk} \quad (3.67)$$

where $J_{ijk} = 1 + \text{step}\,(t_{ijk} - \kappa_{ij})$, and $\text{step}\,(x)$ denotes a function taking the value 0 if $x \leq 0$, and 1 otherwise. Here, the notation is similar to that used for Model 1.1.

The parameters of the regression model in Equation (3.67) are analogous to those of the "by-patient" regression function in Equation (2.34), and the specification of its random effects and prior distributions are similar to those of Model 1.1.

The matrices Z_{ij} associated with the vectors of random intercepts and slopes (see Equation (3.20)) are required for appropriate specification of priors for covariance matrices $\Omega_{\boldsymbol{\mu}j}$ ("default" Wishart). These matrices are defined as follows:

$$Z_{ij} = \begin{bmatrix} 1 & -t_{ij1} & (-1)^{J_{ij1}+1} \cdot t_{ij1} + 2\left(J_{ij1} - 1\right) \cdot \kappa_p \\ \vdots & \vdots & \vdots \\ 1 & -t_{ijk} & (-1)^{J_{ijk}+1} \cdot t_{ij1} + 2\left(J_{ijk} - 1\right) \cdot \kappa_p \\ \vdots & \vdots & \vdots \\ 1 & -t_{ijK_{ij}} & (-1)^{J_{ijK_{ij}}+1} \cdot t_{ijK_{ij}} + 2\left(J_{ijK_{ij}} - 1\right) \cdot \kappa_p \end{bmatrix}$$

Page 320 of Section B.3.2 (Appendix B) provides OpenBUGS example code for the implementation of the primary model (Model 3.1) for a typical 14-day EBA study.

Model 3.2: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Similar to Model 1.5, the primary model (Model 3.1) can incorporate the assumption that the residuals follow *i.i.d.* Student t distributions (i.e. instead of normal distributions).

Page 326 of Section B.3.2 (Appendix B) provides OpenBUGS example code for the implementation of the primary model (Model 3.2) for a typical 14-day EBA study.

3.4.2.3 Bi-Exponential Regression Model

Model 4.1: Residuals: Normal
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

Based on Equation (2.40), one can postulate the following NLME regression model:

$$\log(y_{ijk}) = \log\left(e^{\theta_{1ij}} \cdot e^{-\lambda_{1ij} \cdot t_{ijk}} + e^{\theta_{2ij}} \cdot e^{-\lambda_{2ij} \cdot t_{ijk}}\right) + \varepsilon_{ijk} \tag{3.68}$$

Here, the notation is similar to that used for Model 1.1.

The parameters of the regression model in Equation (3.68) are analogous to those of the "by-patient" regression function in Equation (2.40), and the specification of its random effects and prior distributions are similar to those of Model 1.1. Here, the main difference is that 4-variate (instead of tri-variate) normal and Wishart distributions are specified for the random and fixed effects (e.g. θ_{1ij}, λ_{1ij}, θ_{2ij} and λ_{2ij}).

Since Equation (3.68) is completely nonlinear, the methodology by Kass and Natarajan (2006) can no longer be applied to calculate R_j. Alternatively, one can fit Equation (3.68) using the SAS® procedure NLMIXED via ML estimation (similar to Model 1.3).

The attempt to fit the bi-exponential mixed effects regression model to 14-day EBA data fails since the MCMC samples do not converge for profiles over time with a slow rate of decline early, followed by a faster rate of decline. Moreover, the model lacks identifiability of its parameters when the intercept and slope of the two respective bi-exponential terms are not distinctly different.

Model 4.2: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

Similar to Model 1.5, the primary model (Model 4.1) can incorporate the assumption that the residuals follow *i.i.d.* Student t distributions (i.e. instead of normal distributions).

3.5 Model Selection and Model Checking

From the various mixed effects regression models defined in Section 3.4, one would be interested in selecting the "best" model for inferences of EBA. For this purpose, model selection tools described in Section 2.2.3.2 can be utilized to discriminate between models. Model fit can be checked using CPOs defined in Section 2.2.3.3.

3.5.1 Deviance Information Criterion

The associated DIC statistic (see Section 2.2.3.2) can be obtained directly from OpenBUGS.

For Model 1.4, Model 1.8 and Model 1.9, the likelihood densities for the calculation of DIC statistics in OpenBUGS are conditional also on the nuisance parameters, and should therefore not be reported.

3.5.2 Bayes Factors

For calculation of compound Laplace-Metropolis Bayes factors (see Section 2.2.3.2), the methodology proposed by Lewis and Raftery (1997) suggests the use of the Laplace method to approximate the required integrals: That is, the marginalization of random effects for each patient in Model 1.1. However, the use of Laplace's method for multidimensional integrals can be challenging and cumbersome to implement. In order for asymptotic Laplace approximations to be reliable

for Model 1.1, an adequate amount of observations associated with each patient's likelihood should be available (Shun and McCullagh, 1995). The latter condition can thus be problematic for profiles with a significant amount of missing data.

A workaround for the aforementioned concerns associated with Laplace approximated integrals for Model 1.1 is described here in detail. The workaround provides a generalized approach for NLME regression modeling and is reasonably easy to implement with SAS® and the R project (R Core Team, 2014).

For Model 1.1 (see Page 77), the associated compound Laplace-Metropolis Bayes factor can be calculated by marginalizing the random effects for each patient using the multidimensional numerical integration library "R2Cuba" of the R project (Hahn et al., 2013). This integration package uses sophisticated numerical techniques which do not rely on asymptotic theory, and are particularly appropriate for integration calculations of high dimensions. Similar to OpenBUGS, the R project can be called remotely from SAS®. The marginal likelihood of patient i in treatment group j is expressed as follows:

$$\begin{aligned} & P\left(\boldsymbol{y_{ij}}|\hat{\boldsymbol{\mu}}_j, \hat{\kappa}_j, \hat{\gamma}_j, \hat{\Omega}_{\boldsymbol{\mu}j}, \hat{\sigma}^2_{\kappa_j}, \hat{\sigma}^2_{\gamma_j}, \hat{\sigma}^2_{\varepsilon j}\right) \\ &= \int P\left(\boldsymbol{y_{ij}}|\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \hat{\boldsymbol{\mu}}_j, \hat{\kappa}_j, \hat{\gamma}_j, \hat{\Omega}_{\boldsymbol{\mu}j}, \hat{\sigma}^2_{\kappa_j}, \hat{\sigma}^2_{\gamma_j}, \hat{\sigma}^2_{\varepsilon j}\right) \mathrm{d}\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}\right) \end{aligned} \tag{3.69}$$

Here, $\hat{\boldsymbol{\mu}}_j$, $\hat{\kappa}_j$, $\hat{\gamma}_j$, $\hat{\Omega}_{\boldsymbol{\mu}j}$, $\hat{\sigma}^2_{\kappa_j}$, $\hat{\sigma}^2_{\gamma_j}$ and $\hat{\sigma}^2_{\varepsilon j}$ are the mean of the posterior distribution of $\boldsymbol{\mu}_j$, κ_j, γ_j, $\Omega_{\boldsymbol{\mu}j}$, $\sigma^2_{\kappa_j}$, $\sigma^2_{\gamma_j}$ and $\sigma^2_{\varepsilon j}$, respectively, and

$$\begin{aligned} & P\left(\boldsymbol{y_{ij}}|\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \hat{\boldsymbol{\mu}}_j, \hat{\kappa}_j, \hat{\gamma}_j, \hat{\Omega}_{\boldsymbol{\mu}j}, \hat{\sigma}^2_{\kappa_j}, \hat{\sigma}^2_{\gamma_j}, \hat{\sigma}^2_{\varepsilon j}\right) \\ =& L\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \hat{\sigma}^2_{\varepsilon j}, k = 1, \ldots, K_{ij}|\boldsymbol{y_{ij}}\right) \cdot P\left(\boldsymbol{\mu_{ij}}|\hat{\boldsymbol{\mu}}_j, \hat{\Omega}_{\boldsymbol{\mu}j}\right) \cdot P\left(\kappa_{ij}|\hat{\kappa}_j, \hat{\sigma}^2_{\kappa_j}\right) \cdot \\ & P\left(\gamma_{ij}|\hat{\gamma}_j, \hat{\sigma}^2_{\gamma_j}\right) \end{aligned} \tag{3.70}$$

Let $|R_{\left(\boldsymbol{\mu}_j, \kappa_j, \gamma_j, \sigma^2_{\varepsilon j}, j=1,\ldots,J\right)}|$ and $s_{\left(\boldsymbol{\mu}_j, \kappa_j, \gamma_j, \sigma^2_{\varepsilon j}, j=1,\ldots,J\right)}$ respectively denote the determinant of the correlation matrix and the sum of the logarithm of the SDs of the posterior distributions of $\boldsymbol{\mu}_j$, κ_j, γ_j and $\sigma^2_{\varepsilon j}$. These quantities can respectively be calculated using the SAS® procedures CORR and IML.

Finally, the Laplace-Metropolis marginal likelihood for Model 1.1 can be written as:

$$\log(\hat{f}[\boldsymbol{y}]) = 7 \cdot \log(2\pi) \cdot J + \frac{1}{2}\log|R_{(\boldsymbol{\mu}_j,\kappa_j,\gamma_j,\sigma^2_{\varepsilon j},j=1,\ldots,J)}| + \tag{3.71}$$
$$s_{(\boldsymbol{\mu}_j,\kappa_j,\gamma_j,\sigma^2_{\varepsilon j},j=1,\ldots,J)} + \sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J} P\left(\boldsymbol{y_{ij}}|\hat{\boldsymbol{\mu}}_j,\hat{\kappa}_j,\hat{\gamma}_j,\hat{\Omega}_{\boldsymbol{\mu}j},\hat{\sigma}^2_{\kappa_j},\hat{\sigma}^2_{\gamma_j},\hat{\sigma}^2_{\varepsilon j}\right) +$$
$$\sum_{j=1}^{J}\left(P\left[\hat{\boldsymbol{\mu}}_j\right] + P\left[\hat{\Omega}^{-1}_{\boldsymbol{\mu}j}\right] + P\left[\hat{\kappa}_j\right] + P\left[\hat{\gamma}_j\right] + P\left[\hat{\sigma}^2_{\kappa_j}\right] + P\left[\hat{\sigma}^2_{\gamma_j}\right] + P\left[\hat{\sigma}^{-2}_{\varepsilon j}\right]\right)$$

The following libraries of the R project are used for the specification of the relevant density and cumulative distribution functions in Equation (3.71):

- The normal distribution included in library "sn" (more specifically, using its skew normal distribution with skewness parameter equal to 0) (Azzalini, 2014).
- The multivariate normal distribution included in library "mnormt" (Genz and Azzalini, 2013).
- The truncated normal distribution included in library "truncnorm" (Trautmann et al., 2014).
- The Wishart distribution included in library "mixAK" (Komárek, 2009).

The remainder density and cumulative distribution functions are calculated from the default packages (or "functionalities") included in the R project.

The SAS® and R example code for the calculation of the Laplace-Metropolis marginal likelihood of Model 1.1, Model 1.2, Model 1.4, Model 1.5, Model 1.7, Model 1.8, Model 1.9, Model 2.1 and Model 3.1 are presented in Appendix B. Here, the Student t density and corresponding cumulative distribution function can be specified using the "sn" library of the R project (more specifically, using its skew Student t distribution with skewness parameter equal to 0). The skew densities and corresponding cumulative distribution functions can also be specified using the "sn" library of the R project. However, their parameterizations differ to

that defined by Sahu et al. (2003). The skew densities and cumulative distribution functions therefore has to be specified manually in the R project.

3.5.3 Conditional Posterior Ordinate

The likelihood densities, conditional on each set of posterior MCMC samples, can be obtained directly from OpenBUGS. Straightforward data manipulation of these likelihood densities (on a post-hoc basis) can accordingly be applied to calculate each $\widehat{\text{ICPO}}_i$ (see Section 2.2.3.3).

For Model 1.4, Model 1.8 and Model 1.9, the likelihood densities for the calculation of $\widehat{\text{ICPO}}_i$ in OpenBUGS are conditional also on the nuisance parameters, and should therefore not be reported.

Chapter 4

Application: Colony Forming Unit Count

4.1 Introduction

This chapter presents applications of the methodology described in the preceding chapters to the assessment of CFU data. Section 4.2 summarizes the results of an extensive empirical investigation of the suitability of the proposed model for CFU data (see Equation (2.39)), and Section 4.3 through Section 4.6 are devoted to applications of the methodology presented in Chapter 3 to the CFU data of recently published clinical trials.

4.2 Empirical Study

The purpose of the empirical study, and associated results and findings from the datasets analyzed, are discussed here in detail.

4.2.1 Purpose

While theoretical considerations may assist in the derivation of a suitable regression model for a certain type of data, the most important requirement for a good model is that it should fit the data well. In deriving a regression model for CFU data, an empirical study of a large number of log(CFU) versus time profiles from six EBA trials and one "SSCC" trial was carried out.

The typical shapes of such profiles, identified in the empirical study, confirm observations made previously by other authors, and motivate the theoretical derivation of the differential hyperbolic tangent regression model in Chapter 3 (see Equation (2.39)).

4.2.2 Datasets Analyzed

For the purpose of this empirical study, data from six EBA trials and one "SSCC" trial, comprising the CFU versus time profiles of a total of 661 patients, were available. In each of the EBA trials, CFU data were collected over 14 days of treatment, while in the "SSCC" trial CFU data were collected over 8 weeks of treatment.

Relevant clinical trial characteristics of clinical trial protocols CL001 (Diacon et al., 2013), CL007 (Diacon et al., 2010), CL010 (Diacon et al., 2012c), NC001 (Diacon et al., 2012a), NC002 (both "SSCC" main study and EBA sub-study) (Dawson et al., 2015) and NC003 (Diacon et al., 2015) are summarized in Table 4.1, including the total number of valid patients, and the number of patients with complete profiles (data up to Day 14 (EBA trials) and Day 34 ("SSCC" trial)).

Table 4.1: Characteristics of Trials Included in Empirical Study

Clinical Trial	Scheduled Sample Days	Treatment Group	N	n
CL001	Daily from Day -2 to Day 8;	TMC207 100 mg	15	12
	Day 10, Day 12, Day 14	TMC207 200 mg	15	13
		TMC207 200 mg	15	13
		TMC207 400 mg	15	14
		Rifafour	8	6
		Total	**68**	**58**
CL007	Daily from Day -2 to Day 4;	PA-824 200 mg	15	10
	Day 6, Day 8, Day 10, Day 12,	PA-824 600 mg	15	10
	Day 14	PA-824 1000 mg	16	9
		PA-824 1200 mg	15	11
		Rifafour	8	5
		Total	**69**	**45**
CL010	Daily from Day -2 to Day 4;	PA-824 50 mg	15	12
	Day 6, Day 8, Day 10, Day 12,	PA-824 100 mg	15	15
	Day 14	PA-824 150 mg	15	14
		PA-824 200 mg	16	14
		Rifafour	8	8
		Total	**69**	**63**
NC001	Daily from Day -2 to Day 14	J	15	14
		J-Z	15	12
		J-Pa	15	12
		Pa-Z	15	13
		Pa-Z-M	15	10
		Rifafour	10	8
		Total	**85**	**69**
NC002 (EBA)	Daily from Day -2 to Day 3, Day 5,	M-PA100-Z	16	6
	Day 7, Day 9, Day 11, Day 14	M-PA200-Z	13	7
		M-PA200-Z-MDR	18	4
		Rifafour	15	9
		Total	**62**	**26**
NC002 ("SSCC")	Day -2, Day -1, Day 3, Day 7,	M-PA100-Z	60	3
	Day 14, Day 21, Day 28, Day 35,	M-PA200-Z	61	1
	Day 42, Day 49, Day 56	M-PA200-Z-MDR	26	1
		Rifafour	59	5
		Total	**206**	**10**

Note: Treatment group: J = TMC207, J-Z = TMC207 + Pyrazinamide, J-Pa = TMC207 + PA-824, Pa-Z = PA-824 + Pyrazinamide, Pa-Z-M or M-PA-Z = PA-824 + Pyrazinamide + Moxifloxacin, J-Pa-Z-C = TMC207 + PA-824 + Pyrazinamide + Clofazimine, J-Pa-Z = TMC207 + PA-824 + Pyrazinamide, J-Pa-C = TMC207 + PA-824 + Clofazimine, J-Z-C = TMC207 + Pyrazinamide + Clofazimine, Z = Pyrazinamide, C = Clofazimine, Rifafour = Rifafour e-275®. CFU: Colony forming unit; MDR: Multi-drug resistant. N = Total number of patients. n = Number of patients with complete profiles and no censored log(CFU) counts.

Table 4.1: Characteristics of Trials Included in Empirical Study

Clinical Trial	Scheduled Sample Days	Treatment Group	N	n
NC003	Daily from Day -2 to Day 14	J-Pa-Z-C	14	12
		J-Pa-Z	14	8
		J-Pa-C	15	13
		J-Z-C	14	9
		Z	15	14
		C	15	13
		Rifafour	15	8
		Total	**102**	**77**
Total		**Grand Total**	**661**	**348**

Note: Treatment group: J = TMC207, J-Z = TMC207 + Pyrazinamide, J-Pa = TMC207 + PA-824, Pa-Z = PA-824 + Pyrazinamide, Pa-Z-M or M-PA-Z = PA-824 + Pyrazinamide + Moxifloxacin, J-Pa-Z-C = TMC207 + PA-824 + Pyrazinamide + Clofazimine, J-Pa-Z = TMC207 + PA-824 + Pyrazinamide, J-Pa-C = TMC207 + PA-824 + Clofazimine, J-Z-C = TMC207 + Pyrazinamide + Clofazimine, Z = Pyrazinamide, C = Clofazimine, Rifafour = Rifafour e-275®. CFU: Colony forming unit; MDR: Multi-drug resistant. N = Total number of patients. n = Number of patients with complete profiles and no censored log(CFU) counts.

Detailed summaries of the objectives and study design of clinical trial protocols CL001, CL007, CL010 and NC001 are provided in the literature review of Chapter 1; the corresponding information for protocols NC002 and NC003 is provided below:

NC002 Trial (Dawson et al., 2015)

Objectives

Dawson et al. (2015) investigated the safety and bactericidal activity of 8-week combination therapy of moxifloxacin, PA-824 and pyrazinamide in 207 patients with either drug-sensitive TB or MDR-TB . Bactericidal activity was characterized by the evaluation of CFU count and TTP.

Study Design

Drug-sensitive TB patients were randomized to receive either 8-week combination therapy of moxifloxacin, PA-824 (100 mg) and pyrazinamide (60 patients),

moxifloxacin, PA-824 (200 mg) and pyrazinamide (62 patients), or Rifafour e-275 (59 patients), whereas MDR-TB patients were assigned to receive 8-week combination therapy of moxifloxacin, PA-824 (200 mg) and pyrazinamide (26 patients).

A subset of patients from each treatment group was included in a 14-day EBA sub-study where sputum sampling was performed more frequently.

Two 16-hour overnight sputum samples were collected pre-treatment and were used for the calculation of CFU count at Day 0. In addition, overnight sputum samples were collected on Day 3, Day 7 and Day 14, Day 21, Day 28, Day 35, Day 42, Day 49 and Day 56. Overnight sputum samples for patients in the EBA sub-study were in addition collected daily from Day 0 up to Day 3, and every second day from Day 5 up to Day 14.

NC003 Trial (Diacon et al., 2015)

Objectives

Diacon et al. (2015) report a TB trial whose objectives included the evaluation of the safety, tolerability, PK and EBA of 14-day combination therapy of pyrazinamide, clofazimine, PA-824 and TMC207 in 105 previously untreated TB patients. EBA was characterized by the evaluation of CFU count and TTP.

Study Design

Patients were randomized to receive either daily doses of combination therapy of TMC207, PA-824, pyrazinamide and clofazimine (15 patients), TMC207, PA-824 and pyrazinamide (15 patients), TMC207, pyrazinamide and clofazimine (15 patients), TMC207, pyrazinamide and clofazimine (15 patients), monotherapy of clofazimine (15 patients), and pyrazinamide (15 patients), or Rifafour e-275® (15 patients) (control group) for 14 days.

Two 16-hour overnight sputum samples were collected pre-treatment and were used for the calculation of CFU count at Day 0. In addition, overnight sputum samples were collected daily from Day 1 up to Day 14.

4.2.3 Results and Findings

The model in Equation (2.39) was fitted to the log(CFU) versus time profiles of all patients with complete profiles, separately by patient, using the SAS® procedure NLMIXED (Version 9.2), assuming *i.i.d.* normal residuals. Note that only patients with complete data profiles were used since the primary purpose of the empirical study was to judge the adequacy of the proposed differential hyperbolic tangent regression model specifically when fitted to 14-day CFU versus time profiles of EBA trials, and 8-week data of "SSCC" trials; naturally, when data profiles are (substantially) shorter than 14 days (EBA trials) or 8 weeks ("SSCC" trials) (e.g. due to a patient dropping out of a trial early) a simple (mono-) linear model will often be adequate.

Plots of the data, together with by-patient fits of the hyperbolic tangent regression model, are included in Figure C.1 through Figure C.36 of Appendix C. For the EBA trials, the lower and upper bounds of κ were set to $L_\kappa = 2$ and $U_\kappa = 11$, and for the "SSCC" trial, the lower and upper bounds of κ were set to $L_\kappa = 0.42$ (Day 3) and $U_\kappa = 1.57$ (Day 11). The lower and upper bounds of γ were set to $L_\gamma = 0.1$ and $U_\gamma = 2$ for each of the trials.

Figure 4.1 and Figure 4.2 provide plots and box and whisker plots of the β_2 estimates by study and treatment group.

Studying the data profiles, the following can be noted (see Table 4.2):

- Over the profile period of 14 days (EBA trials) and 8 weeks ("SSCC" trials), the log(CFU) versus time profiles seem either linear (for the minority of patients: 69 out of 348), or biphasic (for the majority of patients: 279 out of 348). For an example of a (near) linear profile, see Figure 4.3a; examples of clearly biphasic profiles are given in Figures 4.3b through Figure 4.3d.

- The rate of decline in log(CFU) count during the initial phase is greater than during the terminal phase for the majority of biphasic profiles (e.g. Figure 4.3b) (170 out of 279 patients); however, the rate of decline in log(CFU) count during the initial phase is smaller than during the terminal phase for a substantial minority of biphasic profiles (e.g. Figure 4.3c) (109 out of 279 patients).

- The transition from the first to the second phase is smooth for a minority of biphasic profiles (e.g. Figure 4.3d) (34 out of 279 patients); a bilinear regression model seems adequate for the majority of biphasic profiles (e.g. Figure 4.3b and Figure 4.3c) (245 out of 279 patients).

- For some treatment regimens, the average rate of decline in log(CFU) count during the initial phase is greater than during the terminal phase (see Figure 4.2). However, for one of the newer compounds under investigation, TMC207, and for some treatment regimens containing TMC207 in combination with other drugs, the average rate of decline in log(CFU) count during the initial phase is smaller than during the terminal phase.

- Whatever the respective *average* rates of decline in log(CFU) count for a given treatment regimen, rates of decline both during the initial and late phase exhibit appreciable inter-individual variability; for individual patients, the rate of decline in log(CFU) count during the initial phase might be smaller than during the late phase, even though the respective average rates for the treatment regimen in question might exhibit the reverse relationship.

- The timepoint (node) at which the initial rate of decline changes to the terminal rate of decline exhibits appreciable individual variability (possibly as a result of little information for the estimation of the node parameter).

Observations from the empirical study suggest the following:

- Bilinear regression models seem adequate for the log(CFU) versus time profiles of many patients, but certainly not for all, since a substantial minority of profiles exhibit a smooth transition between phases. Whatever the case may be, it is preferable to fit a regression model that allows for a smooth transition between

phases, thereby allowing one to judge the adequacy of the bilinear regression model.

- Bilinear regression models need to accommodate individual variation in the node, and should estimate the node parameter from the data, rather than determining it through visual inspection.
- Bi-exponential regression models are not adequate for treatments (and individual profiles) which are associated with terminal rates of decline that are faster than initial rates of decline.
- The log(CFU) versus time profiles suggest that the residual variance is constant over the range of fitted values, i.e. the logarithm is effective as variance stabilizing transformation.

On the whole, a visual inspection of the model fits suggests that the proposed regression model, i.e. the differential hyperbolic tangent regression model, generally fits the CFU data well.

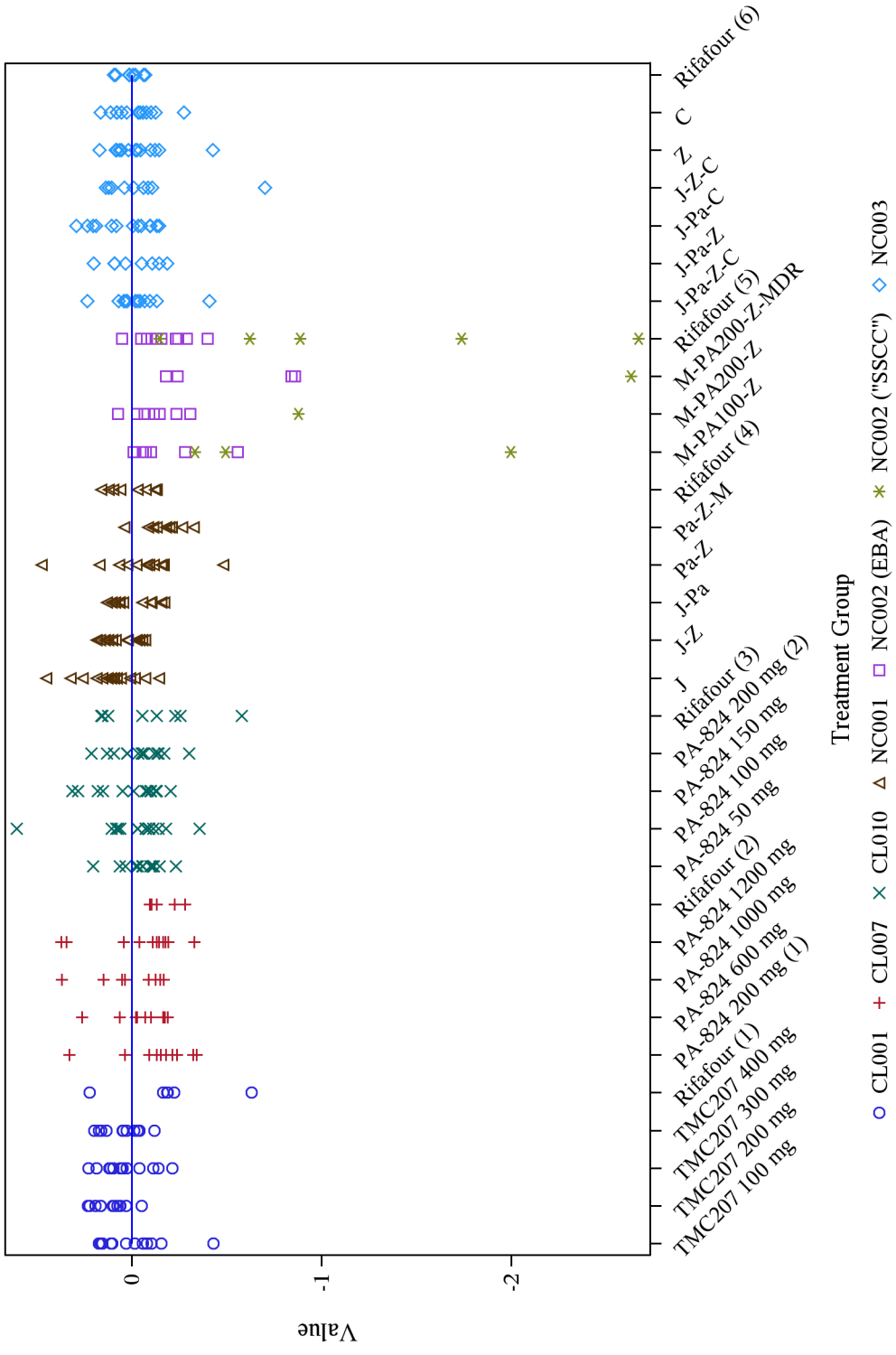
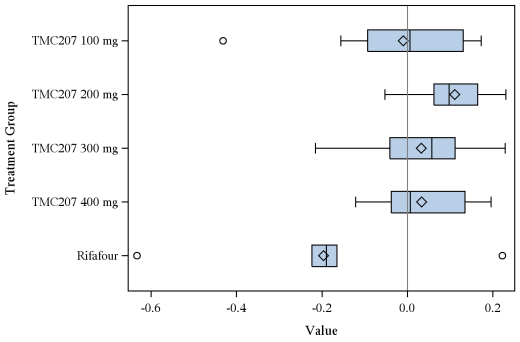
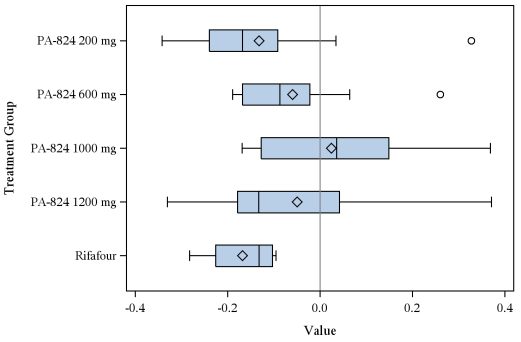


Figure 4.1: By-Patient Estimates of β_2 for Empirical Study

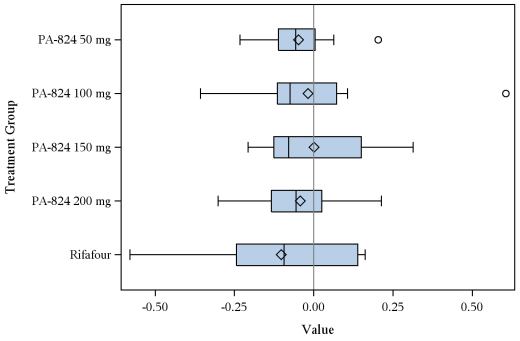
Figure 4.2: Summary of By-Patient Estimates of β_2 for Empirical Study



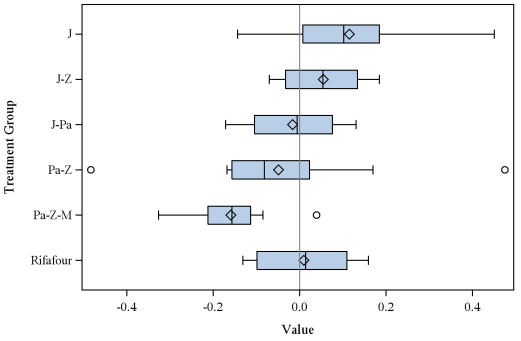
(a) CL001



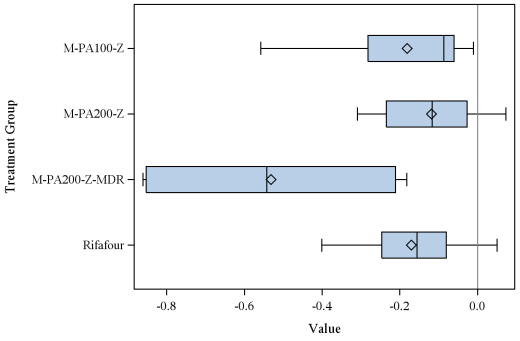
(b) CL007



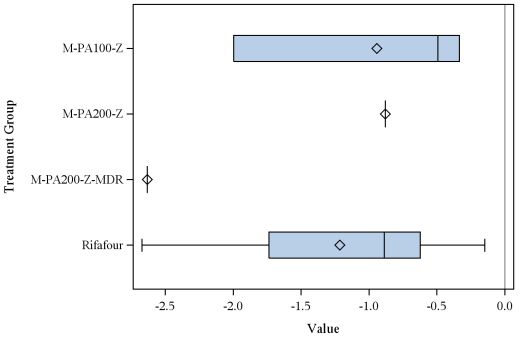
(c) CL010



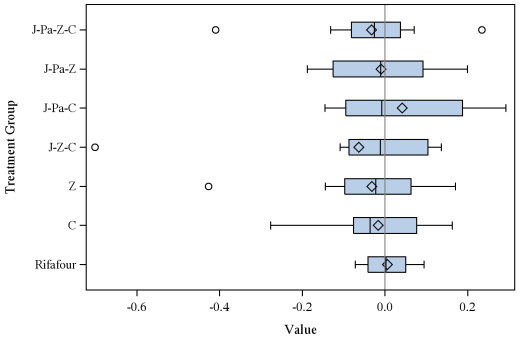
(d) NC001



(e) NC002 (EBA)



(f) NC002 ("SSCC")



(g) NC003

Table 4.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	κ	λ_1	λ_2	n_L	n_B	n_{BFS}	n_{BSF}	n_{BI}	n_{BM}
CL001	TMC207 100 mg	12	5.8 (2.0-11.0)	0.082 (-0.276-0.782)	0.062 (-0.093-0.303)	2	10	5	5	9	1
	TMC207 200 mg	13	6.6 (2.0-10.8)	-0.054 (-0.385-0.099)	0.167 (-0.006-0.497)	1	12	1	11	11	1
	TMC207 300 mg	13	6.3 (2.0-11.0)	0.058 (-0.070-0.446)	0.122 (-0.158-0.388)	3	10	3	7	9	1
	TMC207 400 mg	14	6.8 (2.0-11.0)	0.074 (-0.280-0.289)	0.141 (-0.066-0.463)	9	5	1	4	5	0
	Rifafour	6	3.8 (2.0-11.0)	0.283 (-0.278-0.534)	-0.110 (-0.957-0.167)	0	6	5	1	5	1
	Total	58	6.1 (2.0-11.0)	0.065 (-0.385-0.782)	0.100 (-0.957-0.497)	15	43	15	28	39	4
CL007	PA-824 200 mg	10	6.2 (2.0-11.0)	0.227 (-0.522-0.687)	-0.037 (-0.413-0.133)	1	9	8	1	8	1
	PA-824 600 mg	10	8.3 (2.5-11.0)	0.121 (-0.263-0.300)	0.001 (-0.256-0.258)	2	8	6	2	7	1
	PA-824 1000 mg	9	7.6 (2.2-11.0)	0.037 (-0.571-0.353)	0.086 (-0.172-0.300)	1	8	4	4	7	1
	PA-824 1200 mg	11	7.8 (2.0-11.0)	0.119 (-0.593-0.405)	0.021 (-0.548-0.761)	2	9	7	2	7	2
	Rifafour	5	4.9 (2.0-8.1)	0.358 (0.202-0.655)	0.023 (-0.055-0.124)	0	5	5	0	5	0
	Total	45	7.2 (2.0-11.0)	0.154 (-0.593-0.687)	0.017 (-0.548-0.761)	6	39	30	9	34	5

Note: CFU: Colony forming unit. N = Total number of patients. n = Number of patients with complete profiles and no censored log(CFU) counts. n_L = Number of linearly decreasing profiles ($|\beta_2| \leq 0.05$). n_B = Number of biphasic profiles ($|\beta_2| > 0.05$). n_{BFS} = Number of biphasic profiles which initial rate of decrease is fast, followed by slower rate of decrease ($\beta_2 < -0.05$). n_{BSF} = Number of biphasic profiles which initial rate of decrease is slow, followed by a faster rate of decrease ($\beta_2 > 0.05$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of decrease ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of decrease ($\gamma \geq 1$).

Table 4.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	κ	λ_1	λ_2	n_L	n_B	n_{BFS}	n_{BSF}	n_{BI}	n_{BM}
CL010	PA-824 50 mg	12	6.1 (2.0-11.0)	0.141 (-0.040-0.525)	0.045 (-0.168-0.366)	3	9	7	2	9	0
	PA-824 100 mg	15	6.1 (2.0-11.0)	0.084 (-1.032-0.629)	0.049 (-0.131-0.244)	2	13	8	5	10	3
	PA-824 150 mg	14	6.5 (2.0-11.0)	0.022 (-0.439-0.302)	0.024 (-0.287-0.284)	2	12	8	4	12	0
	PA-824 200 mg	14	5.8 (2.0-10.0)	0.193 (-0.046-0.648)	0.108 (-0.022-0.419)	3	11	8	3	10	1
	Rifafour	8	6.7 (2.0-11.0)	0.370 (0.060-1.144)	0.166 (-0.033-0.397)	0	8	5	3	7	1
	Total	63	6.2 (2.0-11.0)	0.141 (-1.032-1.144)	0.070 (-0.287-0.419)	10	53	36	17	48	5
NC001	J	14	6.9 (2.2-11.0)	-0.014 (-0.433-0.188)	0.216 (-0.099-0.718)	2	12	2	10	10	2
	J-Z	12	5.8 (2.0-11.0)	0.046 (-0.227-0.280)	0.156 (0.042-0.322)	4	8	2	6	7	1
	J-Pa	12	6.3 (2.0-11.0)	0.081 (-0.151-0.321)	0.049 (-0.176-0.155)	1	11	6	5	10	1
	Pa-Z	13	8.0 (2.0-11.0)	0.189 (-0.663-1.122)	0.091 (-0.131-0.451)	2	11	8	3	10	1
	Pa-Z-M	10	5.7 (2.0-11.0)	0.378 (0.080-0.721)	0.060 (-0.229-0.194)	1	9	9	0	7	2
	Rifafour	8	7.3 (2.0-11.0)	0.161 (0.025-0.273)	0.179 (-0.041-0.475)	1	7	3	4	6	1
	Total	69	6.7 (2.0-11.0)	0.128 (-0.663-1.122)	0.126 (-0.229-0.718)	11	58	30	28	50	8

Note: CFU: Colony forming unit. N = Total number of patients. n = Number of patients with complete profiles and no censored log(CFU) counts. n_L = Number of linearly decreasing profiles ($|\beta_2| \leq 0.05$). n_B = Number of biphasic profiles ($|\beta_2| > 0.05$). n_{BFS} = Number of biphasic profiles which initial rate of decrease is fast, followed by slower rate of decrease ($\beta_2 < -0.05$). n_{BSF} = Number of biphasic profiles which initial rate of decrease is slow, followed by a faster rate of decrease ($\beta_2 > 0.05$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of decrease ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of decrease ($\gamma \geq 1$).

Table 4.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	$\boldsymbol{\kappa}$	$\boldsymbol{\lambda_1}$	$\boldsymbol{\lambda_2}$	$\mathbf{n_L}$	$\mathbf{n_B}$	$\mathbf{n_{BFS}}$	$\mathbf{n_{BSF}}$	$\mathbf{n_{BI}}$	$\mathbf{n_{BM}}$
NC002 (EBA)	M-PA100-Z	6	5.8 (2.0-9.1)	0.454 (0.099-1.183)	0.092 (-0.016-0.206)	1	5	5	0	4	1
	M-PA200-Z	7	4.9 (2.0-8.9)	0.298 (0.050-0.715)	0.061 (-0.045-0.196)	1	6	5	1	5	1
	M-PA200-Z-MDR	4	3.2 (2.0-5.0)	0.988 (0.432-1.602)	-0.076 (-0.269-0.068)	0	4	4	0	3	1
	Rifafour	9	6.4 (2.9-11.0)	0.325 (0.050-0.560)	-0.016 (-0.317-0.150)	1	8	8	0	7	1
	Total	26	5.4 (2.0-11.0)	0.449 (0.050-1.602)	0.020 (-0.317-0.206)	3	23	22	1	19	4
NC002 ("SSCC")	M-PA100-Z	3	6.2 (4.3-9.7)	2.223 (1.014-4.351)	0.339 (0.316-0.356)	0	3	3	0	3	0
	M-PA200-Z	1	11.0 (11.0-11.0)	1.676 (1.676-1.676)	-0.085 (-0.085–0.085)	0	1	1	0	0	1
	M-PA200-Z-MDR	1	2.9 (2.9-2.9)	5.239 (5.239-5.239)	-0.028 (-0.028–0.028)	0	1	1	0	1	0
	Rifafour	5	5.5 (2.9-11.0)	2.807 (0.685-5.662)	0.378 (0.099-0.637)	0	5	5	0	4	1
	Total	10	6.0 (2.9-11.0)	2.762 (0.685-5.662)	0.279 (-0.085-0.637)	0	10	10	0	8	2

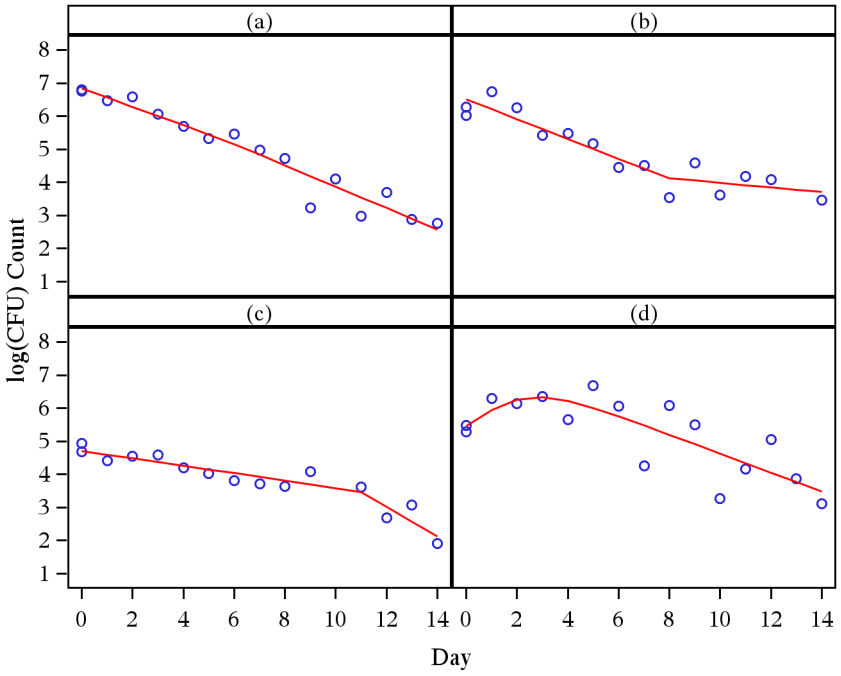
Note: CFU: Colony forming unit. N = Total number of patients. n = Number of patients with complete profiles and no censored log(CFU) counts. n_L = Number of linearly decreasing profiles ($|\beta_2| \leq 0.05$). n_B = Number of biphasic profiles ($|\beta_2| > 0.05$). n_{BFS} = Number of biphasic profiles which initial rate of decrease is fast, followed by slower rate of decrease ($\beta_2 < -0.05$). n_{BSF} = Number of biphasic profiles which initial rate of decrease is slow, followed by a faster rate of decrease ($\beta_2 > 0.05$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of decrease ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of decrease ($\gamma \geq 1$).

Table 4.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	$\boldsymbol{\kappa}$	$\boldsymbol{\lambda_1}$	$\boldsymbol{\lambda_2}$	$\mathbf{n_L}$	$\mathbf{n_B}$	$\mathbf{n_{BFS}}$	$\mathbf{n_{BSF}}$	$\mathbf{n_{BI}}$	$\mathbf{n_{BM}}$
NC003	J-Pa-Z-C	12	8.0 (3.0-11.0)	0.144 (-0.001-0.382)	0.079 (-0.505-0.468)	6	6	4	2	5	1
	J-Pa-Z	8	7.0 (3.0-11.0)	0.134 (-0.085-0.292)	0.114 (-0.151-0.462)	1	7	4	3	7	0
	J-Pa-C	13	6.1 (2.0-10.1)	0.040 (-0.508-0.263)	0.122 (-0.068-0.676)	3	10	4	6	8	2
	J-Z-C	9	5.8 (2.0-8.9)	0.166 (-0.237-1.228)	0.040 (-0.174-0.251)	2	7	4	3	6	1
	Z	14	6.2 (2.0-11.0)	0.093 (-0.232-0.807)	0.030 (-0.241-0.225)	5	9	4	5	7	2
	C	13	6.3 (2.0-11.0)	-0.027 (-0.376-0.186)	-0.059 (-0.410-0.112)	3	10	5	5	10	0
	Rifafour	8	7.4 (2.0-11.0)	0.096 (-0.027-0.196)	0.107 (0.010-0.251)	4	4	2	2	4	0
	Total	77	6.6 (2.0-11.0)	0.085 (-0.508-1.228)	0.056 (-0.505-0.676)	24	53	27	26	47	6
Total	Total	348	6.4 (2.0-11.0)	0.213 (-1.032-5.662)	0.079 (-0.957-0.761)	69	279	170	109	245	34

Note: CFU: Colony forming unit. N = Total number of patients. n = Number of patients with complete profiles and no censored log(CFU) counts. n_L = Number of linearly decreasing profiles ($|\beta_2| \leq 0.05$). n_B = Number of biphasic profiles ($|\beta_2| > 0.05$). n_{BFS} = Number of biphasic profiles which initial rate of decrease is fast, followed by slower rate of decrease ($\beta_2 < -0.05$). n_{BSF} = Number of biphasic profiles which initial rate of decrease is slow, followed by a faster rate of decrease ($\beta_2 > 0.05$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of decrease ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of decrease ($\gamma \geq 1$).

Figure 4.3: Fitted log(CFU) Count for Empirical Study



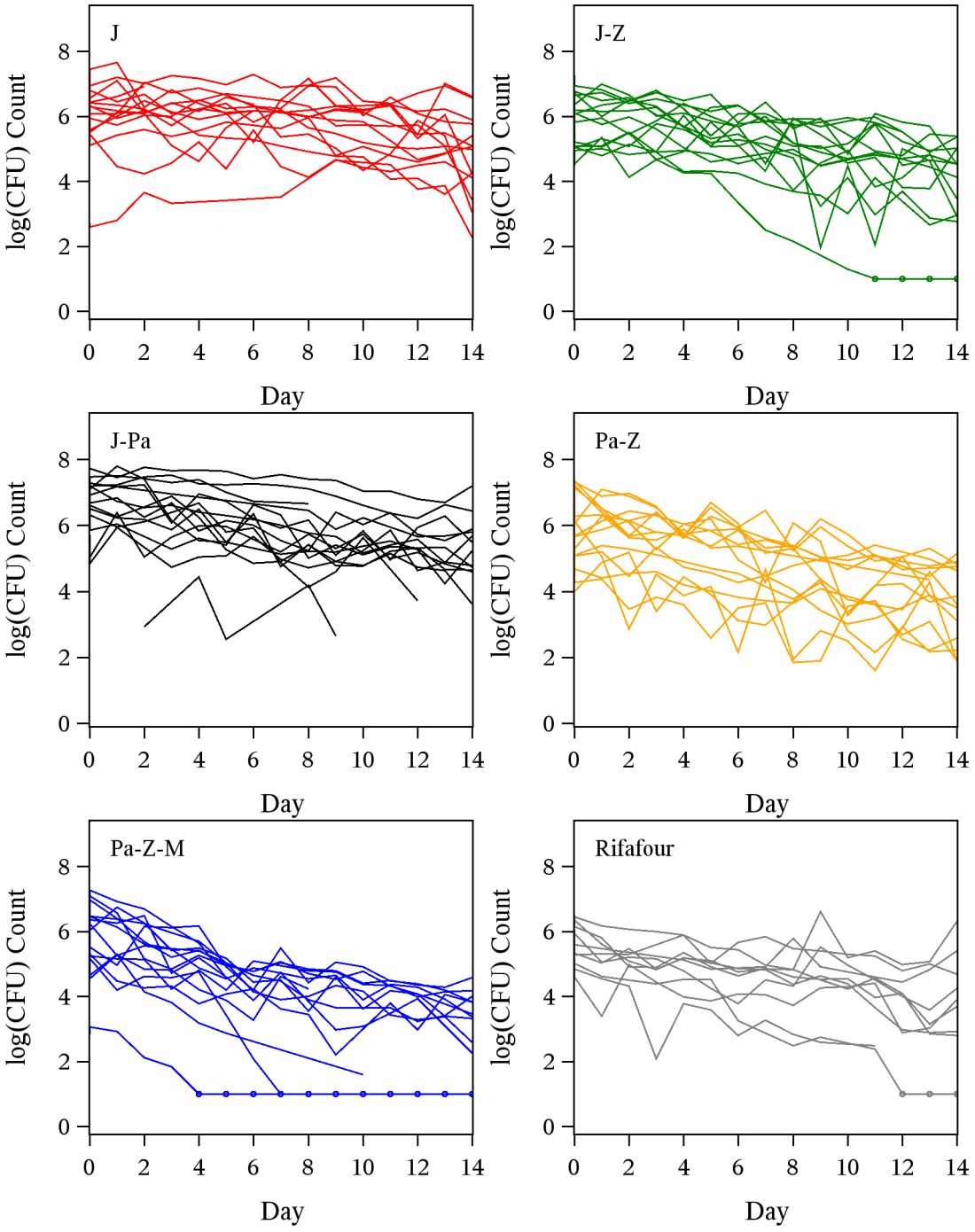
4.3 NC001 Trial

This section provides the results of a reanalysis of CFU data of the NC001 trial (Diacon et al., 2012a) (see Table 4.1) using the models discussed in the previous chapter (Chapter 3).

Results from the fit of the following mixed effects regression models are presented: Model 1.1 (Page 127), Model 1.2 (Page 151), Model 1.3 (Page 151), Model 1.4 (Page 152), Model 1.5 (Page 153), Model 1.6 (Page 154), Model 1.7 (Page 154), Model 1.8 (Page 155), Model 1.9 (Page 156), Model 2.1 (Page 158), Model 2.2 (Page 158), Model 3.1 (Page 159) and Model 3.2 (Page 159).

Figure 4.4 shows nested plots of the observed log(CFU) counts by treatment group.

Figure 4.4: Observed log(CFU) Counts Over Time



4.3.1 Differential Hyperbolic Tangent Regression Model

Results from the by-patient and joint Bayesian NLME fit of the differential hyperbolic tangent regression model (see Section 3.3 and Section 3.4.1, respectively) are provided in the subsections below.

Model 1.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Results from the primary model (Model 1.1) (see Page 77) and the by-patient analysis (see Equation (2.39) and Section 3.3) are discussed here in detail.

4.3.1.1 Markov Chain Monte Carlo Iteration Diagnostics

For the joint Bayesian NLME analysis, a total of 25 000 samples via two independent MCMC chains (12 500 each), with a 'thinning" factor of 200 iterations, were drawn from the posterior distribution of the model parameters. A simulation "burn-in" period of 400 000 iterations was used (constituting a complete total of 5 400 000 simulations). Posterior samples were checked for convergence in accordance with the diagnostics outlined in Section 3.4.1.4.

Figure 4.5 represents an iteration plot of posterior samples for $\sigma^2_{\kappa\{j=2\}}$ from two parallel MCMC chains prior to "burn-in". Here, dispersed starting values were provided for the second MCMC chain. The plot constitutes an example of two MCMC chains reaching convergence after a certain number of iterations. One can note that the efficiency of the Gibbs sampler is relatively "bad" for this particular parameter (as some degree of convergence started only after 500 iterations). The rate of convergence was relatively quick for parameters such as α_{ij}, β_{1ij} and β_{2ij}, and slower for parameters such as κ_{ij}, γ_{ij}, $\sigma^2_{\kappa j}$ and $\sigma^2_{\gamma j}$.

As an example of two MCMC chains converging, Figure 4.6 shows an iteration, autocorrelation and density plot from posterior samples for $\alpha_{\{i=1\}\{j=1\}}$ from two

parallel MCMC chains. Figure 4.7 shows iteration plots of posterior samples of randomly selected parameters from two parallel MCMC chains.

Figure 4.5: Iteration Plot of Posterior Samples of $\sigma^2_{\kappa\{j=2\}}$ from Two Parallel MCMC Chains

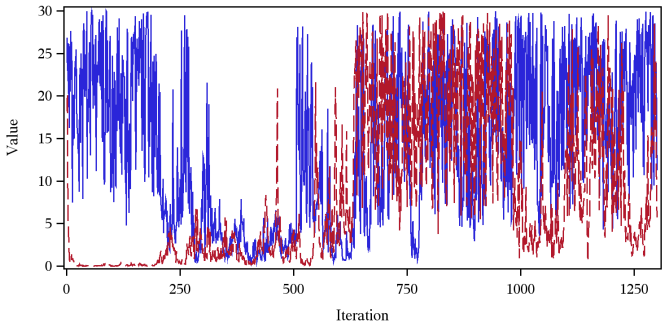


Figure 4.6: Graphical Convergence Diagnostics for Posterior Samples of $\alpha_{\{i=1\}\{j=1\}}$ from Two Parallel MCMC Chains

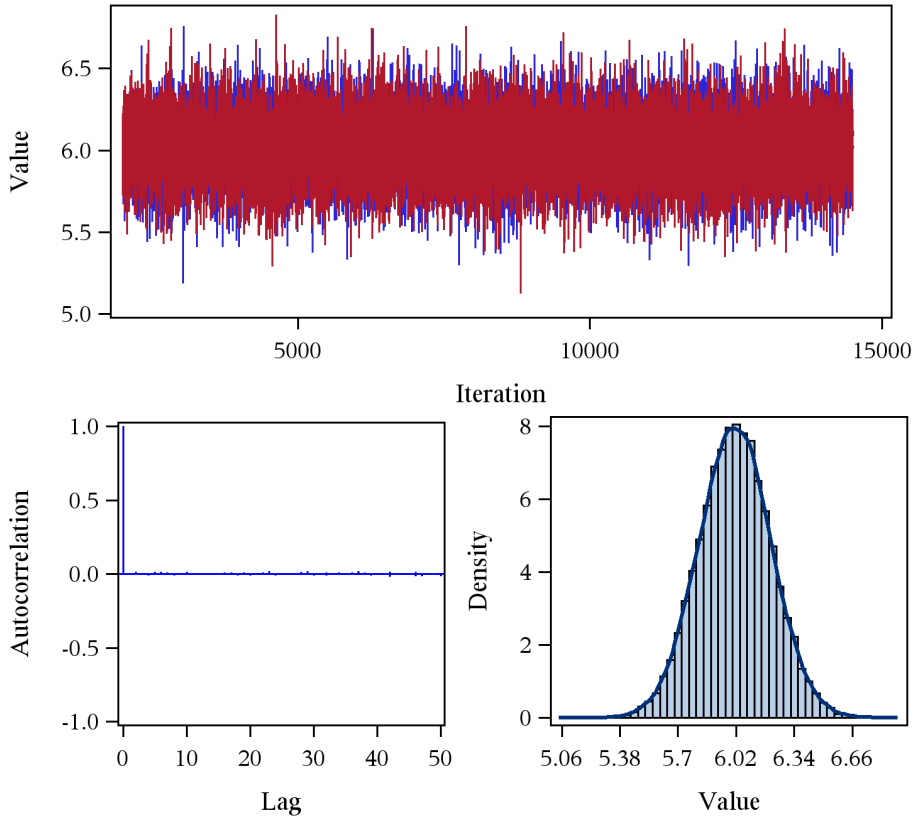
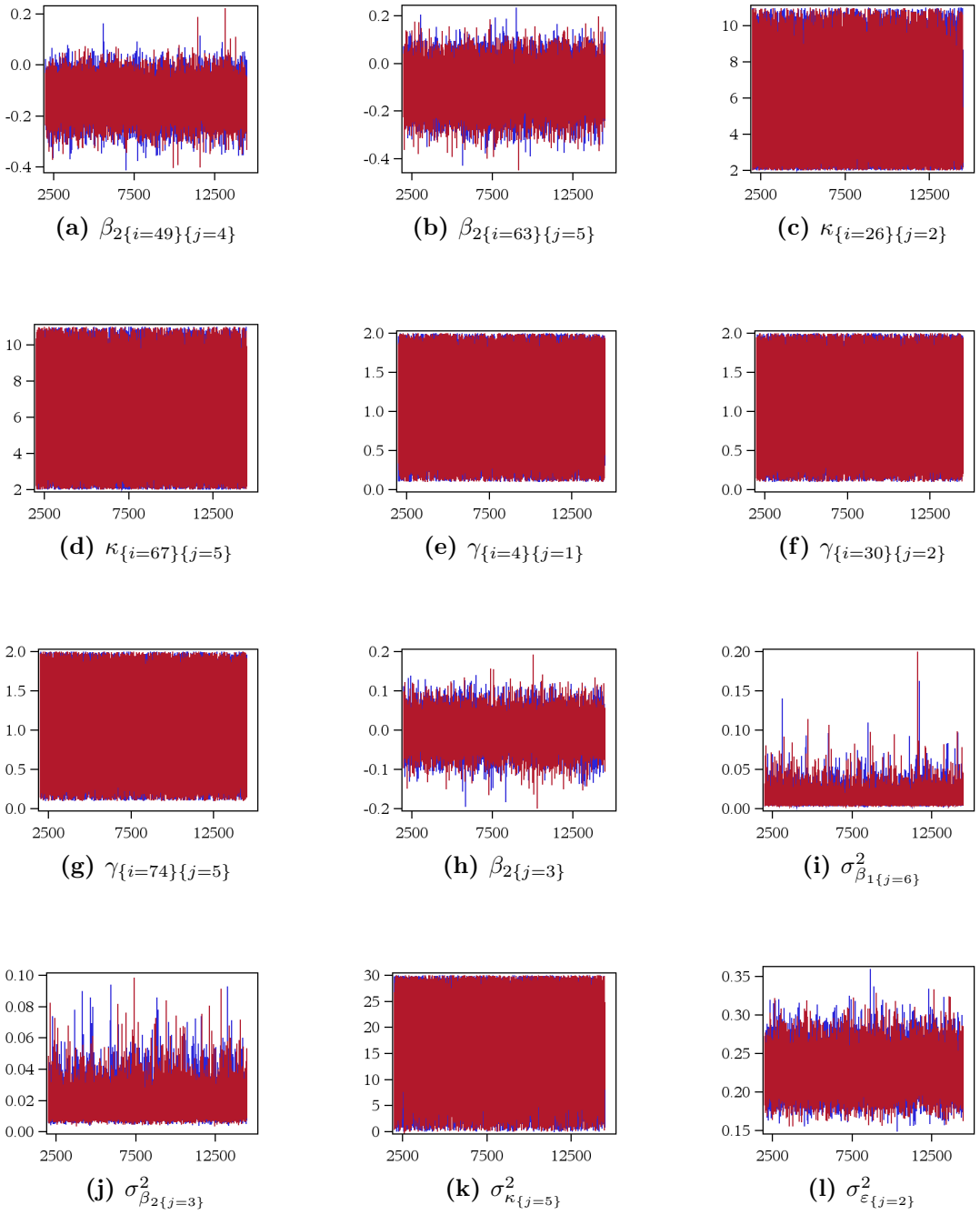


Figure 4.7: Iteration Plots of Posterior Samples of Randomly Selected Parameters from Two Parallel MCMC Chains



(a) $\beta_{2\{i=49\}\{j=4\}}$ **(b)** $\beta_{2\{i=63\}\{j=5\}}$ **(c)** $\kappa_{\{i=26\}\{j=2\}}$

(d) $\kappa_{\{i=67\}\{j=5\}}$ **(e)** $\gamma_{\{i=4\}\{j=1\}}$ **(f)** $\gamma_{\{i=30\}\{j=2\}}$

(g) $\gamma_{\{i=74\}\{j=5\}}$ **(h)** $\beta_{2\{j=3\}}$ **(i)** $\sigma^2_{\beta_{1\{j=6\}}}$

(j) $\sigma^2_{\beta_{2\{j=3\}}}$ **(k)** $\sigma^2_{\kappa_{\{j=5\}}}$ **(l)** $\sigma^2_{\varepsilon_{\{j=2\}}}$

4.3.1.2 Problematic Data Profiles

Plots of the observed log(CFU) counts together with by-patient and joint Bayesian NLME fits of the regression model are included in Figure D.1 through Figure D.6 of Appendix D for each patient. From these plots, one can note that the fit of the by-patient regression model is problematic for the following patients:

- **Patient 002060058** (Figure D.1): This patient withdrew early from the study with CFU data available only up to Day 2. Only the EBA(0–2) estimate (i.e. disregarding EBA(0–14), EBA(0–7), EBA(2–14) and EBA(7–14) estimates) is considered for the by-patient analysis.
- **Patient 002055050** (Figure D.2): The log(CFU) counts at Day 9 and Day 11 are regarded as outliers and therefore excluded from the by-patient analysis.
- **Patient 002085113** (Figure D.3): This patient's data profile is sparse, and therefore, none of the EBA estimates (i.e. EBA(0–14), EBA(0–2), EBA(0–7), EBA(2–14), EBA(7–14)) are considered for the by-patient analysis.
- **Patient 002043044** (Figure D.4): This patient withdrew early from the study with CFU data available only up to Day 3. Only the EBA(0–2) estimate (i.e. disregarding EBA(0–14), EBA(0–7), EBA(2–14) and EBA(7–14) estimates) are considered for the by-patient analysis.
- **Patient 001007003** (Figure D.5): This patient withdrew early from the study with CFU data available only up to Day 8, where log(CFU) counts at Day 7 and Day 8 are regarded as outliers (and are therefore excluded from the by-patient analysis). Valid data are thus available only up to Day 6, and only the EBA(0–2) and EBA(0–7) estimates (i.e. disregarding EBA(0–14), EBA(2–14) and EBA(7–14) estimates) are considered for the by-patient analysis.
- **Patient 001015008** (Figure D.5): This patient withdrew early from the study with CFU data available only up to Day 5. Only the EBA(0–2) estimate (i.e. disregarding EBA(0–14), EBA(0–7), EBA(2–14) and EBA(7–14) estimates) is considered for the by-patient analysis.

- **Patient 002090117** (Figure D.6): The log(CFU) counts at Day 9 and Day 14 are regarded as outliers and therefore excluded from the by-patient analysis.

Note that none of the outliers listed above were excluded from the joint Bayesian NLME analysis.

4.3.1.3 Early Bactericidal Activity

By-Patient Analysis

Descriptive statistics of $\text{EBA}(t_1 - t_2)$ calculated from the by-patient analysis (see Equation (3.5)), including p-Values from the Shapiro-Wilk normality test, are presented in Table 4.3 by treatment group. At a significance level at 5%, the Shapiro-Wilk p-Values indicate non-normality of the $\text{EBA}(t_1 - t_2)$ estimates for some of the EBA categories so that, provided that the sample sizes are small, care should be taken with the interpretation of results from the ANOVA of the $\text{EBA}(t_1 - t_2)$ estimates (by-patient analysis).

Estimates and corresponding 95% CIs for $\text{EBA}_j(t_1 - t_2)$, as calculated from the by-patient analysis (ANOVA), including pairwise comparisons versus Rifafour, are presented in Table 4.4.

Joint Bayesian Mixed Effects Analysis

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table 4.5.

Comparison Between Analyses

Estimates and corresponding 95% CIs for $\text{EBA}_j(t_1 - t_2)$, as calculated from the by-patient analysis (ANOVA), and posterior estimates and corresponding 95% BCIs for

$\text{EBA}_j(t_1-t_2)$, as calculated from the joint Bayesian NLME analysis, are shown in Figure 4.9 ($\text{EBA}_j(0-14)$), Figure 4.11 ($\text{EBA}_j(0-2)$) and Figure 4.13 ($\text{EBA}_j(2-14)$) by treatment group.

Scatter plots of estimates for $\text{EBA}(t_1-t_2)$, as calculated from the by-patient analysis, versus the corresponding posterior estimates for $\text{EBA}_{ij}(t_1-t_2)$, as calculated from the joint Bayesian NLME analysis, are shown in Figure 4.10 ($\text{EBA}_j(0-14)$), Figure 4.12 ($\text{EBA}_j(0-2)$) and Figure 4.14 ($\text{EBA}_j(2-14)$) by treatment group.

The by-patient estimates of $\text{EBA}(t_1-t_2)$, as calculated from the joint Bayesian NLME regression model, relative to the estimates calculated from the by-patient regression model, are in most cases shrunken towards their corresponding mean estimates (see data points in Figure 4.10, Figure 4.12 and Figure 4.14 which are, in particular, farthest away from the respective identity lines).

For both the by-patient and joint Bayesian NLME analysis, $\text{EBA}_j(0-14)$ was significantly different from 0 for each treatment regimen. Treatment with Pa-Z-M had the highest bactericidal activity both over the whole 14-day treatment period, and over the time intervals Day 0 to Day 2 and Day 2 to Day 14. These results can be compared to those published by Diacon et al. (2012a).

Differences between the results obtained from the by-patient and joint Bayesian NLME regression model may be due to the following reasons:

- Different model assumptions that are applied for each of the regression models. The by patient analysis assumes a normal distribution (directly) for the by-patient $\text{EBA}_{ij}(t_1-t_2)$ estimates, whereas the joint Bayesian NLME regression model assumes normal distributions for the residual fits and random effects, including non-informative prior distributions for each of the fixed effects (hence the joint Bayesian NLME regression model does not assume a distribution directly on $\text{EBA}_{ij}(t_1-t_2)$).
- As opposed to the joint Bayesian NLME regression model, the by-patient analysis disregards the variability in residual fits.
- Data for patients with sparse profiles are excluded from the by-patient analysis, but not from the joint Bayesian NLME analysis.

- The joint Bayesian NLME regression model generally provides shrunken by-patient estimates (random effects) towards the overall mean estimates (fixed effects), thus minimizing the occurrence of outliers in by-patient estimates.

As a case in point, the Pa-Z-M regimen includes two patients with zero CFU counts observed towards the end of the data profiles (see Figure D.5 of Appendix D). As a result, the by-patient EBA estimates for these patients are substantially larger than those calculated from the joint Bayesian NLME analysis (see Table 4.3). Figure 4.8 provides an illustration of the shrinkage effect associated with the joint Bayesian NLME analysis (Patient 002053049; Pa-Z-M). Moreover, the posterior estimate for $\text{EBA}_j(0-14)$ of treatment Pa-Z-M (see Table 4.5) is closer to the median of the corresponding by-patient estimates (see Table 4.3). Clearly, the joint Bayesian NLME analysis provides more realistic EBA estimates than those calculated from the by-patient analysis.

Figure 4.8: Observed and Fitted log(CFU) Count With Shrinkage Effect: By-Patient Versus Joint Bayesian NLME Analysis

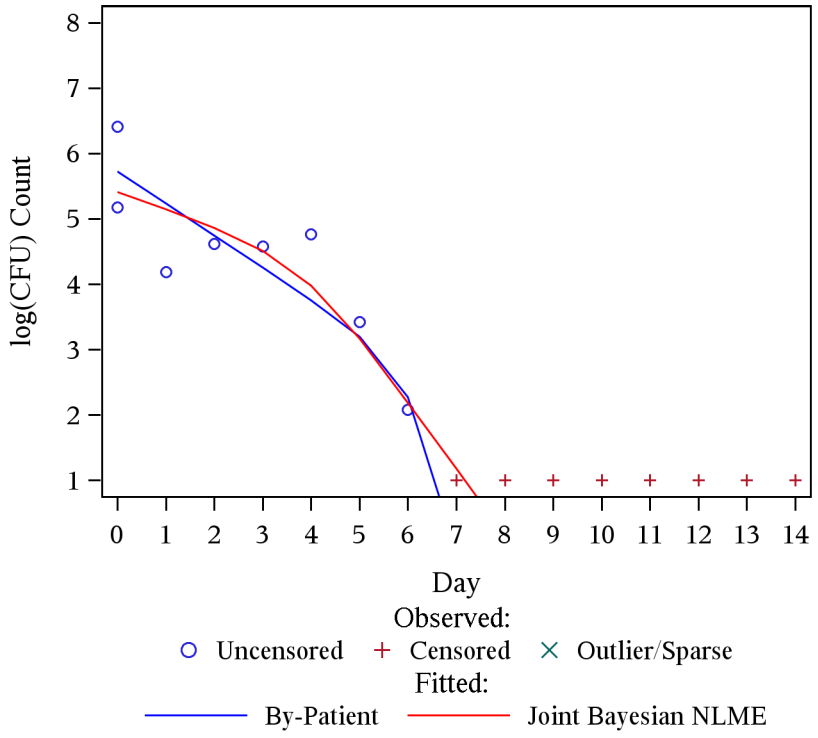


Table 4.3: Descriptive Statistics of EBA($t_1 - t_2$) Calculated from By-Patient Analysis

		Treatment Group					
Parameter	**Statistic**	**J (N=15)**	**J-Z (N=15)**	**J-Pa (N=15)**	**Pa-Z (N=15)**	**Pa-Z-M (N=15)**	**Rifafour (N=10)**
EBA(0 − 14)	n	14	15	14	14	13	10
	Mean	0.073	0.134	0.104	0.153	0.507	0.152
	SD	0.063	0.111	0.045	0.052	0.802	0.092
	Minimum	0.002	0.004	0.054	0.099	0.069	0.033
	Median	0.054	0.111	0.093	0.139	0.200	0.133
	Maximum	0.201	0.433	0.211	0.293	2.783	0.325
	p-Value	0.0671	0.0135	0.1182	0.0172	<0.0001	0.7557
EBA(0 − 2)	n	15	15	14	15	15	10
	Mean	-0.034	0.067	0.067	0.203	0.378	0.201
	SD	0.173	0.168	0.141	0.303	0.177	0.169
	Minimum	-0.433	-0.227	-0.151	-0.395	0.077	0.044
	Median	-0.010	0.108	0.033	0.193	0.393	0.165
	Maximum	0.188	0.314	0.321	1.105	0.721	0.622
	p-Value	0.2816	0.4162	0.6074	0.0018	0.9166	0.0180
EBA(0 − 7)	n	14	15	14	14	14	10
	Mean	0.016	0.115	0.112	0.187	0.337	0.149
	SD	0.097	0.108	0.097	0.110	0.183	0.082
	Minimum	-0.183	-0.064	-0.018	-0.001	0.080	0.044
	Median	0.017	0.108	0.111	0.190	0.301	0.148
	Maximum	0.168	0.287	0.320	0.431	0.830	0.311
	p-Value	0.9858	0.6840	0.3412	0.9698	0.0345	0.7581
EBA(2 − 14)	n	14	15	14	14	13	10
	Mean	0.088	0.145	0.110	0.143	0.525	0.144
	SD	0.065	0.118	0.047	0.044	0.928	0.107
	Minimum	-0.008	-0.007	0.054	0.091	0.045	0.018
	Median	0.074	0.110	0.103	0.127	0.176	0.114
	Maximum	0.215	0.486	0.241	0.231	3.165	0.360
	p-Value	0.4228	0.0036	0.0206	0.0685	<0.0001	0.3842

Note: CFU: Colony forming unit; EBA($t_1 - t_2$): Daily rate of change in log(CFU) count from Day t_1 to Day t_2; SD: Standard deviation. N = Total number of patients. n = Number of patients in each category. p-Value: Shapiro-Wilk normality test for hypothesis that values are normally distributed.

Table 4.3: Descriptive Statistics of EBA($t_1 - t_2$) Calculated from By-Patient Analysis

		Treatment Group					
Parameter	**Statistic**	**J (N=15)**	**J-Z (N=15)**	**J-Pa (N=15)**	**Pa-Z (N=15)**	**Pa-Z-M (N=15)**	**Rifafour (N=10)**
EBA(7 − 14)	n	14	15	14	14	13	10
	Mean	0.131	0.153	0.095	0.120	0.676	0.156
	SD	0.103	0.152	0.077	0.085	1.432	0.142
	Minimum	-0.099	-0.065	-0.027	-0.028	-0.071	0.010
	Median	0.162	0.129	0.098	0.128	0.157	0.103
	Maximum	0.281	0.581	0.280	0.285	4.735	0.428
	p-Value	0.3912	0.0232	0.6226	0.6585	<0.0001	0.1728

Note: CFU: Colony forming unit; EBA($t_1 - t_2$): Daily rate of change in log(CFU) count from Day t_1 to Day t_2; SD: Standard deviation. N = Total number of patients. n = Number of patients in each category. p-Value: Shapiro-Wilk normality test for hypothesis that values are normally distributed.

Table 4.4: Estimates and Corresponding 95% CIs for EBA$_j$($t_1 - t_2$) Calculated from By-Patient Analysis

					<u>Difference Versus Rifafour</u>	
Parameter	**Treatment Group**	**n**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
EBA$_j$(0 − 14)	J (N=15)	14	0.073	[0.037; 0.110]	−0.079	[-0.150; -0.007]
	J-Z (N=15)	15	0.134	[0.073; 0.195]	−0.018	[-0.103; 0.067]
	J-Pa (N=15)	14	0.104	[0.078; 0.130]	−0.048	[-0.117; 0.020]
	Pa-Z (N=15)	14	0.153	[0.123; 0.183]	0.001	[-0.069; 0.071]
	Pa-Z-M (N=15)	13	0.507	[0.022; 0.991]	0.355	[-0.133; 0.842]
	Rifafour (N=10)	10	0.152	[0.086; 0.218]		

Note: ANOVA: Analysis of variance; CFU: Colony forming unit; CI: Confidence interval; EBA($t_1 - t_2$): Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Inferential statistics: Calculated from ANOVA of individual EBA estimates from by-patient regression model fits (ANOVA allowed for different variances across treatment groups).

Table 4.4: Estimates and Corresponding 95% CIs for $\text{EBA}_j(t_1 - t_2)$ Calculated from By-Patient Analysis

	Treatment				**Difference Versus Rifafour**	
Parameter	**Group**	**n**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	−0.034	[-0.129; 0.062]	−0.234	[-0.379; -0.089]
	J-Z (N=15)	15	0.067	[-0.026; 0.160]	−0.134	[-0.278; 0.010]
	J-Pa (N=15)	14	0.067	[-0.014; 0.148]	−0.133	[-0.271; 0.004]
	Pa-Z (N=15)	15	0.203	[0.035; 0.371]	0.003	[-0.193; 0.199]
	Pa-Z-M (N=15)	15	0.378	[0.281; 0.476]	0.178	[0.031; 0.324]
	Rifafour (N=10)	10	0.201	[0.080; 0.321]		
$\mathbf{EBA_j(0-7)}$	J (N=15)	14	0.016	[-0.040; 0.072]	−0.133	[-0.209; -0.057]
	J-Z (N=15)	15	0.115	[0.055; 0.175]	−0.034	[-0.113; 0.045]
	J-Pa (N=15)	14	0.112	[0.056; 0.168]	−0.037	[-0.113; 0.040]
	Pa-Z (N=15)	14	0.187	[0.124; 0.250]	0.038	[-0.043; 0.120]
	Pa-Z-M (N=15)	14	0.337	[0.232; 0.443]	0.189	[0.073; 0.304]
	Rifafour (N=10)	10	0.149	[0.090; 0.208]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	14	0.088	[0.050; 0.126]	−0.056	[-0.138; 0.026]
	J-Z (N=15)	15	0.145	[0.080; 0.211]	0.001	[-0.094; 0.096]
	J-Pa (N=15)	14	0.110	[0.083; 0.137]	−0.034	[-0.113; 0.045]
	Pa-Z (N=15)	14	0.143	[0.117; 0.168]	−0.002	[-0.080; 0.077]
	Pa-Z-M (N=15)	13	0.525	[-0.035; 1.086]	0.381	[-0.182; 0.945]
	Rifafour (N=10)	10	0.144	[0.067; 0.221]		
$\mathbf{EBA_j(7-14)}$	J (N=15)	14	0.131	[0.072; 0.191]	−0.024	[-0.137; 0.088]
	J-Z (N=15)	15	0.153	[0.069; 0.237]	−0.002	[-0.127; 0.122]
	J-Pa (N=15)	14	0.095	[0.051; 0.140]	−0.060	[-0.167; 0.047]
	Pa-Z (N=15)	14	0.120	[0.071; 0.169]	−0.036	[-0.144; 0.072]
	Pa-Z-M (N=15)	13	0.676	[-0.189; 1.542]	0.521	[-0.347; 1.389]
	Rifafour (N=10)	10	0.156	[0.054; 0.257]		

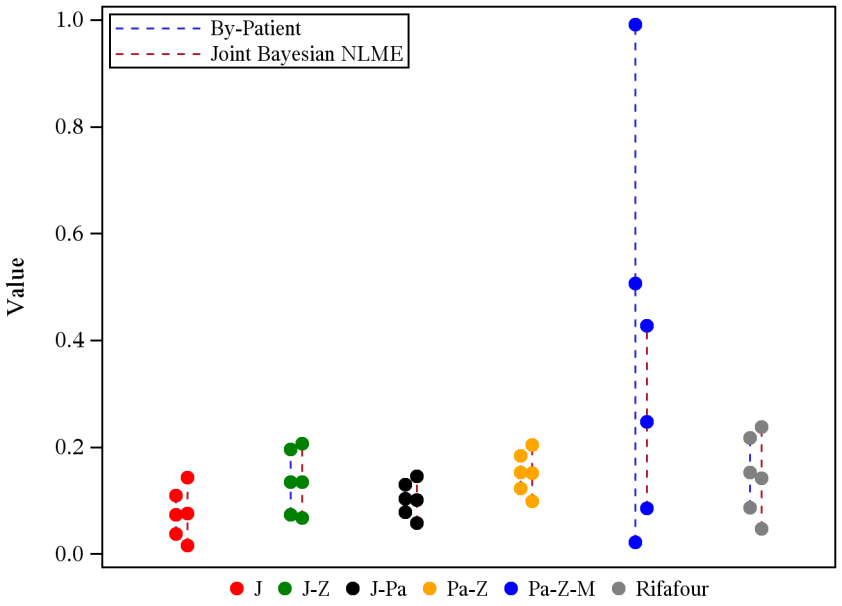
Note: ANOVA: Analysis of variance; CFU: Colony forming unit; CI: Confidence interval; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Inferential statistics: Calculated from ANOVA of individual EBA estimates from by-patient regression model fits (ANOVA allowed for different variances across treatment groups).

Table 4.5: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.076	[0.016; 0.143]	−0.066	[-0.179; 0.047]
	J-Z (N=15)	15	0.135	[0.067; 0.206]	−0.007	[-0.125; 0.110]
	J-Pa (N=15)	15	0.101	[0.057; 0.146]	−0.041	[-0.147; 0.064]
	Pa-Z (N=15)	15	0.152	[0.098; 0.204]	0.009	[-0.100; 0.116]
	Pa-Z-M (N=15)	15	**0.248**	[0.085; 0.428]	0.106	[-0.082; 0.304]
	Rifafour (N=10)	10	0.142	[0.047; 0.238]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	0.004	[-0.082; 0.089]	−0.157	[-0.332; 0.011]
	J-Z (N=15)	15	0.084	[-0.030; 0.193]	−0.076	[-0.268; 0.105]
	J-Pa (N=15)	15	0.105	[0.022; 0.187]	−0.055	[-0.229; 0.111]
	Pa-Z (N=15)	15	0.180	[0.084; 0.276]	0.019	[-0.161; 0.193]
	Pa-Z-M (N=15)	15	0.313	[0.167; 0.459]	0.153	[-0.058; 0.359]
	Rifafour (N=10)	10	0.160	[0.015; 0.314]		
$\mathbf{EBA_j(0-7)}$	J (N=15)	15	0.018	[-0.068; 0.103]	−0.129	[-0.258; 0.001]
	J-Z (N=15)	15	0.114	[0.028; 0.186]	−0.034	[-0.160; 0.090]
	J-Pa (N=15)	15	0.105	[0.033; 0.179]	−0.042	[-0.164; 0.081]
	Pa-Z (N=15)	15	0.172	[0.091; 0.259]	0.025	[-0.102; 0.157]
	Pa-Z-M (N=15)	15	0.281	[0.149; 0.420]	0.134	[-0.030; 0.306]
	Rifafour (N=10)	10	0.147	[0.046; 0.246]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.088	[0.026; 0.167]	−0.051	[-0.179; 0.081]
	J-Z (N=15)	15	0.144	[0.065; 0.229]	0.005	[-0.131; 0.142]
	J-Pa (N=15)	15	0.101	[0.054; 0.147]	−0.038	[-0.159; 0.082]
	Pa-Z (N=15)	15	0.147	[0.089; 0.201]	0.008	[-0.118; 0.131]
	Pa-Z-M (N=15)	15	0.237	[0.045; 0.450]	0.098	[-0.123; 0.331]
	Rifafour (N=10)	10	0.139	[0.027; 0.251]		
$\mathbf{EBA_j(7-14)}$	J (N=15)	15	0.134	[0.058; 0.236]	−0.003	[-0.165; 0.165]
	J-Z (N=15)	15	0.157	[0.058; 0.258]	0.020	[-0.151; 0.190]
	J-Pa (N=15)	15	0.098	[0.031; 0.166]	−0.039	[-0.195; 0.116]
	Pa-Z (N=15)	15	0.131	[0.049; 0.203]	−0.006	[-0.166; 0.151]
	Pa-Z-M (N=15)	15	0.214	[-0.025; 0.484]	0.077	[-0.202; 0.373]
	Rifafour (N=10)	10	0.137	[-0.002; 0.278]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure 4.9: Estimates and Corresponding 95% CIs for $\text{EBA}_j(0-14)$ Calculated from By-Patient and Joint Bayesian NLME Analysis



Vertical bars represent estimates (midpoint) and 95% CIs (endpoints).

Figure 4.10: Estimates for $\text{EBA}_{ij}(0-14)$ Calculated from By-Patient and Joint Bayesian NLME Analysis

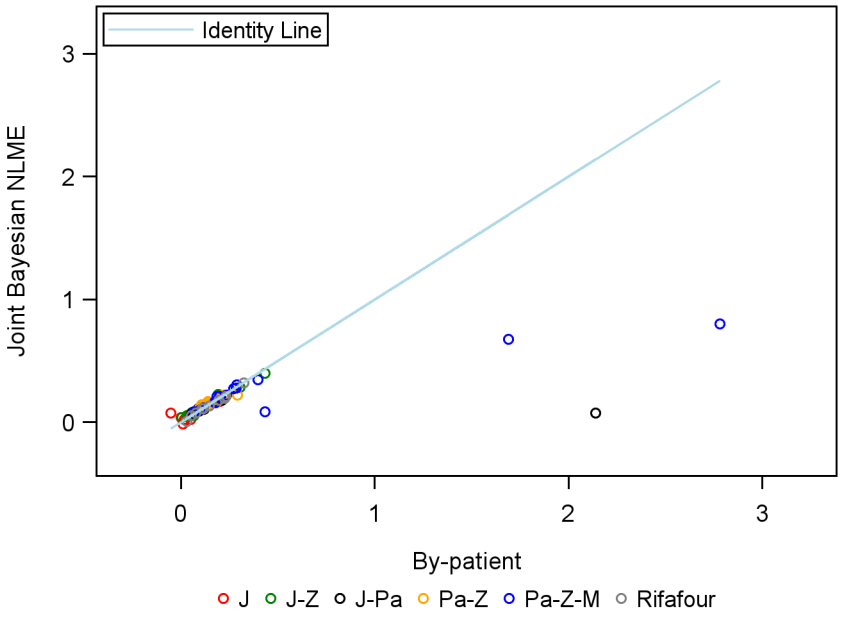
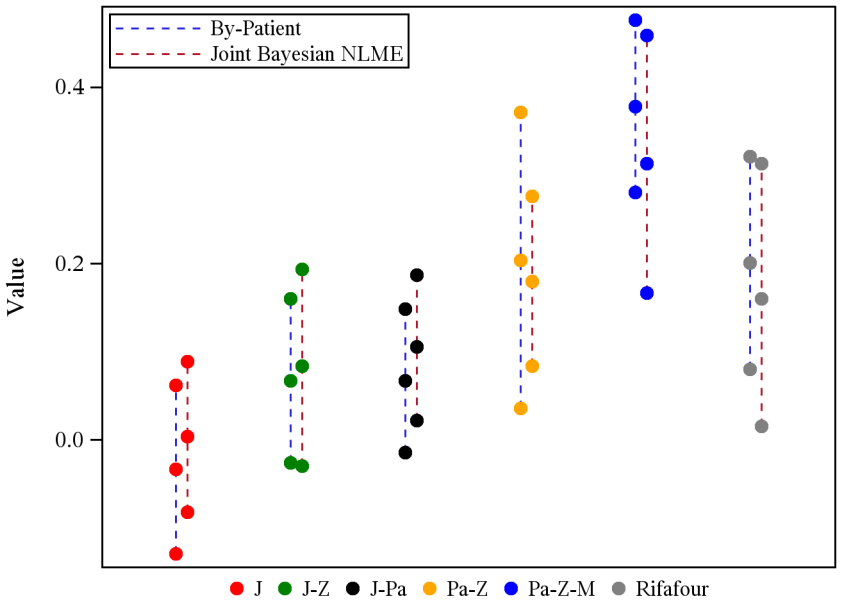


Figure 4.11: Estimates and Corresponding 95% CIs for $\text{EBA}_j(0-2)$ Calculated from By-Patient and Joint Bayesian NLME Analysis



Vertical bars represent estimates (midpoint) and 95% CIs (endpoints).

Figure 4.12: Estimates for $\text{EBA}_{ij}(0-2)$ Calculated from By-Patient and Joint Bayesian NLME Analysis

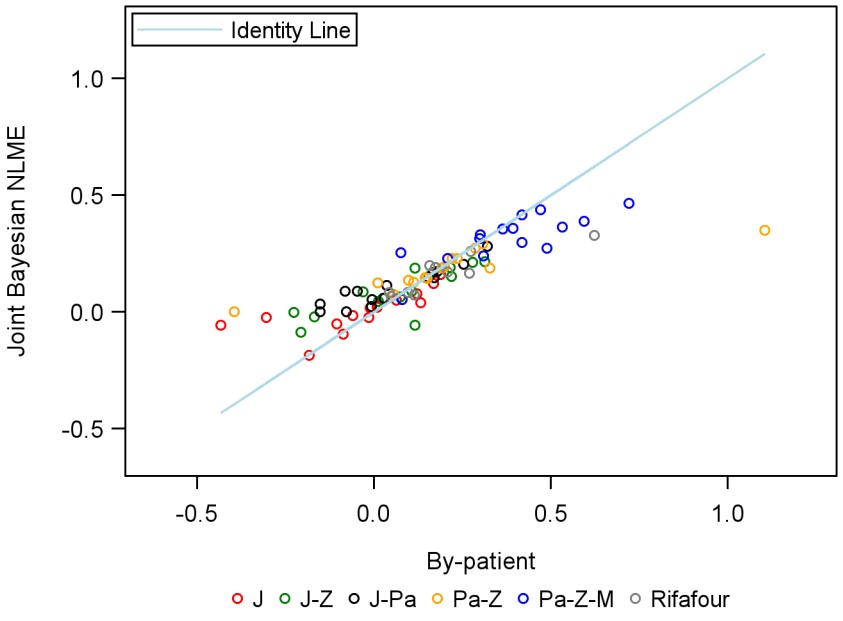
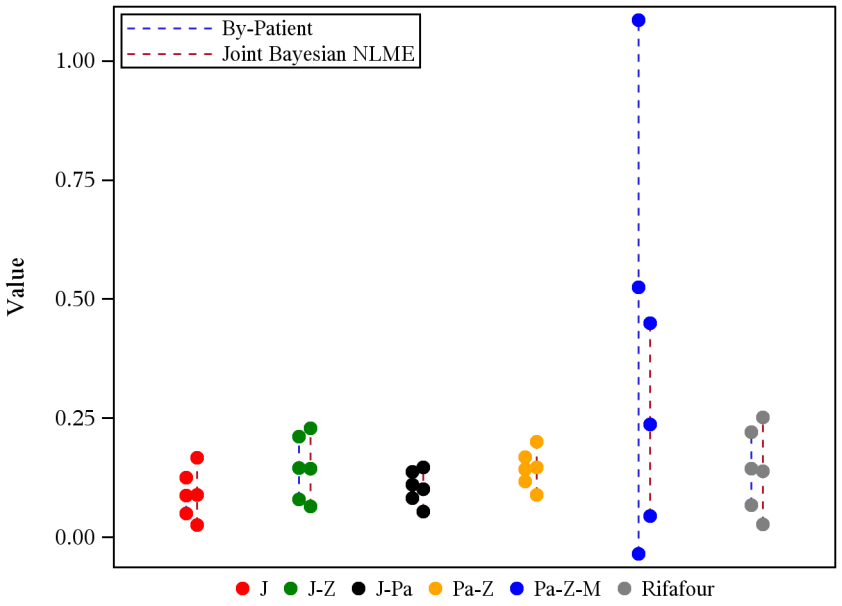
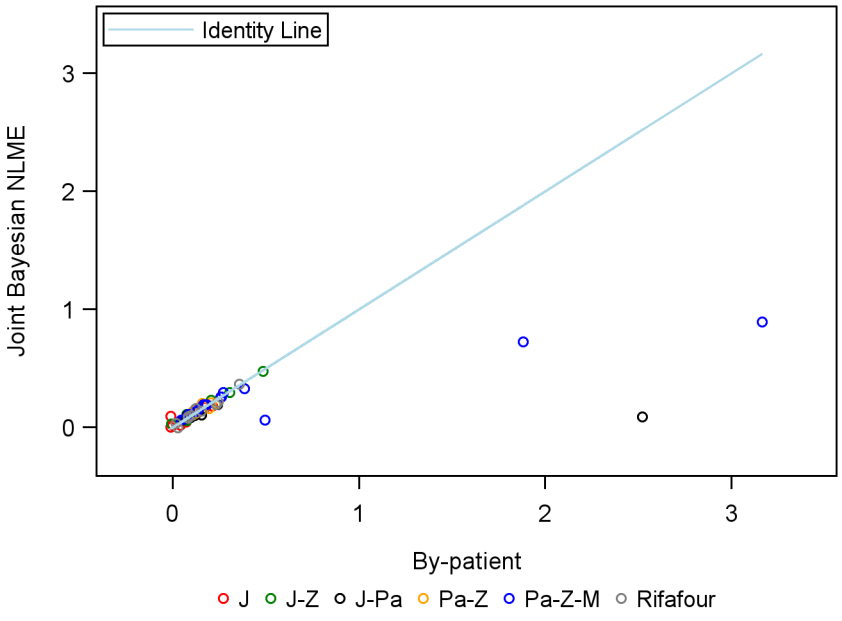


Figure 4.13: Estimates and Corresponding 95% CIs for $\text{EBA}_j(2-14)$ Calculated from By-Patient and Joint Bayesian NLME Analysis



Vertical bars represent estimates (midpoint) and 95% CIs (endpoints).

Figure 4.14: Estimates for $\text{EBA}_{ij}(2-14)$ Calculated from By-Patient and Joint Bayesian NLME Analysis



4.3.1.4 Regression Model Parameters

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table 4.6 by treatment group. The kernel posterior distributions of the mean regression model parameters are shown in Figure 4.15 by treatment group. Contour plots of the joint posterior distributions of λ_{1j} and λ_{2j} are shown in Figure 4.16 by treatment group.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are presented in Figure 4.17a by study day and treatment group.

The posterior predictive distributions of β_{2j} (i.e. β_{2fj}) are presented in Figure 4.17b by treatment group. The estimates for β_{2j} and β_{2fj} suggest that the initial rate of decrease in CFU count for some treatments containing TMC207 (i.e. J and J-Z) is slow, followed by a faster rate, and *vice versa* for the treatments not containing TMC207 (Pa-Z and Pa-Z-M and Rifafour). The decrease in mean log(CFU) count of J-Pa is effectively linear over time. The estimates for γ_j suggest that the mean log(CFU) count switches from one rate of decrease to another smoothly, although their posterior distributions are fairly uniform over the defined parameter space.

Table 4.6: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J (N=15)	15	5.980	[5.367; 6.589]
	J-Z (N=15)	15	5.939	[5.447; 6.427]
	J-Pa (N=15)	15	6.539	[5.917; 7.157]
	Pa-Z (N=15)	15	5.914	[5.354; 6.473]
	Pa-Z-M (N=15)	15	5.843	[5.123; 6.562]
	Rifafour (N=10)	10	5.493	[4.895; 6.106]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 4.6: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\beta_{1j}}$	J (N=15)	15	0.087	[0.039; 0.137]
	J-Z (N=15)	15	0.120	[0.061; 0.179]
	J-Pa (N=15)	15	0.100	[0.060; 0.141]
	Pa-Z (N=15)	15	0.149	[0.100; 0.199]
	Pa-Z-M (N=15)	15	0.261	[0.134; 0.394]
	Rifafour (N=10)	10	0.150	[0.069; 0.234]
$\boldsymbol{\lambda_{1j}}$	J (N=15)	15	0.003	[-0.084; 0.089]
	J-Z (N=15)	15	0.080	[-0.041; 0.196]
	J-Pa (N=15)	15	0.105	[0.021; 0.187]
	Pa-Z (N=15)	15	0.180	[0.083; 0.279]
	Pa-Z-M (N=15)	15	0.316	[0.161; 0.467]
	Rifafour (N=10)	10	0.162	[0.011; 0.329]
$\boldsymbol{\beta_{2j}}$	J (N=15)	15	0.084	[0.002; 0.167]
	J-Z (N=15)	15	0.040	[-0.057; 0.136]
	J-Pa (N=15)	15	−0.005	[-0.079; 0.071]
	Pa-Z (N=15)	15	−0.031	[-0.117; 0.054]
	Pa-Z-M (N=15)	15	−0.055	[-0.227; 0.131]
	Rifafour (N=10)	10	−0.012	[-0.142; 0.115]
$\boldsymbol{\beta_{2fj}}$	J (N=15)	15	0.085	[-0.215; 0.384]
	J-Z (N=15)	15	0.041	[-0.300; 0.384]
	J-Pa (N=15)	15	−0.005	[-0.266; 0.261]
	Pa-Z (N=15)	15	−0.032	[-0.334; 0.264]
	Pa-Z-M (N=15)	15	−0.057	[-0.660; 0.558]
	Rifafour (N=10)	10	−0.011	[-0.407; 0.379]
$\boldsymbol{\lambda_{2j}}$	J (N=15)	15	0.171	[0.071; 0.278]
	J-Z (N=15)	15	0.160	[0.053; 0.266]
	J-Pa (N=15)	15	0.095	[0.009; 0.183]
	Pa-Z (N=15)	15	0.118	[0.015; 0.213]
	Pa-Z-M (N=15)	15	0.206	[-0.054; 0.489]
	Rifafour (N=10)	10	0.138	[-0.009; 0.288]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 4.6: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
κ_j	J (N=15)	15	7.883	[3.008; 10.870]
	J-Z (N=15)	15	4.628	[2.066; 10.210]
	J-Pa (N=15)	15	7.574	[2.687; 10.840]
	Pa-Z (N=15)	15	7.462	[2.445; 10.850]
	Pa-Z-M (N=15)	15	4.720	[2.085; 10.050]
	Rifafour (N=10)	10	4.564	[2.068; 10.180]
γ_j	J (N=15)	15	1.048	[0.148; 1.953]
	J-Z (N=15)	15	1.098	[0.152; 1.957]
	J-Pa (N=15)	15	1.066	[0.149; 1.956]
	Pa-Z (N=15)	15	1.072	[0.152; 1.957]
	Pa-Z-M (N=15)	15	1.029	[0.144; 1.948]
	Rifafour (N=10)	10	1.066	[0.148; 1.955]

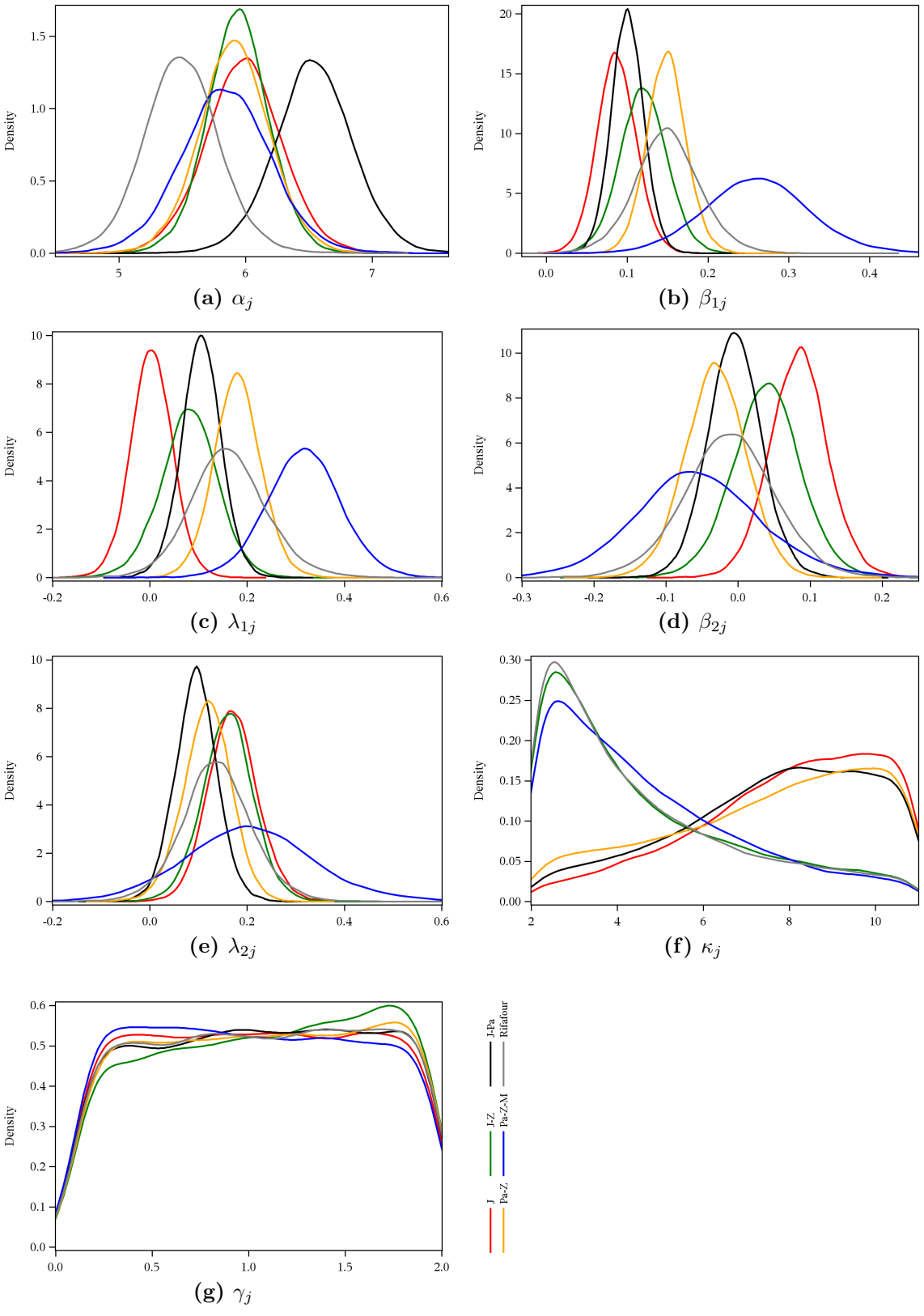
Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Posterior estimates for the variances of random effects are included in Table 4.7, and their corresponding posterior distributions are shown in Figure 4.18 ($\sigma^2_{\lambda_{1j}}$) and Figure 4.19 ($\sigma^2_{\lambda_{2j}}$) by treatment. The posterior estimates for random slope variances of Pa-Z-M ($\sigma^2_{\lambda_{1j}}$ and $\sigma^2_{\lambda_{2j}}$) are substantially larger than those compared to other treatment regimens.

Posterior estimates for the correlation coefficients between random effects are included in Table 4.8, and their corresponding kernel posterior distributions are shown in Figure 4.20 by treatment.

The estimates for $\rho_{\alpha_j\lambda_{1j}}$, $\rho_{\alpha_j\lambda_{2j}}$ and $\rho_{\lambda_{1j}\lambda_{2j}}$ suggest that random intercepts and slopes are correlated to some extent.

Figure 4.15: Posterior Distributions of Mean Regression Model Parameters



(a) α_j **(b)** β_{1j}

(c) λ_{1j} **(d)** β_{2j}

(e) λ_{2j} **(f)** κ_j

(g) γ_j

Figure 4.16: Joint Posterior Distributions of λ_{1j} and λ_{2j}

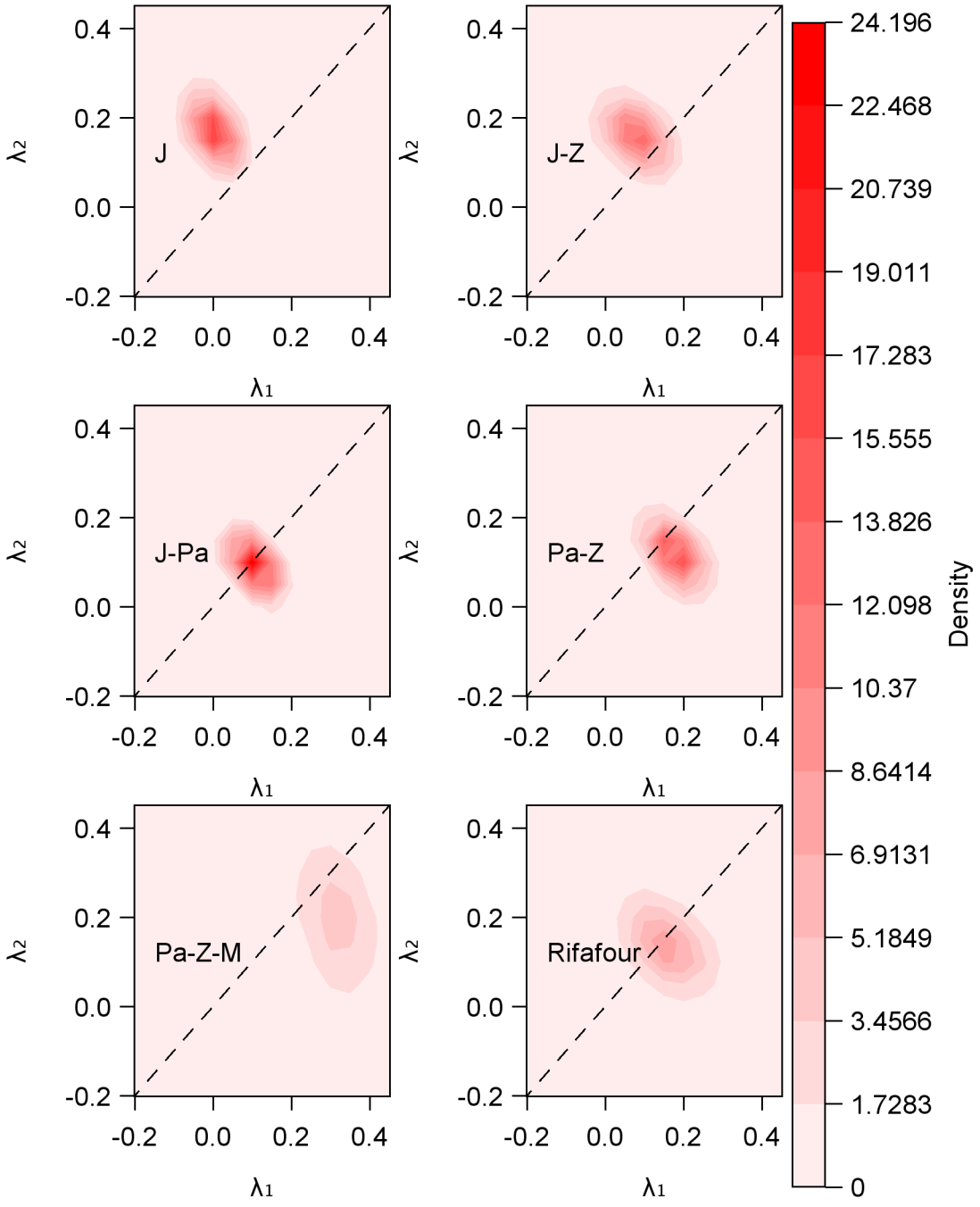
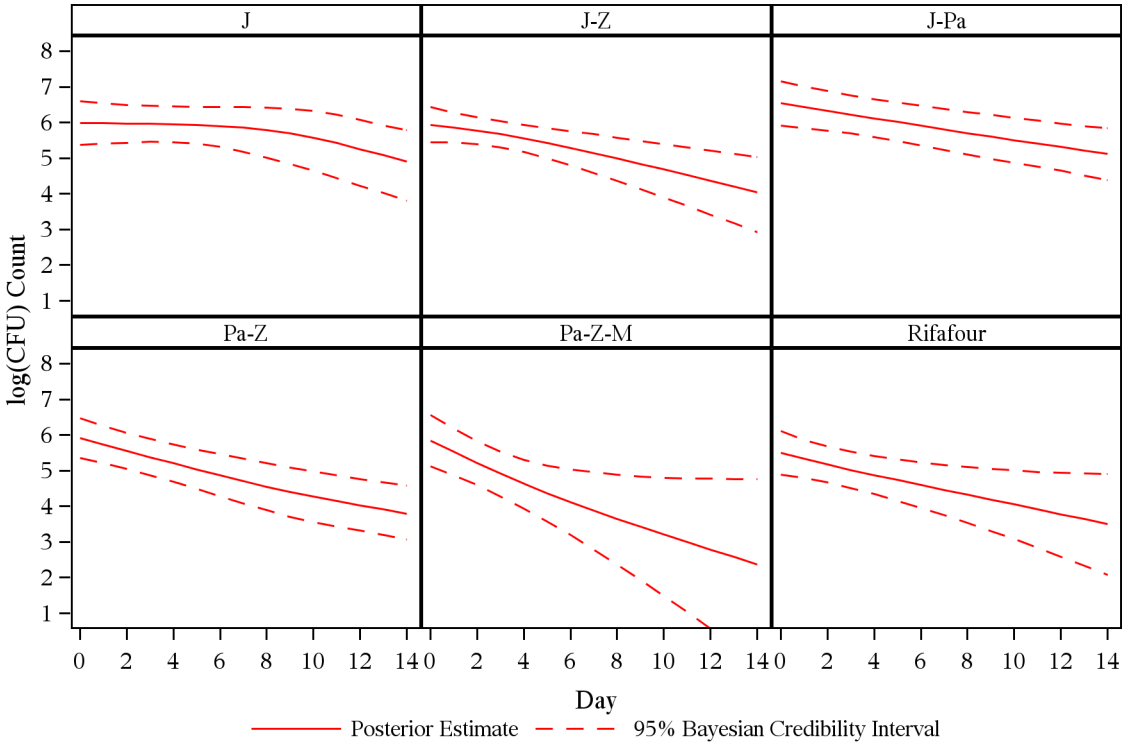
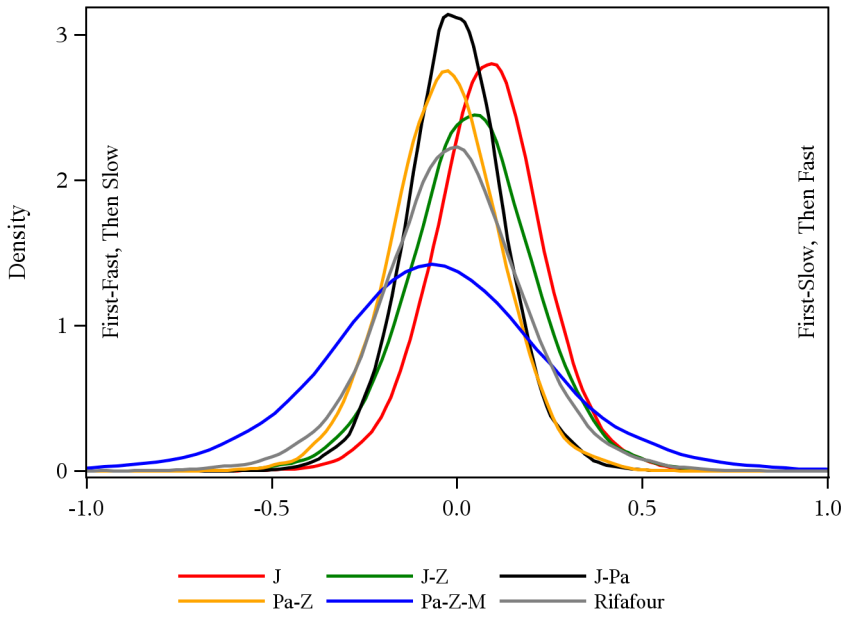


Figure 4.17: Mean log(CFU) Count and Posterior Predictive Distributions



(a) Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



(b) Posterior Predictive Distribution of β_2 (i.e. β_{2f})

Table 4.7: Posterior Estimates for Variances of Random Effects

Treatment Group	**n**	$\boldsymbol{\sigma^2_{\alpha_j}}$	$\boldsymbol{\sigma^2_{\beta_{1j}}}$	$\boldsymbol{\sigma^2_{\lambda_{1j}}}$	$\boldsymbol{\sigma^2_{\beta_{2j}}}$	$\boldsymbol{\sigma^2_{\lambda_{2j}}}$	$\boldsymbol{\sigma^2_{\kappa_j}}$	$\boldsymbol{\sigma^2_{\gamma_{1j}}}$
J (N=15)	15	1.264	0.005	0.020	0.019	0.027	17.570	2.508
J-Z (N=15)	15	0.777	0.008	0.033	0.024	0.032	14.460	2.515
J-Pa (N=15)	15	1.274	0.003	0.019	0.014	0.017	14.170	2.521
Pa-Z (N=15)	15	1.005	0.004	0.024	0.019	0.022	14.775	2.497
Pa-Z-M (N=15)	15	1.731	0.035	0.061	0.071	0.151	17.650	2.522
Rifafour (N=10)	10	0.725	0.011	0.037	0.029	0.040	12.560	2.497

Note: N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the median of the associated posterior distribution.

Table 4.8: Posterior Estimates for Correlations of Random Effects

Treatment Group	**n**	$\boldsymbol{\rho_{\alpha_j\lambda_{1j}}}$	$\boldsymbol{\rho_{\alpha_j\lambda_{2j}}}$	$\boldsymbol{\rho_{\lambda_{1j}\lambda_{2j}}}$
J (N=15)	15	0.602	-0.422	-0.603
J-Z (N=15)	15	0.702	-0.268	-0.471
J-Pa (N=15)	15	0.493	-0.255	-0.607
Pa-Z (N=15)	15	0.375	-0.044	-0.610
Pa-Z-M (N=15)	15	0.543	-0.244	-0.370
Rifafour (N=10)	10	0.544	-0.181	-0.443

Note: N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure 4.18: Posterior Distributions of $\sigma^2_{\lambda_{1j}}$

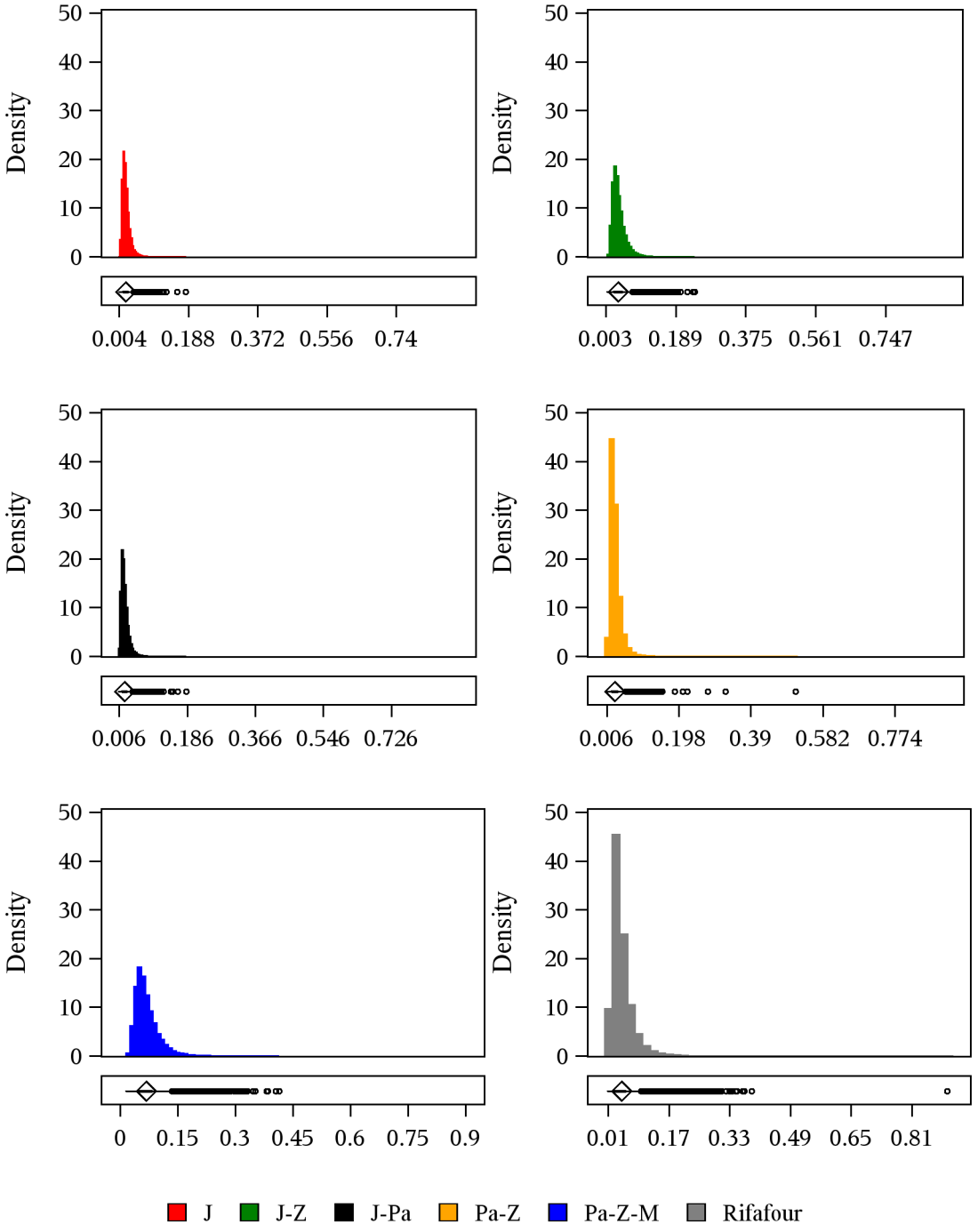


Figure 4.19: Posterior Distributions of $\sigma^2_{\lambda_{2j}}$

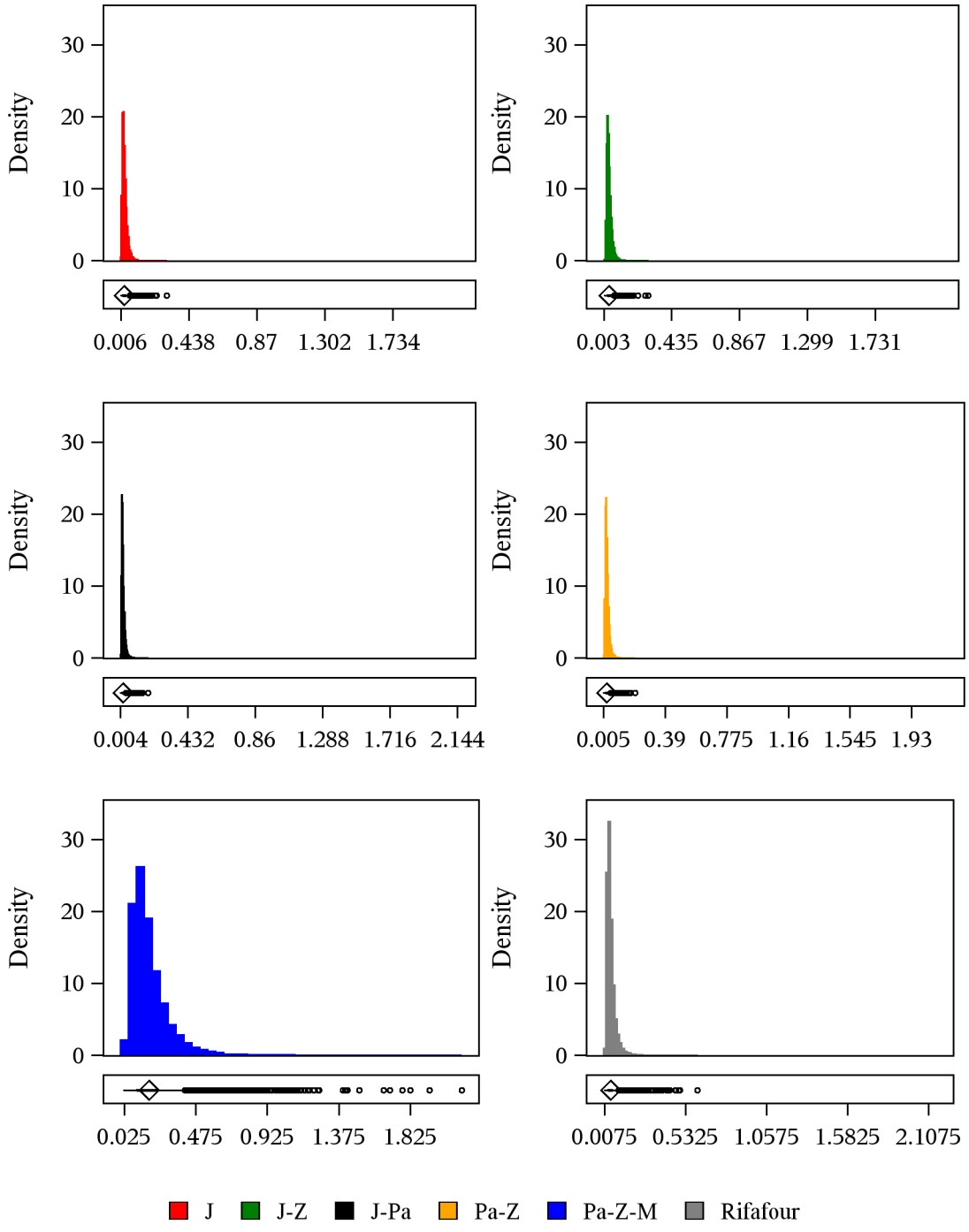
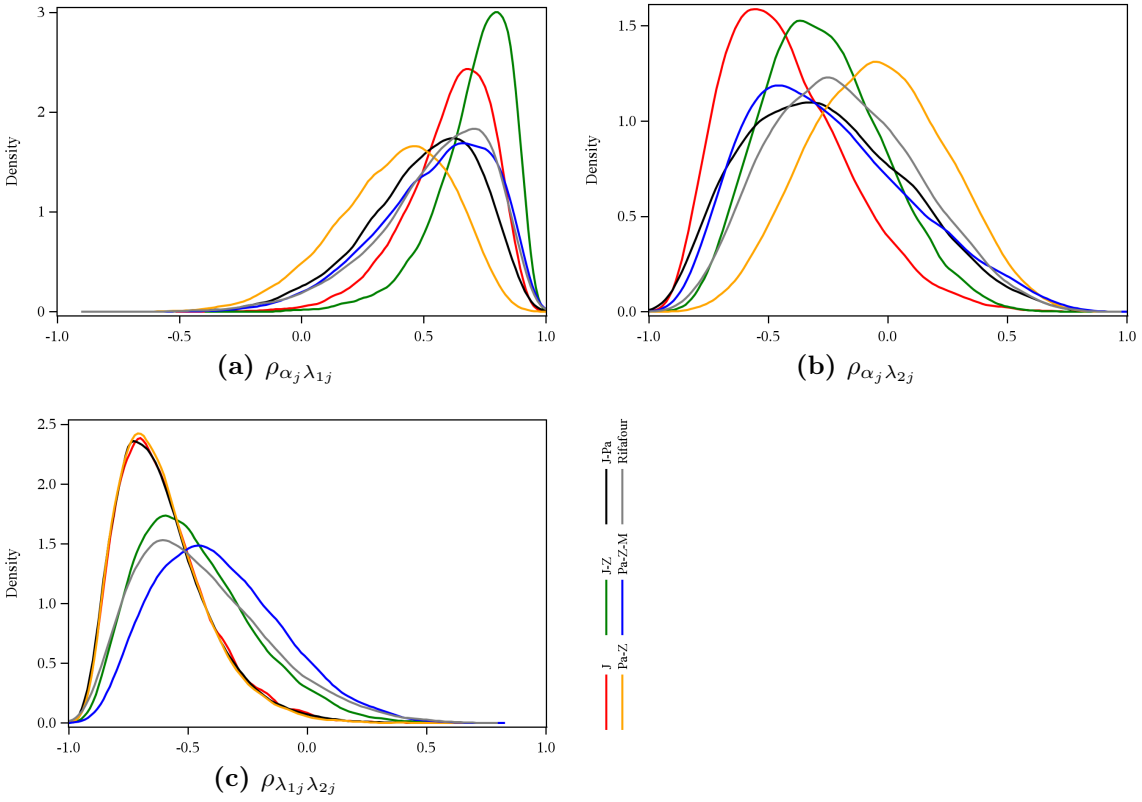


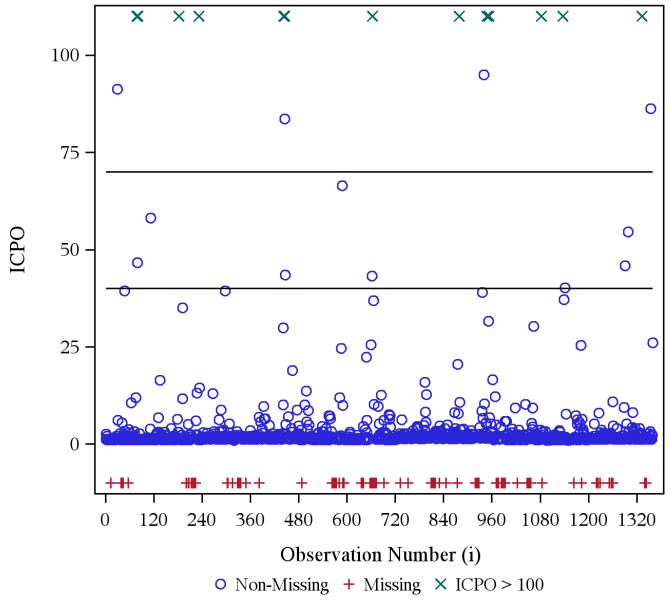
Figure 4.20: Posterior Distributions of Correlation Coefficients Between Random Effects



4.3.1.5 Conditional Posterior Ordinates

Figure 4.21 depicts the ICPO for each observed data point. The ICPOs suggest the model fits the data reasonably well.

Figure 4.21: ICPO Plot



Model 1.2: **Residuals: Normal**
Random Coefficients: Normal, Fixed Smoothness
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.1 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.1 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Model 1.3: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.2 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.2 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Model 1.4: Residuals: Skew Normal
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.3 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the skewness parameters (of residuals) are included in Table 4.9 by treatment group. The estimates for δ_j do not provide sufficient evidence that the residuals in log(CFU) count are skew distributed. Even though relatively small, the J and J-Z regimen show statistically significant negative skewness in the data (see Figure D.1 and Figure D.2, respectively).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.3 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.9: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\delta_j}$	J (N=15)	15	−0.543	[-0.745; -0.014]
	J-Z (N=15)	15	−0.738	[-0.877; -0.582]
	J-Pa (N=15)	15	0.435	[-0.411; 0.742]
	Pa-Z (N=15)	15	−0.454	[-0.888; 0.484]
	Pa-Z-M (N=15)	15	−0.560	[-0.802; 0.261]
	Rifafour (N=10)	10	−0.355	[-0.705; 0.348]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Model 1.5: Residuals: Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.4 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the degrees of freedom (of residuals) are included in Table 4.10 by treatment group. The estimates for v_j provide some indication that the distribution of residuals in log(CFU) count are heavy tailed (degrees of freedom below 30).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.4 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.10: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
v_j	J (N=15)	15	4.599	[2.115; 12.170]
	J-Z (N=15)	15	3.607	[2.157; 6.437]
	J-Pa (N=15)	15	44.480	[4.053; 96.890]
	Pa-Z (N=15)	15	18.060	[3.133; 86.110]
	Pa-Z-M (N=15)	15	47.630	[5.766; 97.180]
	Rifafour (N=10)	10	10.210	[2.238; 61.090]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Model 1.6: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.5 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.5 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Model 1.7: **Residuals: Student t**
Random Coefficients: Student t
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.6 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the degrees of freedom (of random effects) are included in Table 4.11 by treatment group. The estimates for w_j do not provide strong indication that the distributions of random intercepts and slopes are heavy tailed (degrees of freedom above 30). However, the estimate for $\text{EBA}_j(0 - 14)$ of the Pa-Z-M regimen is slightly lower than that calculated by Model 1.1. Hence that the Student t distribution is robust to the outliers related to the two data profiles which exhibit steep slopes in log(CFU) count over time (see Figure D.5).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.6 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.11: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{w_j}$	J (N=15)	15	44.580	[3.549; 97.040]
	J-Z (N=15)	15	55.460	[8.939; 97.920]
	J-Pa (N=15)	15	50.280	[5.067; 97.530]
	Pa-Z (N=15)	15	57.200	[10.220; 98.090]
	Pa-Z-M (N=15)	15	39.670	[2.539; 96.850]
	Rifafour (N=10)	10	55.130	[7.926; 97.900]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Model 1.8: **Residuals: Student t**
Random Coefficients: Skew Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.7 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the skewness parameters (of random effects) are included in Table 4.12 by treatment group. The estimates for $\boldsymbol{\delta_j} = \left(\delta_{\alpha_j}, \delta_{\beta_{1j}}, \delta_{\beta_{2j}}\right)'$ provide some evidence that the random slopes in log(CFU) count are skew distributed (see $\delta_{\beta_{1j}}$ of the Pa-Z-M regimen, taking into account the small scale on which values for β_{1j} are based (see Figure D.5)).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.7 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.12: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\delta_{\alpha_j}}$	J (N=15)	15	−1.280	[-2.446; 0.912]
	J-Z (N=15)	15	−0.105	[-1.451; 1.325]
	J-Pa (N=15)	15	−1.184	[-2.677; 1.546]
	Pa-Z (N=15)	15	−0.719	[-2.361; 1.994]
	Pa-Z-M (N=15)	15	−0.704	[-2.608; 1.567]
	Rifafour (N=10)	10	−0.069	[-1.720; 1.638]
$\boldsymbol{\delta_{\beta_{1j}}}$	J (N=15)	15	0.001	[-0.145; 0.139]
	J-Z (N=15)	15	0.029	[-0.170; 0.215]
	J-Pa (N=15)	15	0.002	[-0.098; 0.102]
	Pa-Z (N=15)	15	0.002	[-0.110; 0.116]
	Pa-Z-M (N=15)	15	0.098	[-0.263; 0.438]
	Rifafour (N=10)	10	0.010	[-0.261; 0.282]
$\boldsymbol{\delta_{\beta_{2j}}}$	J (N=15)	15	−0.001	[-0.207; 0.206]
	J-Z (N=15)	15	−0.001	[-0.202; 0.202]
	J-Pa (N=15)	15	−0.001	[-0.183; 0.183]
	Pa-Z (N=15)	15	0.003	[-0.223; 0.230]
	Pa-Z-M (N=15)	15	−0.001	[-0.339; 0.339]
	Rifafour (N=10)	10	−0.006	[-0.318; 0.306]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Model 1.9: Residuals: Skew Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.8 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the skewness parameters (of residuals) are included in Table 4.13 by treatment group. The estimates for δ_j

do not provide sufficient evidence that the residuals in log(CFU) count are skew distributed. Even though relatively small, the J-Z regimen shows statistically significant negative skewness in the data (see Figure D.2).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.8 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.13: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\delta_j}$	J (N=15)	15	−0.233	[-0.640; 0.193]
	J-Z (N=15)	15	−0.286	[-0.566; -0.001]
	J-Pa (N=15)	15	0.386	[-0.373; 0.716]
	Pa-Z (N=15)	15	−0.307	[-0.791; 0.369]
	Pa-Z-M (N=15)	15	−0.513	[-0.778; 0.243]
	Rifafour (N=10)	10	−0.153	[-0.583; 0.300]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

4.3.2 Other Regression Models

Results from the other joint Bayesian mixed effects regression models (see Section 3.4.2) are provided in the subsections below.

4.3.2.1 Linear Regression Model

Model 2.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table E.9 (Appendix E) by treatment group. The 95% BCIs of λ_{1j} (i.e. $\text{EBA}_j(t_1 - t_2)$) are narrower than those of Model 1.1 since the slopes over time are described only by a single parameter. (For this type of data, the linear regression model cannot take into account the variability between two distinct slopes over time.)

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.9 (Appendix E) by study day and treatment group.

Model 2.2: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table E.10 (Appendix E) by treatment group. These results ($\text{EBA}_j(t_1 - t_2)$ included) are similar to those of Model 2.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.10 (Appendix E) by study day and treatment group. These results are similar to those of Model 2.1.

4.3.2.2 Conventional Bilinear Regression Model

Model 3.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.11 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table E.12 (Appendix E) by treatment group. These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.11 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Model 3.2: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.13 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.12 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

4.3.3 Model Selection and Model Checking

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$ are shown in Figure 4.22 ($\text{EBA}_j(0-14)$), Figure 4.23 ($\text{EBA}_j(0-2)$) and Figure 4.24 ($\text{EBA}_j(2-14)$)

by treatment group and model. The results for each treatment group compare well across models, except for the linear models (Model 2.1 and Model 2.2) which, for some EBA characteristics and treatments, yield posterior estimates substantially different to those from other models. The linear models yield 95% BCIs substantially narrower compared to other models.

Model comparison statistics for the various Bayesian NLME regression models fitted are provided in Table 4.14.

The model comparison statistics appear to be sensitive to the choice of the hyper parameters of the Wishart prior distributions ("default" versus "frequentist"): The sensitivity of Bayes factors to the choice of priors, however, is a well known drawback of Bayes factors (Lindley, 1993).

The DIC favors conventional bilinear regression models slightly over differential hyperbolic tangent regression models, followed by linear regression models. Bayes factors (marginal likelihoods) favor linear regression models, followed by differential hyperbolic tangent and conventional bilinear regression models.

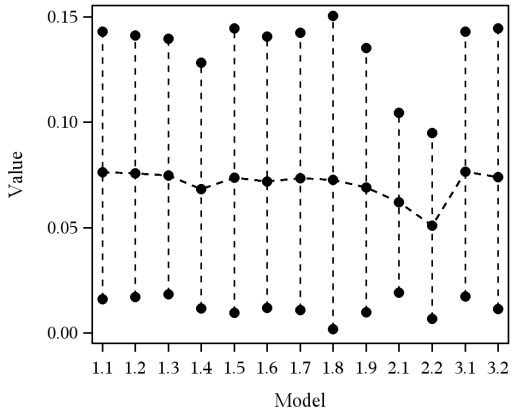
The model with "smoothness" treated as fixed effects per treatment group is favored by Bayes factors over those models which incorporate "smoothness" as random effects. The opposite applies to the DIC criterion: The DIC favors random "smoothness" over fixed "smoothness".

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals, and all the more the model with both Student t distributed residuals and random coefficients.

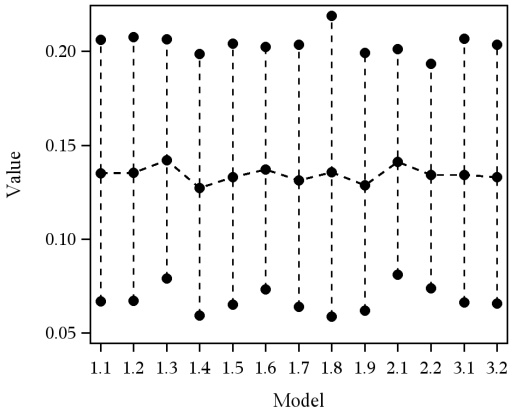
The Bayes factors indicate that building skewness into the distributions of residuals and random coefficients does not improve model fitting.

The ICPOs suggest the models fit the data reasonably well.

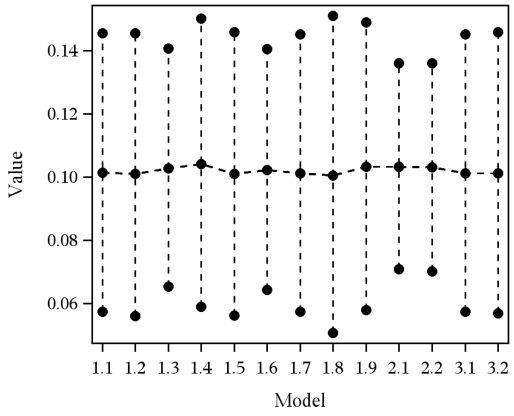
Figure 4.22: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-14)$ by Treatment Group and Model



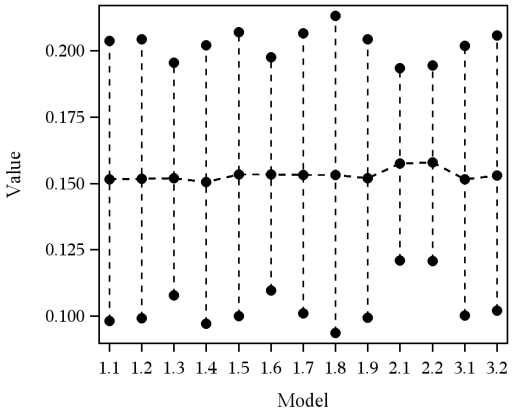
(a) J



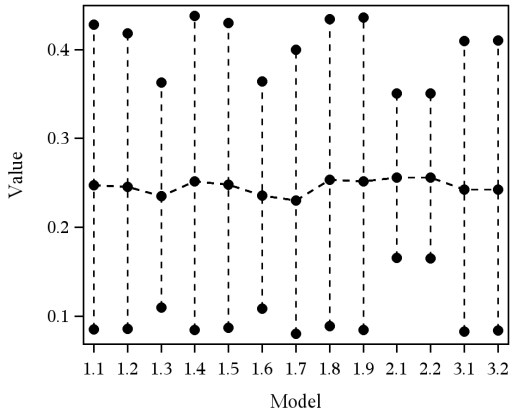
(b) J-Z



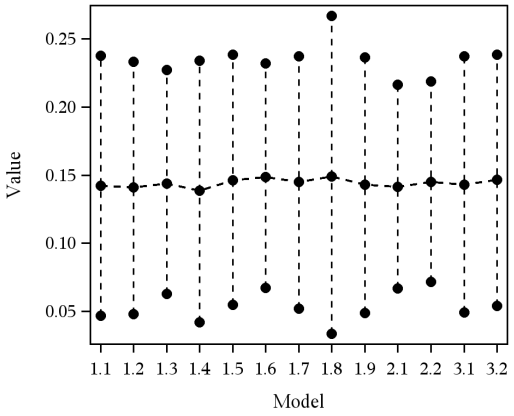
(c) J-Pa



(d) Pa-Z

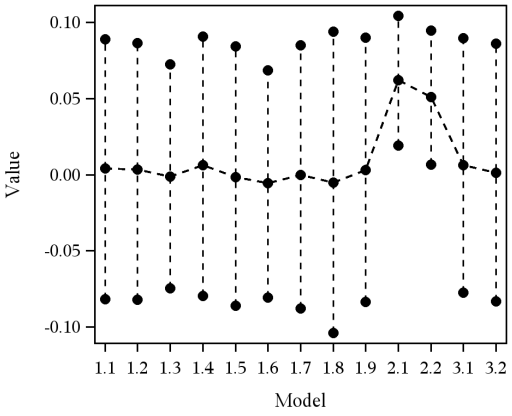


(e) Pa-Z-M

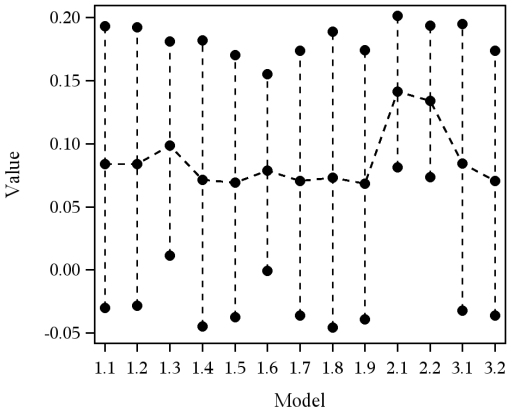


(f) Rifafour

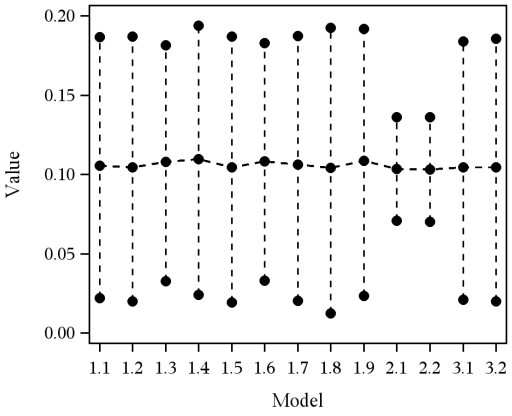
Figure 4.23: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-2)$ by Treatment Group and Model



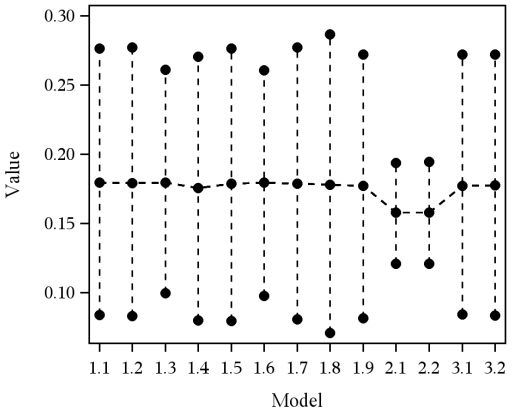
(a) J



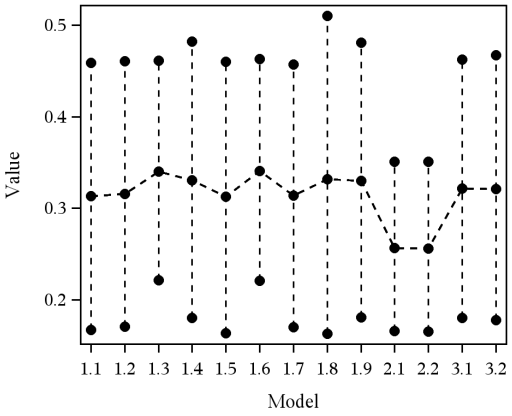
(b) J-Z



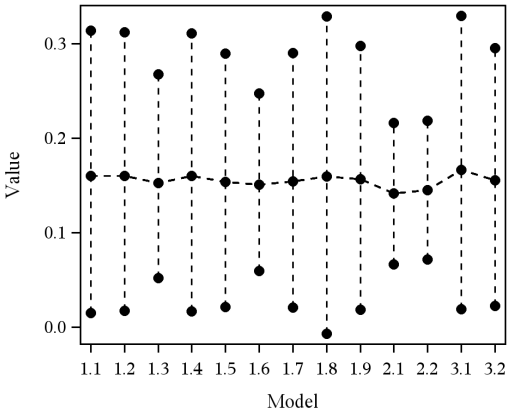
(c) J-Pa



(d) Pa-Z

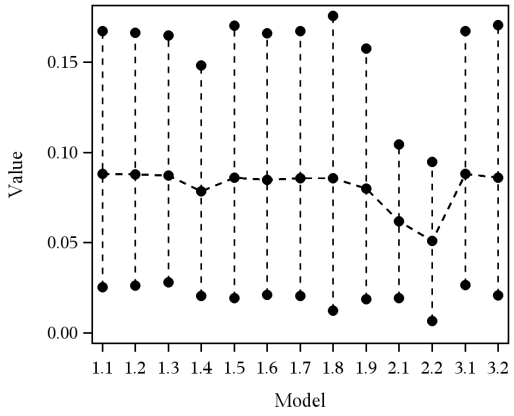


(e) Pa-Z-M

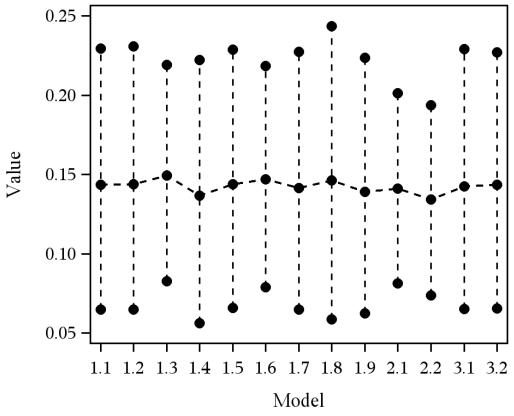


(f) Rifafour

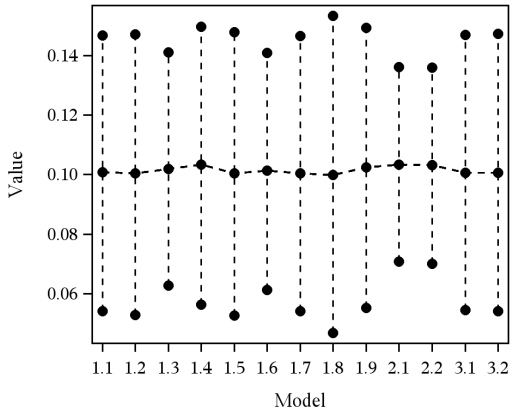
Figure 4.24: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(2-14)$ by Treatment Group and Model



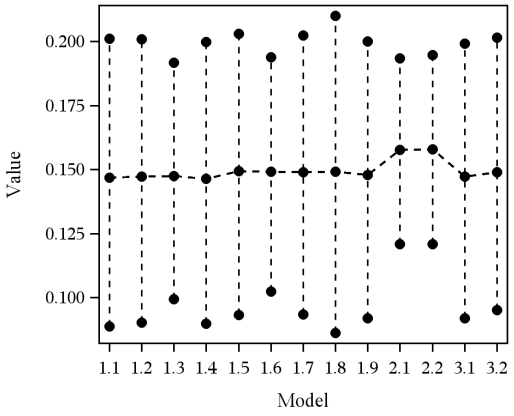
(a) J



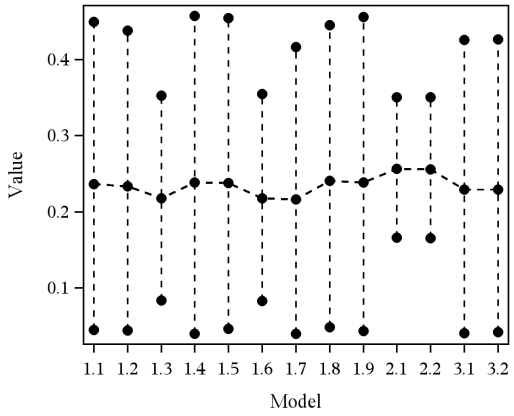
(b) J-Z



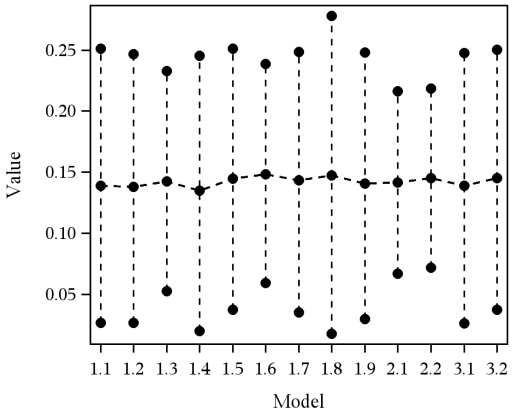
(c) J-Pa



(d) Pa-Z



(e) Pa-Z-M



(f) Rifafour

Table 4.14: Comparison of Bayesian NLME Regression Models

		DIC					% ICPO $< x$		
Regression Function	**Model**	$\overline{D(\theta_m, M)}$	$D(\bar{\theta}_m, M)$	p_m	$DIC(M)$	$\ln(\hat{f}(y\|M))$	$x = 40$	$x = 70$	$x = 100$
Differential	Model 1.1	1454.00	1273.00	180.70	1635.00^{7}	-1382.12^{9}	97.98	98.62	98.95
hyperbolic	Model 1.2	1454.00	1271.00	182.80	1637.00^{8}	-1364.04^{5}	97.89	98.62	99.03
tangent	Model 1.3	1476.00	1282.00	194.40	1671.00^{9}	-1367.23^{7}	97.73	98.70	99.03
	Model 1.4	NR	NR	NR	NR	-1413.81^{12}	NR	NR	NR
	Model 1.5	1335.00	1144.00	191.00	1526.00^{2}	-1365.66^{6}	97.57	98.87	99.11
	Model 1.6	1360.00	1158.00	202.70	1563.00^{5}	-1336.71^{3}	97.73	98.95	99.19
	Model 1.7	1334.00	1139.00	195.20	1529.00^{3}	-1350.93^{4}	97.65	98.87	99.19
	Model 1.8	NR	NR	NR	NR	-1494.72^{13}	NR	NR	NR
	Model 1.9	NR	NR	NR	NR	-1396.89^{10}	NR	NR	NR
Linear	Model 2.1	1644.00	1481.00	162.50	1806.00^{11}	-1262.32^{2}	98.54	98.95	99.11
	Model 2.2	1565.00	1398.00	167.50	1733.00^{10}	-1236.99^{1}	98.54	99.11	99.19
Conventional	Model 3.1	1445.00	1257.00	187.40	1632.00^{6}	-1408.10^{11}	97.89	98.54	98.95
bilinear	Model 3.2	1324.00	1127.00	197.20	1521.00^{1}	-1376.75^{8}	97.57	98.87	99.19

Note: CPO: Conditional posterior ordinate; ICPO: Reciprocal of CPO; DIC: Deviance information criterion; NLME: Nonlinear mixed effects; NR: Not reported. See Table 3.1 for the specifications of each Bayesian mixed effects regression model. Superscripts indicate the ranking of model comparison statistics from least favored to most favored.

4.4 NC002 ("SSCC") Trial

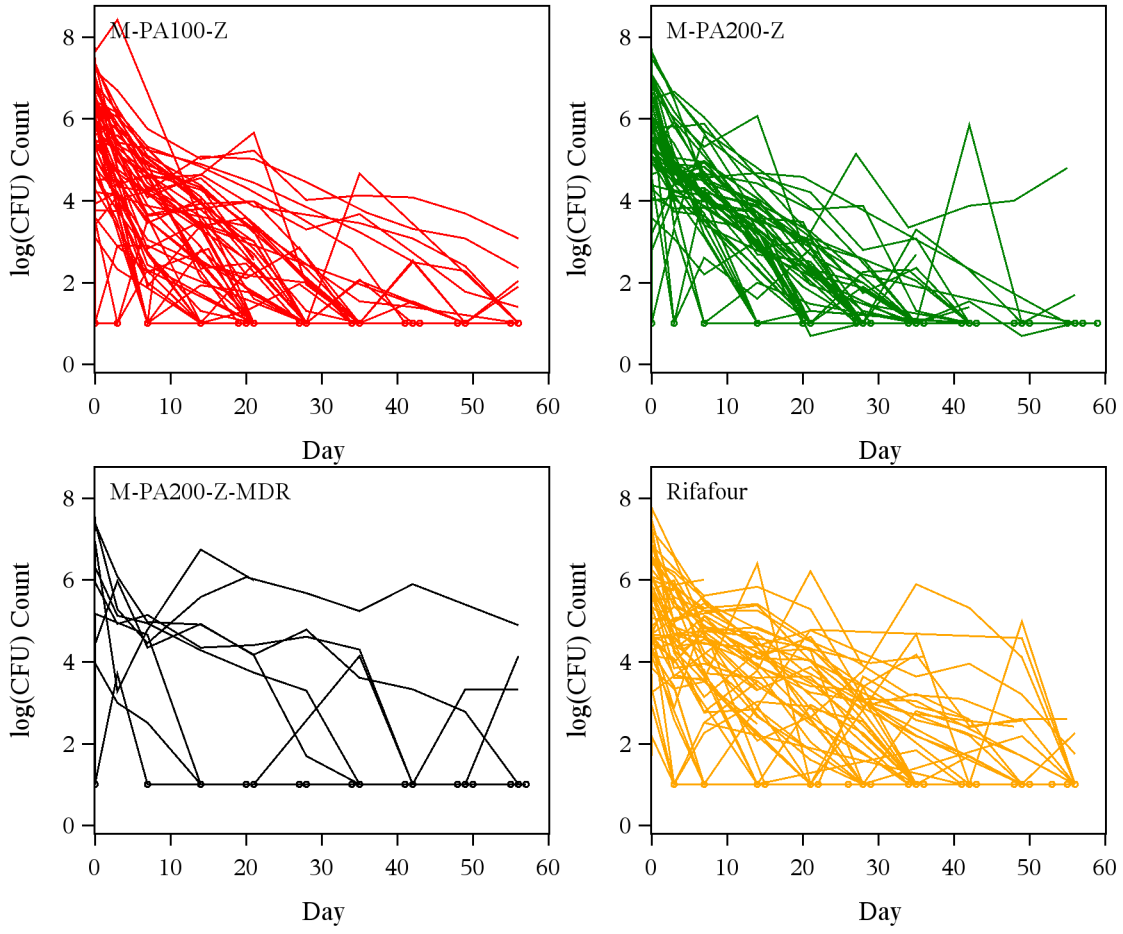
This section provides results from the reanalysis of the CFU data of the NC002 ("SSCC") trial (see Table 4.1).

Results from the fit of the following mixed effects regression models are presented: Model 1.3 (Page 165) and Model 1.6 (Page 169). None of the outliers were excluded from the joint Bayesian NLME analyses.

The bi-exponential mixed effects regression models (Model 4.1 and Model 4.2) failed to converge since some profiles over time decrease slow early (followed by a faster rate of decline), and some others increase over time.

Figure 4.25 shows nested plots of the observed log(CFU) counts by treatment group.

Figure 4.25: Observed log(CFU) Counts Over Time



Results from the joint Bayesian NLME fit of the differential hyperbolic tangent regression model (see Section 3.4) are provided in the subsections below.

4.4.1 Differential Hyperbolic Tangent Regression Model

Model 1.3: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{BA}_j(t_1 - t_2)$ and v_{50j}, including pairwise comparisons versus Rifafour, are presented respectively in Table 4.15

and Table 4.16. The difference between M-PA200-Z versus Rifafour with respect to $\text{BA}_j(0-56)$ and $\text{BA}_j(7-56)$ is statistically significantly different from 0. The time at which the percentage change from baseline in CFU count reaches 50% is statistically significantly shorter for M-PA100-Z and M-PA200-Z compared to Rifafour.

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table 4.17 by treatment group. As indicated by the estimates of β_{2j} (which are statistically significantly different from 0), the mean log(CFU) count for M-PA100-Z, M-PA200-Z and Rifafour initially decreases fast, followed by a slower rate of decrease.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure 4.26 by study day and treatment group.

Table 4.15: Posterior Estimates and Corresponding 95% BCIs for $\text{BA}_j(t_1 - t_2)$

					Difference vs Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{BA_j(0-56)}$	M-PA100-Z (N=60)	56	0.135	[0.112; 0.157]	0.022	[-0.009; 0.051]
	M-PA200-Z (N=61)	54	0.162	[0.138; 0.190]	0.050	[0.018; 0.083]
	M-PA200-Z-MDR (N=26)	9	0.106	[0.036; 0.193]	−0.007	[-0.079; 0.082]
	Rifafour (N=59)	54	0.113	[0.092; 0.135]		
$\mathbf{BA_j(7-56)}$	M-PA100-Z (N=60)	56	0.116	[0.091; 0.142]	0.010	[-0.025; 0.044]
	M-PA200-Z (N=61)	54	0.154	[0.126; 0.186]	0.048	[0.011; 0.088]
	M-PA200-Z-MDR (N=26)	9	0.095	[0.019; 0.190]	−0.011	[-0.091; 0.084]
	Rifafour (N=59)	54	0.106	[0.082; 0.132]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{BA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 4.16: Posterior Estimates and Corresponding 95% BCIs for v_{50j}

				Difference Versus Rifafour	
Treatment		**Posterior**		**Posterior**	
Group	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
M-PA100-Z (N=60)	56	12.760	[8.686; 18.030]	-7.721	[-13.800; -1.049]
M-PA200-Z (N=61)	54	14.110	[11.420; 16.690]	-6.371	[-11.570; -1.429]
M-PA200-Z-MDR (N=26)	9	NE	NE	NE	NE
Rifafour (N=59)	54	20.480	[16.280; 24.910]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; NE: Not estimable; v_{50j}: Time at which the percentage change from baseline in CFU count reaches 50%. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 4.17: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

	Treatment		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**
$\boldsymbol{\alpha_j}$	M-PA100-Z (N=60)	56	5.583	[5.263; 5.904]
	M-PA200-Z (N=61)	54	5.570	[5.278; 5.870]
	M-PA200-Z-MDR (N=26)	9	5.489	[4.277; 6.713]
	Rifafour (N=59)	54	5.279	[4.953; 5.606]
$\boldsymbol{\beta_{1j}}$	M-PA100-Z (N=60)	56	1.531	[1.315; 1.774]
	M-PA200-Z (N=61)	54	1.417	[1.226; 1.636]
	M-PA200-Z-MDR (N=26)	9	1.127	[0.478; 1.856]
	Rifafour (N=59)	54	1.025	[0.835; 1.256]
$\boldsymbol{\lambda_{1j}}$	M-PA100-Z (N=60)	56	2.334	[1.856; 2.863]
	M-PA200-Z (N=61)	54	1.794	[1.336; 2.301]
	M-PA200-Z-MDR (N=26)	9	1.642	[0.344; 3.079]
	Rifafour (N=59)	54	1.330	[0.888; 1.845]

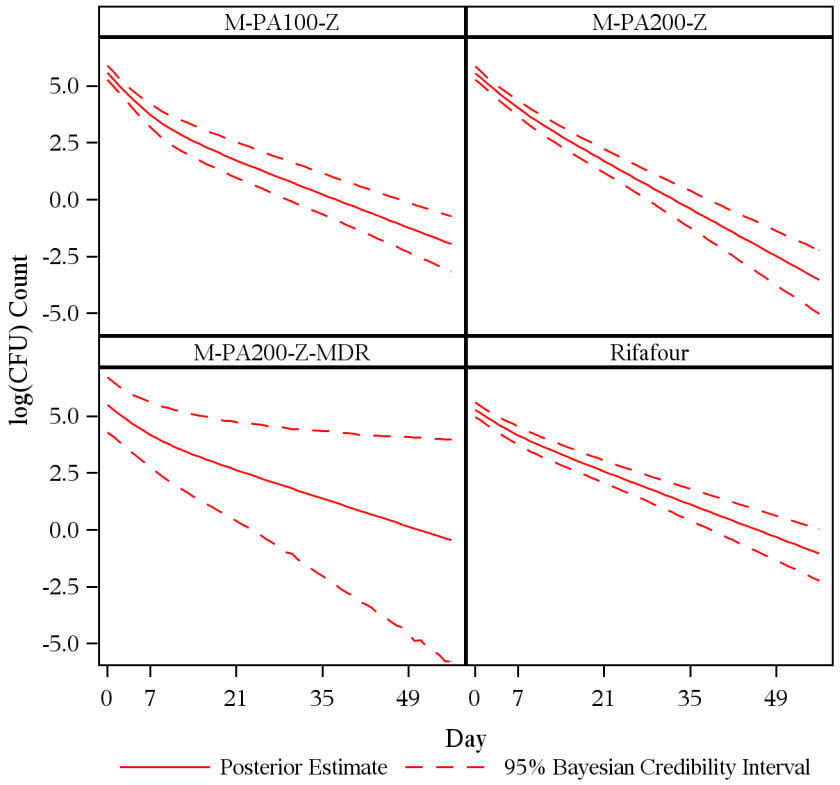
Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 4.17: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\beta_{2j}}$	M-PA100-Z (N=60)	56	−0.803	[-1.110; -0.511]
	M-PA200-Z (N=61)	54	−0.377	[-0.692; -0.066]
	M-PA200-Z-MDR (N=26)	9	−0.515	[-1.349; 0.296]
	Rifafour (N=59)	54	−0.305	[-0.610; -0.025]
$\boldsymbol{\beta_{2fj}}$	M-PA100-Z (N=60)	56	−0.804	[-2.114; 0.525]
	M-PA200-Z (N=61)	54	−0.374	[-1.409; 0.663]
	M-PA200-Z-MDR (N=26)	9	−0.516	[-1.783; 0.765]
	Rifafour (N=59)	54	−0.305	[-1.355; 0.732]
$\boldsymbol{\lambda_{2j}}$	M-PA100-Z (N=60)	56	0.728	[0.564; 0.909]
	M-PA200-Z (N=61)	54	1.040	[0.834; 1.280]
	M-PA200-Z-MDR (N=26)	9	0.613	[0.057; 1.315]
	Rifafour (N=59)	54	0.720	[0.550; 0.910]
$\boldsymbol{\kappa_j}$	M-PA100-Z (N=60)	56	0.975	[0.451; 1.533]
	M-PA200-Z (N=61)	54	0.930	[0.440; 1.533]
	M-PA200-Z-MDR (N=26)	9	0.929	[0.441; 1.533]
	Rifafour (N=59)	54	0.857	[0.437; 1.513]
$\boldsymbol{\gamma_j}$	M-PA100-Z (N=60)	56	1.028	[0.143; 1.947]
	M-PA200-Z (N=61)	54	1.052	[0.147; 1.951]
	M-PA200-Z-MDR (N=26)	9	1.037	[0.147; 1.954]
	Rifafour (N=59)	54	0.883	[0.128; 1.926]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure 4.26: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



Model 1.6: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Frequentist" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{BA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.14 (Appendix E). These results are similar to those of Model 1.3.

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table 4.18 by treatment group. The estimates for v_j provide very strong indication that the distribution of residuals in log(CFU) count are heavy tailed (degrees of freedom below 30).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.13 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.3.

Table 4.18: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
v_j	M-PA100-Z (N=60)	56	2.153	[2.004; 2.563]
	M-PA200-Z (N=61)	54	2.455	[2.017; 3.420]
	M-PA200-Z-MDR (N=26)	9	31.400	[2.086; 95.240]
	Rifafour (N=59)	54	2.132	[2.004; 2.479]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

4.4.2 Model Selection and Model Checking

The DIC, marginal likelihood and ICPO < 40 for the model with normally distributed residuals are respectively 3368.00, -1996.60 and 96.76%, and for the model with Student t distributed residuals are respectively 2985.00, -1933.43 and 96.37%.

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

The ICPOs suggest the models fit the data reasonably well.

4.5 NC003 Trial

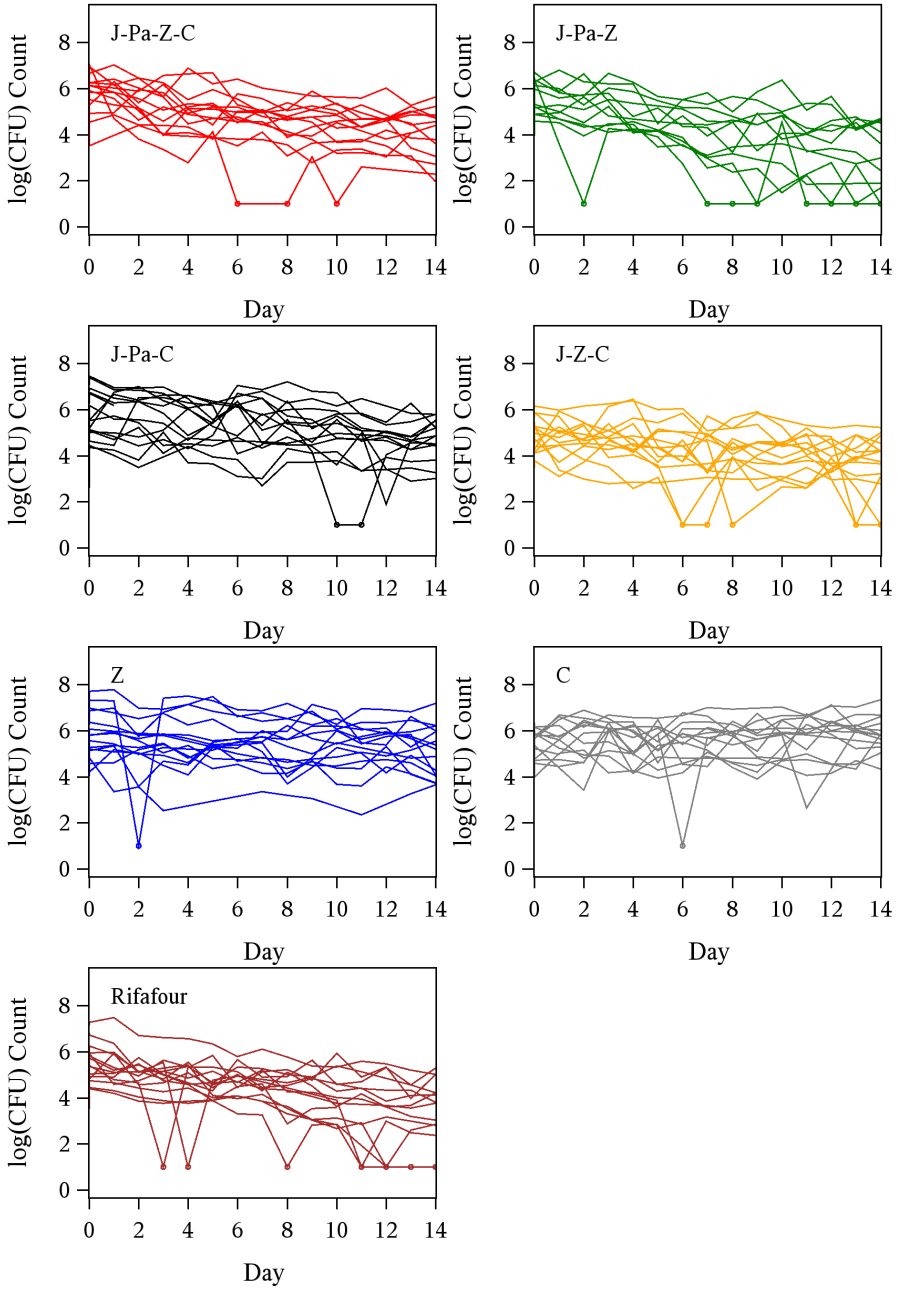
This section provides results from the reanalysis of the CFU data of the NC003 trial (see Table 4.1).

Results from the fit of the following mixed effects regression models are presented: Model 1.1 (Page 172), Model 1.5 (Page 177), Model 1.7 (Page 178), Model 1.9

(Page 179), Model 2.1 (Page 180), Model 2.2 (Page 180), Model 3.1 (Page 181) and Model 3.2 (Page 181). None of the outliers were excluded from the joint Bayesian NLME analyses.

Figure 4.27 shows nested plots of the observed log(CFU) counts by treatment group. The log(CFU) versus time profiles seem erratic for some patients.

Figure 4.27: Observed log(CFU) Counts Over Time



4.5.1 Differential Hyperbolic Tangent Regression Model

Results from the joint Bayesian NLME fit of the differential hyperbolic tangent regression model (see Section 3.4) are provided in the subsections below.

Model 1.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Plots of the observed log(CFU) counts together with by-patient and joint Bayesian NLME fits of the regression model are included in Figure D.7 through Figure D.13 of Appendix D for each patient.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table 4.19. The monotherapy regimens (Z and C) show little to no bactericidal activity over 14 days of treatment.

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table 4.20 by treatment group.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure 4.28 by study day and treatment group.

Table 4.19: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{EBA_j(0-14)}$	J-Pa-Z-C (N=14)	14	0.116	[0.050; 0.183]	−0.036	[-0.148; 0.072]
	J-Pa-Z (N=14)	12	0.172	[0.075; 0.272]	0.020	[-0.110; 0.150]
	J-Pa-C (N=15)	15	0.083	[0.018; 0.149]	−0.069	[-0.180; 0.038]
	J-Z-C (N=14)	14	0.101	[0.022; 0.183]	−0.050	[-0.169; 0.066]
	Z (N=15)	15	0.036	[-0.019; 0.088]	−0.116	[-0.218; -0.017]
	C (N=15)	14	-0.022	[-0.077; 0.034]	−0.174	[-0.277; -0.073]
	Rifafour (N=15)	15	0.152	[0.067; 0.241]		
$\mathbf{EBA_j(0-2)}$	J-Pa-Z-C (N=14)	14	0.168	[0.049; 0.289]	0.043	[-0.138; 0.226]
	J-Pa-Z (N=14)	12	0.206	[0.020; 0.387]	0.081	[-0.145; 0.310]
	J-Pa-C (N=15)	15	0.069	[-0.044; 0.179]	−0.056	[-0.232; 0.118]
	J-Z-C (N=14)	14	0.123	[-0.014; 0.261]	−0.003	[-0.197; 0.193]
	Z (N=15)	15	0.082	[-0.026; 0.207]	−0.044	[-0.218; 0.138]
	C (N=15)	14	0.012	[-0.090; 0.114]	−0.114	[-0.284; 0.057]
	Rifafour (N=15)	15	0.126	[-0.013; 0.262]		
$\mathbf{EBA_j(2-14)}$	J-Pa-Z-C (N=14)	14	0.107	[0.029; 0.175]	−0.049	[-0.179; 0.072]
	J-Pa-Z (N=14)	12	0.167	[0.057; 0.271]	0.010	[-0.139; 0.152]
	J-Pa-C (N=15)	15	0.085	[0.020; 0.155]	−0.072	[-0.196; 0.049]
	J-Z-C (N=14)	14	0.098	[0.006; 0.187]	−0.058	[-0.197; 0.074]
	Z (N=15)	15	0.028	[-0.038; 0.089]	−0.128	[-0.251; -0.012]
	C (N=15)	14	-0.027	[-0.088; 0.029]	−0.184	[-0.303; -0.071]
	Rifafour (N=15)	15	0.156	[0.058; 0.262]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 4.20: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J-Pa-Z-C (N=14)	14	5.665	[5.161; 6.173]
	J-Pa-Z (N=14)	12	5.545	[4.823; 6.263]
	J-Pa-C (N=15)	15	5.763	[5.147; 6.379]
	J-Z-C (N=14)	14	4.929	[4.399; 5.451]
	Z (N=15)	15	5.722	[5.128; 6.315]
	C (N=15)	14	5.524	[5.086; 5.955]
	Rifafour (N=15)	15	5.316	[4.732; 5.901]
$\boldsymbol{\beta_{1j}}$	J-Pa-Z-C (N=14)	14	0.117	[0.064; 0.173]
	J-Pa-Z (N=14)	12	0.174	[0.089; 0.260]
	J-Pa-C (N=15)	15	0.084	[0.022; 0.147]
	J-Z-C (N=14)	14	0.103	[0.031; 0.178]
	Z (N=15)	15	0.052	[-0.001; 0.115]
	C (N=15)	14	−0.024	[-0.072; 0.025]
	Rifafour (N=15)	15	0.146	[0.073; 0.220]
$\boldsymbol{\lambda_{1j}}$	J-Pa-Z-C (N=14)	14	0.169	[0.049; 0.292]
	J-Pa-Z (N=14)	12	0.207	[0.017; 0.391]
	J-Pa-C (N=15)	15	0.069	[-0.045; 0.179]
	J-Z-C (N=14)	14	0.123	[-0.015; 0.264]
	Z (N=15)	15	0.086	[-0.029; 0.224]
	C (N=15)	14	0.012	[-0.091; 0.116]
	Rifafour (N=15)	15	0.124	[-0.022; 0.269]
$\boldsymbol{\beta_{2j}}$	J-Pa-Z-C (N=14)	14	−0.052	[-0.152; 0.049]
	J-Pa-Z (N=14)	12	−0.033	[-0.183; 0.119]
	J-Pa-C (N=15)	15	0.014	[-0.095; 0.121]
	J-Z-C (N=14)	14	−0.020	[-0.156; 0.116]
	Z (N=15)	15	−0.034	[-0.127; 0.054]
	C (N=15)	14	−0.036	[-0.124; 0.052]
	Rifafour (N=15)	15	0.022	[-0.097; 0.140]

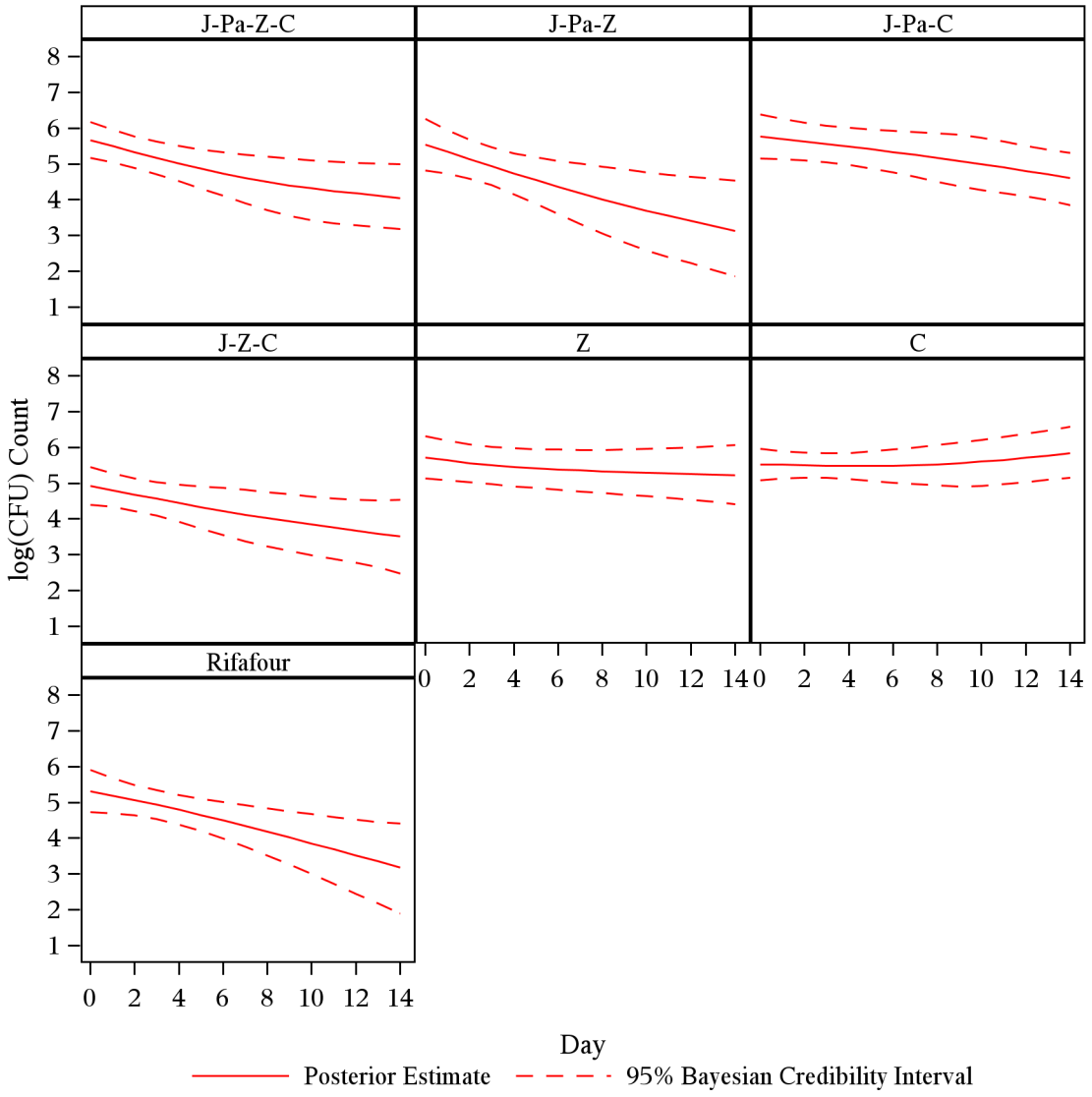
Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 4.20: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\beta_{2fj}}$	J-Pa-Z-C (N=14)	14	−0.052	[-0.415; 0.305]
	J-Pa-Z (N=14)	12	−0.034	[-0.540; 0.475]
	J-Pa-C (N=15)	15	0.016	[-0.361; 0.386]
	J-Z-C (N=14)	14	−0.020	[-0.510; 0.477]
	Z (N=15)	15	−0.035	[-0.324; 0.256]
	C (N=15)	14	−0.037	[-0.326; 0.252]
	Rifafour (N=15)	15	0.022	[-0.403; 0.442]
$\boldsymbol{\lambda_{2j}}$	J-Pa-Z-C (N=14)	14	0.065	[-0.042; 0.169]
	J-Pa-Z (N=14)	12	0.140	[-0.019; 0.302]
	J-Pa-C (N=15)	15	0.098	[-0.042; 0.232]
	J-Z-C (N=14)	14	0.082	[-0.080; 0.256]
	Z (N=15)	15	0.018	[-0.066; 0.101]
	C (N=15)	14	−0.060	[-0.160; 0.035]
	Rifafour (N=15)	15	0.167	[0.036; 0.303]
$\boldsymbol{\kappa_j}$	J-Pa-Z-C (N=14)	14	6.888	[2.333; 10.800]
	J-Pa-Z (N=14)	12	6.610	[2.261; 10.750]
	J-Pa-C (N=15)	15	8.621	[3.202; 10.930]
	J-Z-C (N=14)	14	7.132	[2.651; 10.740]
	Z (N=15)	15	4.381	[2.048; 10.350]
	C (N=15)	14	7.156	[2.376; 10.830]
	Rifafour (N=15)	15	4.409	[2.066; 9.896]
$\boldsymbol{\gamma_j}$	J-Pa-Z-C (N=14)	14	1.064	[0.148; 1.954]
	J-Pa-Z (N=14)	12	1.042	[0.146; 1.953]
	J-Pa-C (N=15)	15	1.017	[0.140; 1.949]
	J-Z-C (N=14)	14	1.041	[0.150; 1.956]
	Z (N=15)	15	1.036	[0.146; 1.950]
	C (N=15)	14	1.033	[0.145; 1.951]
	Rifafour (N=15)	15	1.067	[0.148; 1.952]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure 4.28: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



Model 1.5: Residuals: Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.15 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the degrees of freedom (of residuals) are included in Table 4.21 by treatment group. The estimates for v_j provide very strong indication that the distribution of residuals in log(CFU) count are heavy tailed (degrees of freedom below 30).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.14 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.21: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
v_j	J-Pa-Z-C (N=14)	14	6.123	[2.188; 22.220]
	J-Pa-Z (N=14)	12	2.540	[2.019; 3.759]
	J-Pa-C (N=15)	15	3.051	[2.064; 4.980]
	J-Z-C (N=14)	14	2.408	[2.012; 3.414]
	Z (N=15)	15	2.570	[2.023; 3.762]
	C (N=15)	14	2.955	[2.063; 4.688]
	Rifafour (N=15)	15	2.237	[2.007; 2.831]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Model 1.7: **Residuals: Student t**
Random Coefficients: Student t
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.16 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the degrees of freedom (of random effects) are included in Table 4.22 by treatment group. The estimates for w_j do not provide strong indication that the distributions of random intercepts and slopes are heavy tailed (degrees of freedom above 30).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.15 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.22: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
w_j	J-Pa-Z-C (N=14)	14	53.460	[6.768; 97.530]
	J-Pa-Z (N=14)	12	55.660	[8.838; 97.700]
	J-Pa-C (N=15)	15	55.840	[8.891; 97.900]
	J-Z-C (N=14)	14	55.260	[8.378; 97.850]
	Z (N=15)	15	55.860	[8.922; 97.850]
	C (N=15)	14	56.640	[9.904; 98.120]
	Rifafour (N=15)	15	51.760	[5.367; 97.680]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Model 1.9: Residuals: Skew Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.17 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the skewness parameters (of residuals) are included in Table 4.23 by treatment group. The estimates for δ_j do provide evidence that the residuals in log(CFU) count are skew distributed. The J-Pa-C and J-Z-C regimens, and Rifafour, show statistically significant negative skewness in the data (see Figure D.9, Figure D.10 and Figure D.13).

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.16 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Table 4.23: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\delta_j}$	J-Pa-Z-C (N=14)	14	0.096	[-0.374; 0.585]
	J-Pa-Z (N=14)	12	0.092	[-0.182; 0.338]
	J-Pa-C (N=15)	15	−0.500	[-0.817; -0.178]
	J-Z-C (N=14)	14	−0.407	[-0.705; -0.127]
	Z (N=15)	15	−0.143	[-0.327; 0.036]
	C (N=15)	14	−0.284	[-0.624; 0.013]
	Rifafour (N=15)	15	−0.272	[-0.448; -0.093]

Note: BCI: Bayesian credibility interval. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

4.5.2 Other Regression Models

Results from the other joint Bayesian mixed effects regression models (see Section 3.4.2) are provided in the subsections below.

4.5.2.1 Linear Regression Model

Model 2.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table E.18 (Appendix E) by treatment group.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.17 (Appendix E) by study day and treatment group.

Model 2.2: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table E.19 (Appendix E) by treatment group. These results ($\text{EBA}_j(t_1 - t_2)$ included) are similar to those of Model 2.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.18 (Appendix E) by study day and treatment group. These results are similar to those of Model 2.1.

4.5.2.2 Conventional Bilinear Regression Model

Model 3.1: **Residuals: Normal**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.20 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean regression model parameters are included in Table E.21 (Appendix E) by treatment group. These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.19 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

Model 3.2: **Residuals: Student t**
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.22 (Appendix E). These results are similar to those of Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.20 (Appendix E) by study day and treatment group. These results are similar to those of Model 1.1.

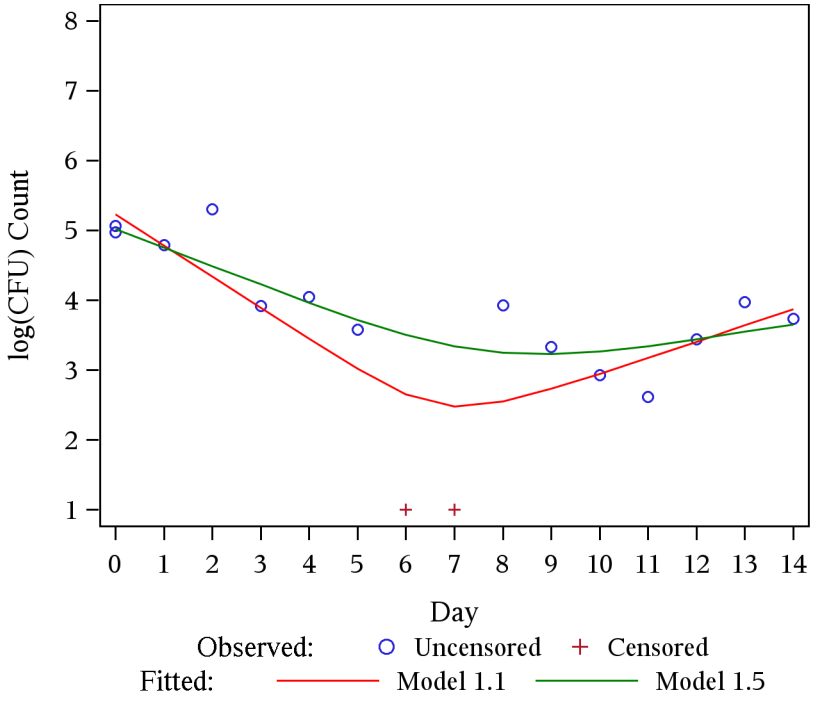
4.5.3 Robust Regression Modeling

As indicated previously, EBA estimates calculated from the joint Bayesian NLME analysis are generally shrunken towards their corresponding mean estimates. It is

therefore preferred to analyze CFU count using mixed effects regression modeling instead of regressing CFU count on a by-patient basis. However, despite this characteristic (of shrinkage effect), extreme outliers in log(CFU) count have previously been shown to have a significant impact on the estimation of and inferences on EBA. The estimates for the degrees of freedom associated with the specification of heavy tailed distributions (in particular, the Student t distribution) for residuals provide strong evidence that outliers in log(CFU) count are present in the data. For this type of data, the specification of heavy tailed distributions clearly provides an even greater shrinkage effect compared to normal mixed effects regression modeling. To illustrate how the Student t distribution (for residuals) is associated with more robust fits (relative to the normal distribution), a plot of observed log(CFU) counts for Patient 002040083 together with joint Bayesian NLME fits calculated from Model 1.1 and Model 1.5 is presented in Figure 4.29.

Clearly, Model 1.5 provides a robust fit of the regression curve, with little weight given to the two clinically implausible zero counts observed on Day 6 and Day 7.

Figure 4.29: log(CFU) Versus Time Profile: Model 1.1 Versus Model 1.5



4.5.4 Model Selection and Model Checking

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1-t_2)$ are shown in Figure 4.30 ($\text{EBA}_j(0-14)$), Figure 4.31 ($\text{EBA}_j(0-2)$) and Figure 4.32 ($\text{EBA}_j(2-14)$) by treatment group and model. Similar to the NC001 trial, the linear models (Model 2.1 and Model 2.2) occasionally yield results substantially different to those of other models. The posterior estimates for $\text{EBA}_j(t_1 - t_2)$ of the models with normally distributed residuals are in general higher than those of the Student t distributed residuals. This is due to the presence of extreme outliers in the data which heavily influence the posterior estimates for the mean log(CFU) versus time profiles. The Student t distribution allows for heavier tails than the normal distribution and thus better accommodates occasional outliers seen in the data.

Model comparison statistics for the various Bayesian NLME regression models fitted are provided in Table 4.24.

As a result of extreme outliers present in the data, DIC statistics cannot be calculated by OpenBUGS for models with normally distributed residuals (as some densities associated with the calculation of DIC statistics are close to zero). The DIC favors conventional bilinear regression models over differential hyperbolic tangent regression models, followed by linear regression models.

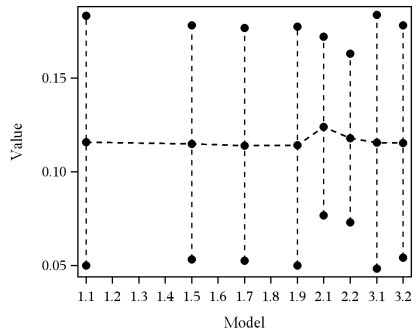
Bayes factors (marginal likelihoods) favor linear regression models, followed by differential hyperbolic tangent and conventional bilinear regression models.

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals, and all the more the model with both Student t distributed residuals and random coefficients.

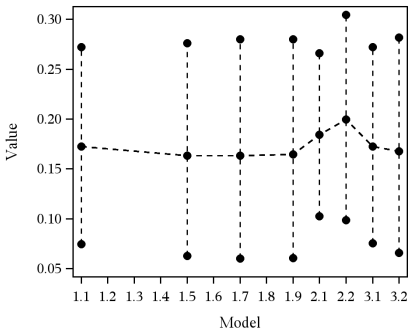
The Bayes factors indicate that building skewness into the distributions of residuals does not improve model fitting.

The ICPOs suggest the models fit the data reasonably well.

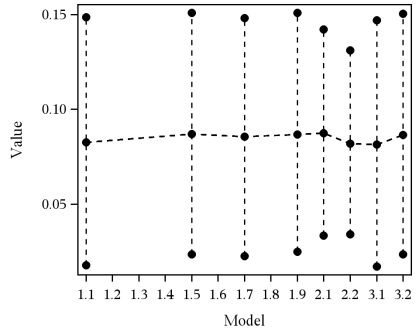
Figure 4.30: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-14)$ by Treatment Group and Model



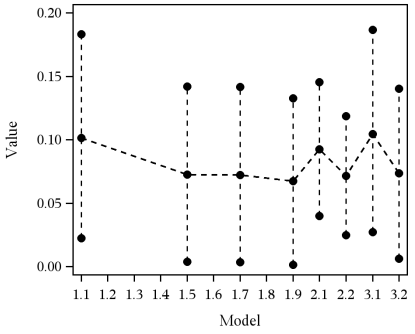
(a) J-Pa-Z-C



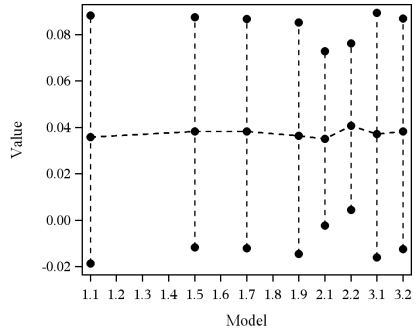
(b) J-Pa-Z



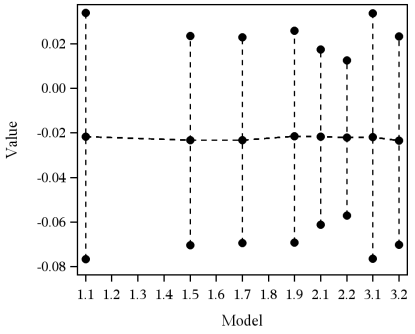
(c) J-Pa-C



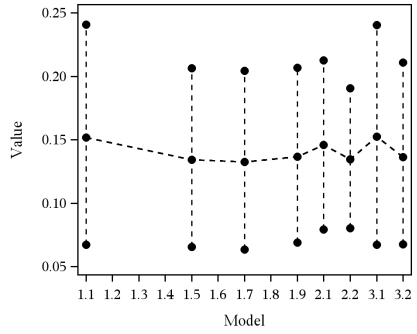
(d) J-Z-C



(e) Z

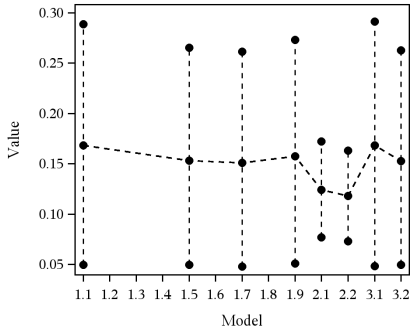


(f) C

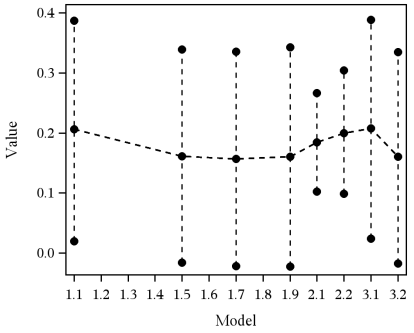


(g) Rifafour

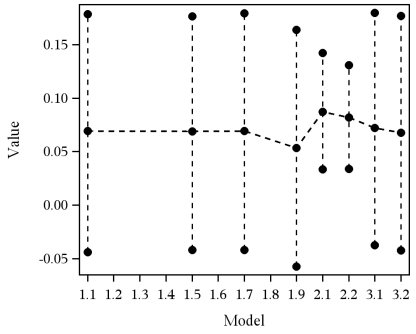
Figure 4.31: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-2)$ by Treatment Group and Model



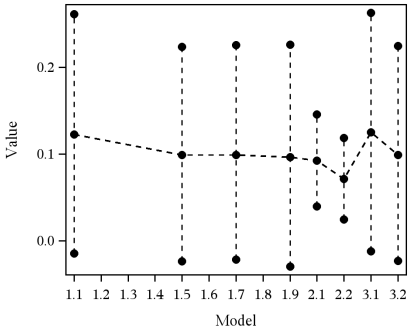
(a) J-Pa-Z-C



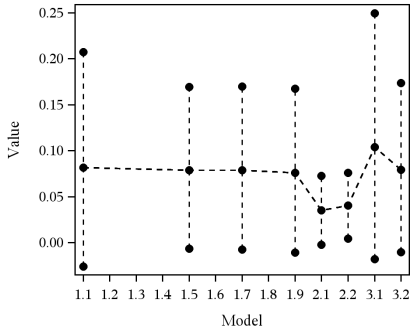
(b) J-Pa-Z



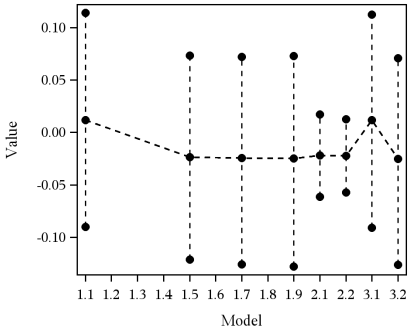
(c) J-Pa-C



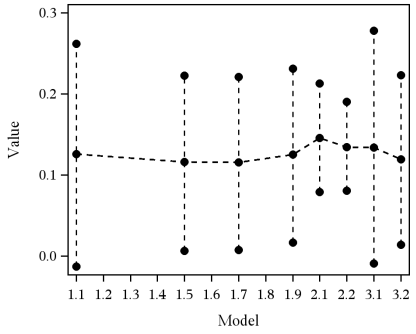
(d) J-Z-C



(e) Z

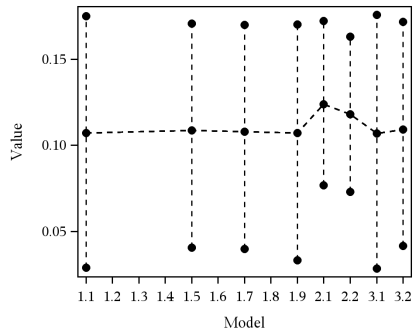


(f) C

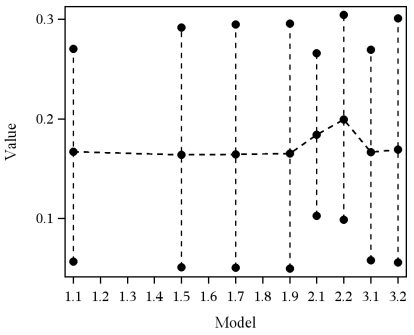


(g) Rifafour

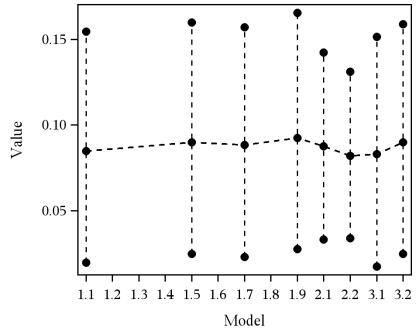
Figure 4.32: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(2-14)$ by Treatment Group and Model



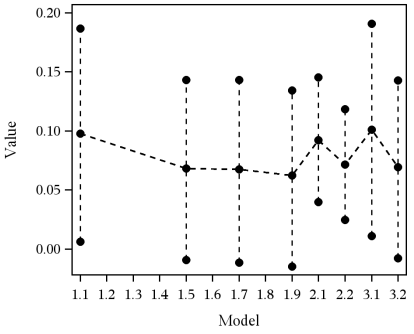
(a) J-Pa-Z-C



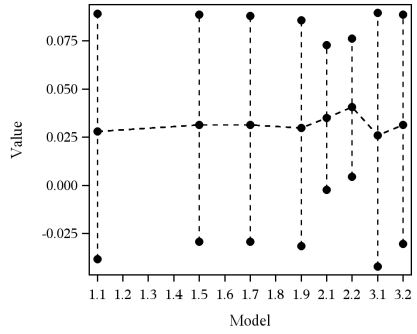
(b) J-Pa-Z



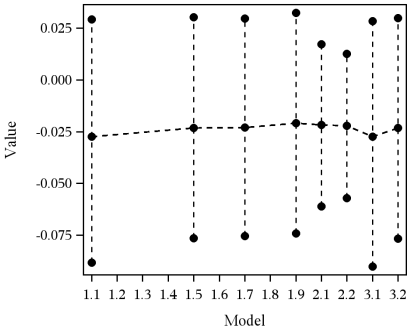
(c) J-Pa-C



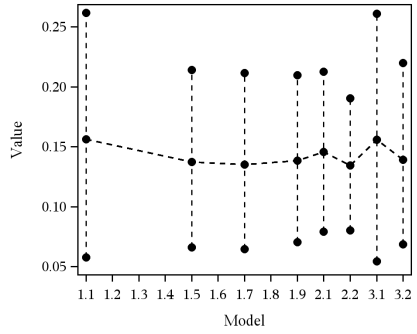
(d) J-Z-C



(e) Z



(f) C



(g) Rifafour

Table 4.24: Comparison of Bayesian NLME Regression Models

		DIC					% ICPO $< x$		
Regression Function	**Model**	$\overline{D(\theta_m, M)}$	$D(\bar{\theta}_m, M)$	p_m	DIC(M)	$\ln(\hat{f}(y\|M))$	$x = 40$	$x = 70$	$x = 100$
Differential	Model 1.1	NE	NE	NE	NE	-2087.08[7]	97.56	98.15	98.28
hyperbolic	Model 1.5	2073.00	1827.00	245.00	2318.00[3]	-1855.22[3]	97.16	97.76	98.02
tangent	Model 1.7	2071.00	1828.00	243.40	2315.00[2]	-1834.36[2]	97.16	97.76	98.02
	Model 1.9	NR	NR	NR	NR	-1880.69[4]	NR	NR	NR
Linear	Model 2.1	NE	NE	NE	NE	-1937.72[6]	97.62	97.89	98.02
	Model 2.2	2296.00	2092.00	203.80	2500.00[4]	-1693.35[1]	97.29	97.89	98.15
Conventional	Model 3.1	NE	NE	NE	NE	-2139.69[8]	97.56	98.02	98.28
bilinear	Model 3.2	2063.00	1822.00	241.10	2305.00[1]	-1898.90[5]	97.10	97.76	98.02

Note: CPO: Conditional posterior ordinate; ICPO: Reciprocal of CPO; DIC: Deviance information criterion; NLME: Nonlinear mixed effects; NE: Not estimable; NR: Not reported. See Table 3.1 for the specifications of each Bayesian mixed effects regression model. Superscripts indicate the ranking of model comparison statistics from least favored to most favored.

4.6 Other Datasets

Section E.4 (Appendix E) provides the results of a reanalysis of CFU data of the CL001 (Diacon et al., 2013), CL007 (Diacon et al., 2010), CL010 (Diacon et al., 2012c) and NC002 (EBA) (Dawson et al., 2015) trials (see Table 4.1) using the models discussed in the previous chapter (Chapter 3).

Results from the fit of the following mixed effects regression models are presented: Model 1.1, Model 1.5, Model 1.7, Model 1.9, Model 2.1, Model 2.2, Model 3.1 and Model 3.2. None of the outliers were excluded from the joint Bayesian NLME analyses.

The ranking of model comparison statistics for these datasets is similar to that of the NC001 and NC003 trials.

Chapter 5

Statistical Methods and Application: Time to Positivity

5.1 Introduction

This chapter presents statistical methods for the assessment of TTP data and their application. Regression models can be fitted to TTP data either on a by-patient basis (see Section 2.3), or fitted to the data of all patients jointly as mixed effects regression models (see Section 2.2). This chapter, in addition, summarizes the results of an extensive empirical investigation of the suitability of the proposed model for TTP data (see Equation 2.39). Applications of the methodology in Chapter 3 to the TTP data of recently published clinical trials are presented.

5.2 General Considerations

When fitting regression models to TTP data, the following important aspects, in addition to those applicable to CFU data (see Section 3.2), should be considered (Burger and Schall, 2014b):

- **Data or "analysis variable"**: Provided that two TTP values, denoted by TTP_1 and TTP_2, are associated with a given sputum sample from two different sets, TTP is calculated as follows:

$$\text{TTP} = \frac{1}{2}\left(\text{TTP}_1 + \text{TTP}_2\right) \tag{5.1}$$

  Then $\log\left(\text{TTP}\right)$ is given by:

$$\log\left(\text{TTP}\right) = \log_{10}\left(\text{TTP}\right) \tag{5.2}$$

- **Censored data**: TTP values might be reported as "negative" (i.e., no mycobacterial growth). The manufacturer's recommended incubation time before reporting a result as "negative" is 42 days (equivalently, 1008 hours). Thus the largest possible numeric TTP value that can be observed is 1008 hours, for an incubation time of 1008 hours. When regressing log(TTP) against time, the log(TTP) values reported as "negative" are specified as right censored values. In the REMoxTB Phase 3 study (Gillespie et al., 2014), where sputa from approximately 2000 patients were collected serially over 18 months of treatment and follow-up, only 6.8% of the reported positive liquid cultures had TTP values exceeding 600 hours. The censoring time could be chosen to be equal to the incubation time (1008 hours); however, because experience suggests that TTP values reported above 600 hours are rare, the following censoring rule is used: TTP values reported as "negative" should be right-censored at 600 hours, or the maximum TTP value observed in the study, whichever is greater.

5.3 Mean-Variance Relationship

TTP data are continuous measurements where, as inspection of TTP data from previous trials (e.g. Diacon et al. (2012a)) shows, the variance increases with the mean. If one assumes that the variance of the data Y is of the form:

$$\mathrm{Var}\,(Y) = \sigma^2 \left[\mathrm{E}\,(Y)\right]^2 = \sigma^2 \mu^2 \tag{5.3}$$

for some constant σ^2, then Equation 5.3 implies that:

$$\mathrm{CV}\,(Y) = \frac{\sqrt{\mathrm{Var}\,(Y)}}{\mathrm{E}\,(Y)} = \frac{\sigma\mu}{\mu} = \sigma \tag{5.4}$$

Thus, under the assumption provided in Equation 5.4, the CV of Y is constant over all μ.

One option for handling data with constant CV is the logarithmic transformation of data. The log-transformation is variance stabilizing (as shown in Section 5.5). After logarithmic transformation, the data can be analyzed using normal linear (or nonlinear) regression.

5.4 Regression Models

In this chapter, let $y(t)$ be the TTP at time t. Similarly, let $\mu(t)$ denote the expected TTP at time t. Similarly to Equation (2.21), if it is assumed that the rate of change (increase) in expected TTP is proportional to $\mu(t)$, the following differential equation is obtained:

$$\frac{\mathrm{d}\mu(t)}{\mu(t)} = \lambda(t)\mathrm{d}t \tag{5.5}$$

Here $\lambda(t) > 0$ is the proportionality function and characterizes the rate of increase.

As with the CFU data, one can fit the regression models outlined in Chapter 2 to $\log(y)$, the log-transformed TTP data, e.g. the differential hyperbolic tangent regression model, namely:

$$\log(y[t]) = \alpha + \beta_1 \cdot t + \beta_2 \cdot \gamma \cdot \log\left(\frac{e^{\frac{t-\kappa}{\gamma}} + e^{-\frac{t-\kappa}{\gamma}}}{e^{\frac{\kappa}{\gamma}} + e^{-\frac{\kappa}{\gamma}}}\right) + \varepsilon(t) \tag{5.6}$$

The parameters of the regression model in Equation (5.6) are analogous to those discussed for CFU data, however, incorporating a slight modification in the sign of the slope parameters, i.e. '$+\ \beta_1$' and '$+\ \beta_2$' instead of '$-\ \beta_1$' and '$-\ \beta_2$'. As a result, the joint Bayesian NLME regression models discussed in Chapter 3 can be fitted to the log(TTP) versus time data.

Similar to CFU count, EBA values can be sampled from the posterior output of the MCMC samples (see Equation (1.7)). However, it should be noted that Equation (1.7) uses the base of e for the logarithm of TTP.

EBA values can be compared between treatment groups using the ratio of EBA in one treatment group versus the other, expressed as percentages. Given Equation (1.6) and Equation (1.7), the quantity is expressed as follows:

$$100 \cdot \left(\exp\left[\text{EBA}_{Lj}(t_1 - t_2) - \text{EBA}_{Lj'}(t_1 - t_2)\right] - 1\right) \tag{5.7}$$

Here, the EBA values come from different treatment groups (i.e. $j \neq j^{'}$).

In Equation (5.2), the base of 10 is applicable to the analysis of log(TTP). Equation (1.7) and Equation (5.7) should therefore be adjusted accordingly.

5.5 Empirical Study

For the purpose of this empirical study, TTP data from the seven trials described in Section 4.2 were available. Relevant clinical trial characteristics of clinical trial protocols (see Chapter 4) are summarized in Table 5.1, including the total number of valid patients, and the number of patients with complete profiles.

Table 5.1: Characteristics of Trials Included in Empirical Study

Clinical Trial	Scheduled Sample Days	Treatment Group	N	n
CL001	Daily from Day -2 to Day 8;	TMC207 100 mg	15	13
	Day 10, Day 12, Day 14	TMC207 200 mg	15	11
		TMC207 200 mg	15	12
		TMC207 400 mg	15	10
		Rifafour	8	8
		Total	**68**	**54**
CL007	Daily from Day -2 to Day 4;	PA-824 200 mg	15	12
	Day 6, Day 8, Day 10, Day 12,	PA-824 600 mg	15	15
	Day 14	PA-824 1000 mg	16	15
		PA-824 1200 mg	15	12
		Rifafour	8	8
		Total	**69**	**62**
CL010	Daily from Day -2 to Day 4;	PA-824 50 mg	15	13
	Day 6, Day 8, Day 10, Day 12,	PA-824 100 mg	15	14
	Day 14	PA-824 150 mg	15	15
		PA-824 200 mg	16	16
		Rifafour	8	8
		Total	**69**	**66**
NC001	Daily from Day -2 to Day 14	J	15	14
		J-Z	15	14
		J-Pa	15	13
		Pa-Z	15	14
		Pa-Z-M	15	11
		Rifafour	10	10
		Total	**85**	**76**
NC002 (EBA)	Daily from Day -2 to Day 3, Day 5,	M-PA100-Z	16	11
	Day 7, Day 9, Day 11, Day 14	M-PA200-Z	13	10
		M-PA200-Z-MDR	18	6
		Rifafour	15	9
		Total	**62**	**36**
NC002 ("SSCC")	Day -2, Day -1, Day 3, Day 7,	M-PA100-Z	60	15
	Day 14, Day 21, Day 28, Day 35,	M-PA200-Z	61	13
	Day 42, Day 49, Day 56	M-PA200-Z-MDR	26	3
		Rifafour	59	21
		Total	**206**	**52**

Note: Treatment group: J = TMC207, J-Z = TMC207 + Pyrazinamide, J-Pa = TMC207 + PA-824, Pa-Z = PA-824 + Pyrazinamide, Pa-Z-M or M-PA-Z = PA-824 + Pyrazinamide + Moxifloxacin, J-Pa-Z-C = TMC207 + PA-824 + Pyrazinamide + Clofazimine, J-Pa-Z = TMC207 + PA-824 + Pyrazinamide, J-Pa-C = TMC207 + PA-824 + Clofazimine, J-Z-C = TMC207 + Pyrazinamide + Clofazimine, Z = Pyrazinamide, C = Clofazimine, Rifafour = Rifafour e-275®. MDR: Multi-drug resistant; TTP: Time to positivity. N = Total number of patients. n = Number of patients with complete profiles and no censored log(TTP) values.

Table 5.1: Characteristics of Trials Included in Empirical Study

Clinical Trial	Scheduled Sample Days	Treatment Group	N	n
NC003	Daily from Day -2 to Day 14	J-Pa-Z-C	14	13
		J-Pa-Z	14	12
		J-Pa-C	15	12
		J-Z-C	14	14
		Z	15	14
		C	15	13
		Rifafour	15	13
		Total	**102**	**91**
Total		**Grand Total**	**661**	**437**

Note: Treatment group: J = TMC207, J-Z = TMC207 + Pyrazinamide, J-Pa = TMC207 + PA-824, Pa-Z = PA-824 + Pyrazinamide, Pa-Z-M or M-PA-Z = PA-824 + Pyrazinamide + Moxifloxacin, J-Pa-Z-C = TMC207 + PA-824 + Pyrazinamide + Clofazimine, J-Pa-Z = TMC207 + PA-824 + Pyrazinamide, J-Pa-C = TMC207 + PA-824 + Clofazimine, J-Z-C = TMC207 + Pyrazinamide + Clofazimine, Z = Pyrazinamide, C = Clofazimine, Rifafour = Rifafour e-275®. MDR: Multi-drug resistant; TTP: Time to positivity. N = Total number of patients. n = Number of patients with complete profiles and no censored log(TTP) values.

The empirical study was carried out similarly to that done for CFU data (see Section 4.2 and Equation (5.6)).

Plots of the data together with by-patient fits of the hyperbolic tangent regression model are included in Figure C.37 through Figure C.74 of Appendix C.

Figure 5.1 and Figure 5.2 provide plots of residuals for fitted TTP and log(TTP), respectively (i.e. fitted to data on both the original and log-scale) by study. These graphs show that the log-transformation of TTP data stabilizes the variance of the associated residuals (i.e. near constant mean-variance relationship). The normality assumption for TTP data on the logarithmic scale therefore seems reasonable.

Figure 5.3 and Figure 5.4 provide plots and box and whisker plots of the β_2 estimates by study and treatment group.

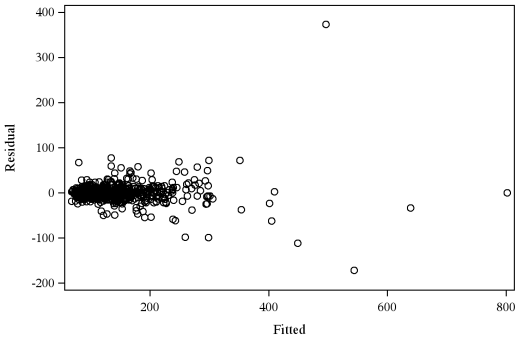
A summary of the by-patient regression model parameter estimates are presented in Table 5.2.

Conclusions drawn from the empirical study are similar to those of the empirical analysis of CFU data (see Section 4.2). The majority of the log(TTP) versus time

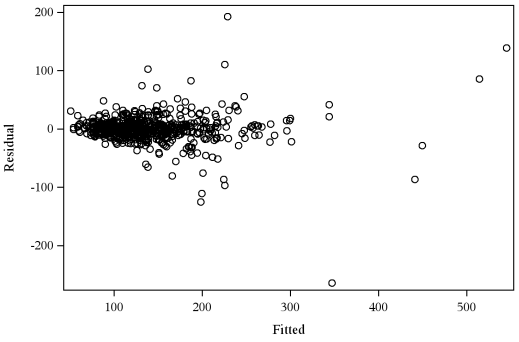
profiles are linear over time, and the majority of the biphasic log(TTP) versus time profiles are increasing fastest during the early phase of treatment.

Even though the evidence of bilinearity in log(TTP) versus time profiles on the whole is not strong, a visual inspection of the model fits suggests that the proposed regression model, i.e. the differential hyperbolic tangent regression model, generally fits the TTP data well.

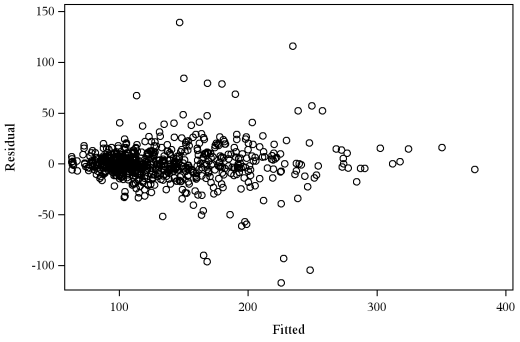
Figure 5.1: Residuals of Fitted TTP for Empirical Study



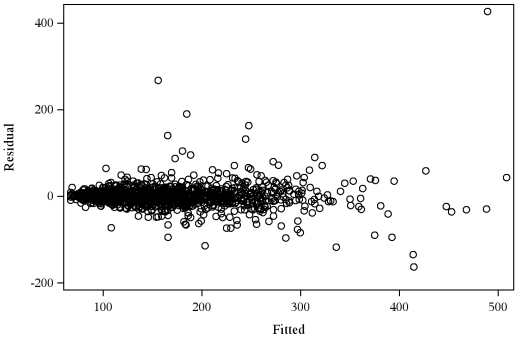
(a) CL001



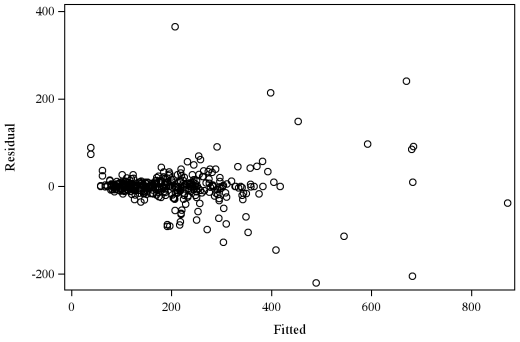
(b) CL007



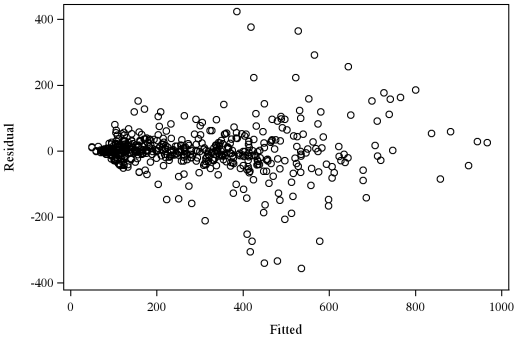
(c) CL010



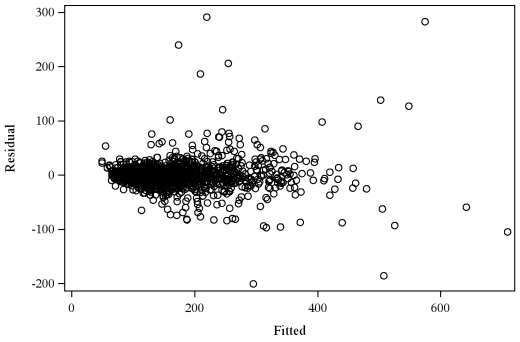
(d) NC001



(e) NC002 (EBA)

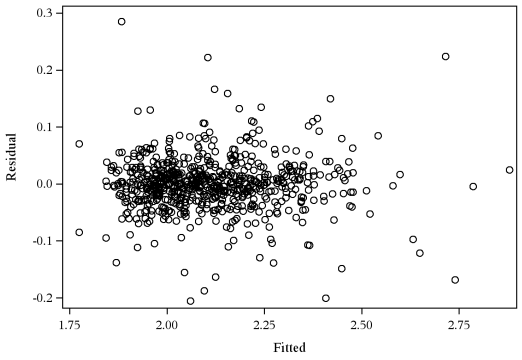


(f) NC002 ("SSCC")

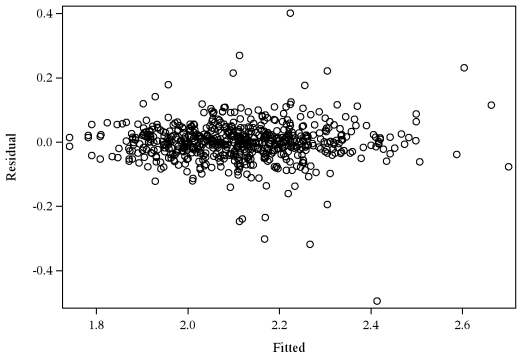


(g) NC003

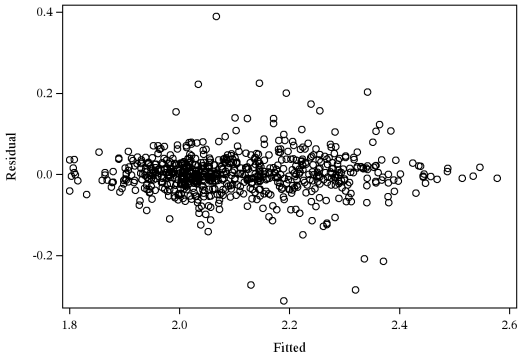
Figure 5.2: Residuals of Fitted log(TTP) for Empirical Study



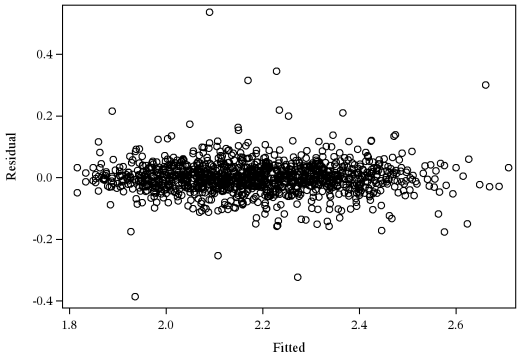
(a) CL001



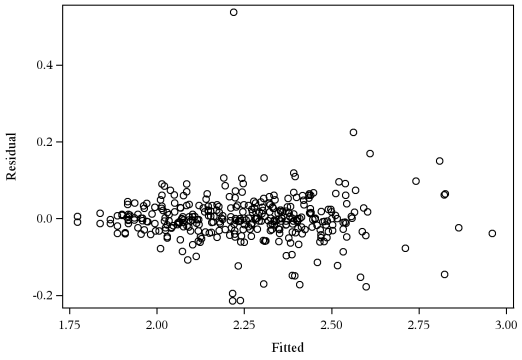
(b) CL007



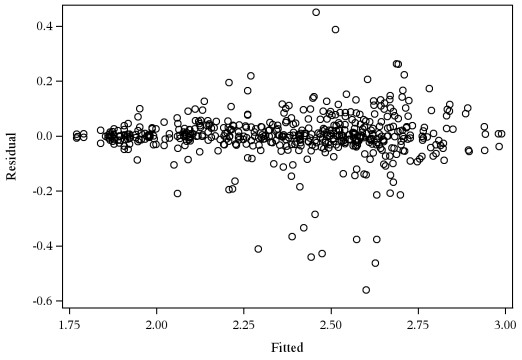
(c) CL010



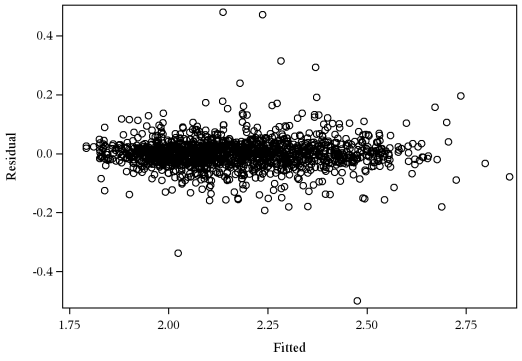
(d) NC001



(e) NC002 (EBA)



(f) NC002 ("SSCC")



(g) NC003

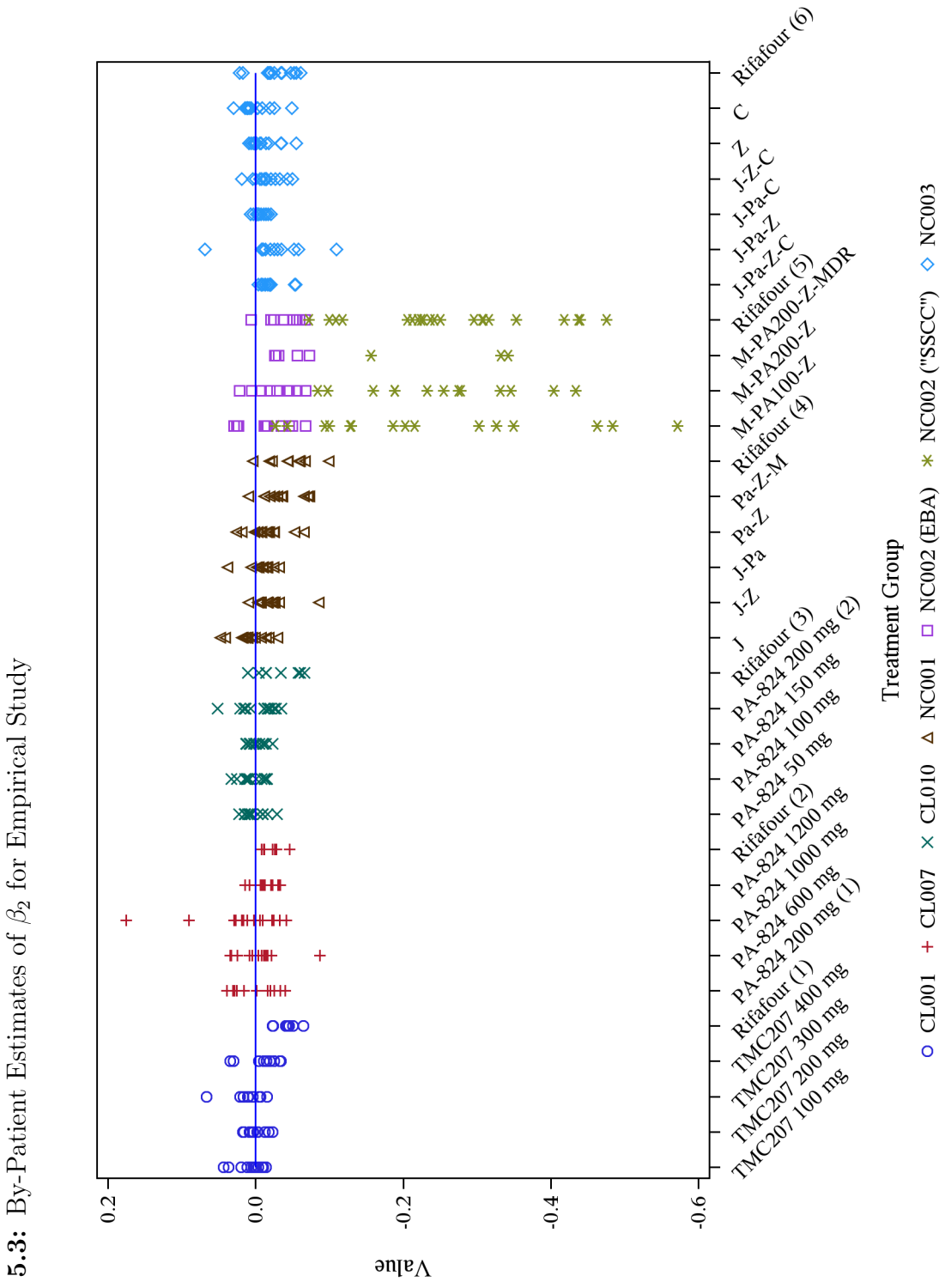
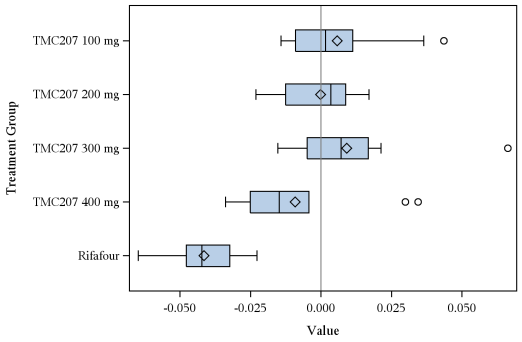
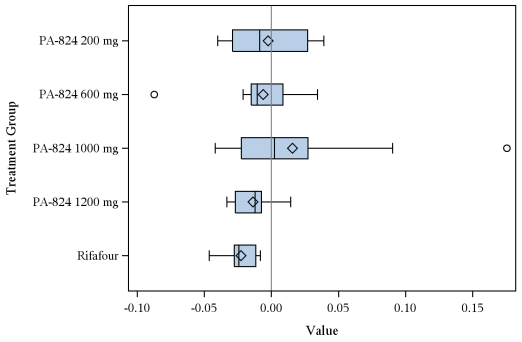


Figure 5.3: By-Patient Estimates of β_2 for Empirical Study

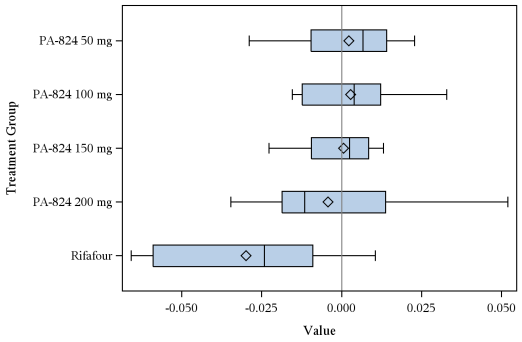
Figure 5.4: Summary of By-Patient Estimates of β_2 for Empirical Study



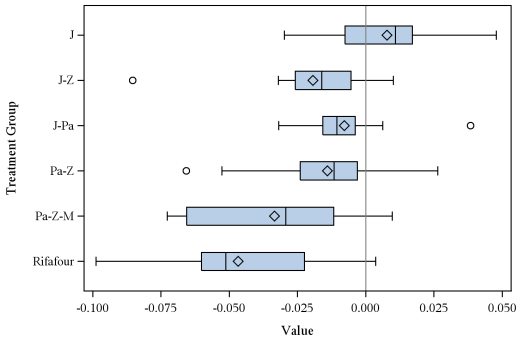
(a) CL001



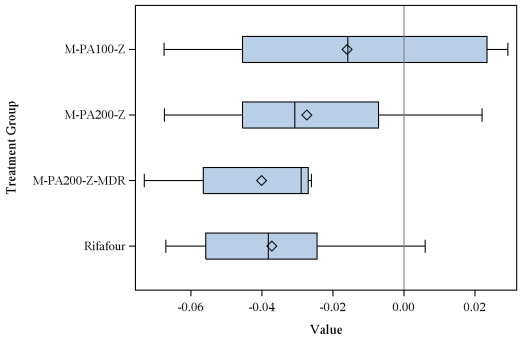
(b) CL007



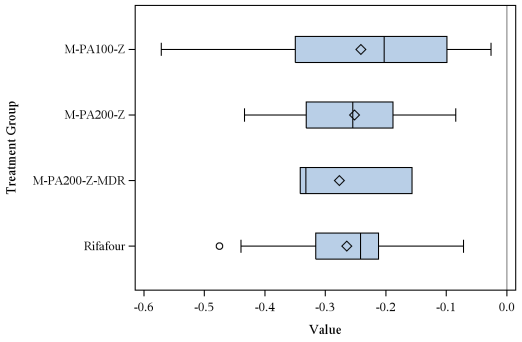
(c) CL010



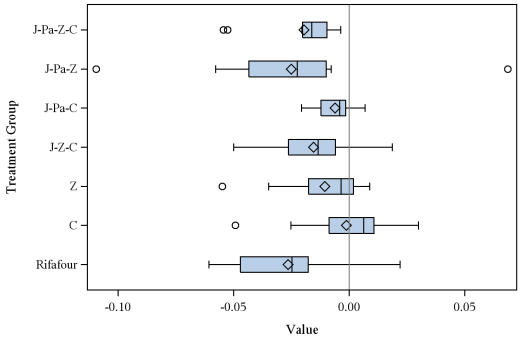
(d) NC001



(e) NC002 (EBA)



(f) NC002 ("SSCC")



(g) NC003

Table 5.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	$\boldsymbol{\kappa}$	$\boldsymbol{\lambda_1}$	$\boldsymbol{\lambda_2}$	$\mathbf{n_L}$	$\mathbf{n_B}$	$\mathbf{n_{BFS}}$	$\mathbf{n_{BSF}}$	$\mathbf{n_{BI}}$	$\mathbf{n_{BM}}$
CL001	TMC207 100 mg	13	7.1 (2.0-11.0)	0.005 (-0.044-0.027)	0.017 (-0.019-0.087)	11	2	0	2	1	1
	TMC207 200 mg	11	7.7 (4.0-11.0)	0.013 (0.001-0.035)	0.013 (-0.023-0.040)	10	1	1	0	1	0
	TMC207 300 mg	12	5.8 (2.4-11.0)	0.002 (-0.100-0.030)	0.020 (-0.003-0.058)	10	2	0	2	2	0
	TMC207 400 mg	10	4.8 (2.0-11.0)	0.026 (-0.044-0.077)	0.008 (-0.034-0.044)	5	5	3	2	4	1
	Rifafour	8	3.2 (2.0-7.0)	0.096 (0.069-0.152)	0.013 (-0.011-0.023)	0	8	8	0	6	2
	Total	54	5.9 (2.0-11.0)	0.023 (-0.100-0.152)	0.014 (-0.034-0.087)	36	18	12	6	14	4
CL007	PA-824 200 mg	12	5.7 (2.0-11.0)	0.009 (-0.054-0.091)	0.004 (-0.043-0.037)	4	8	4	4	7	1
	PA-824 600 mg	15	6.5 (2.0-11.0)	0.017 (-0.044-0.063)	0.004 (-0.111-0.049)	10	5	2	3	4	1
	PA-824 1000 mg	15	5.3 (2.0-10.0)	-0.017 (-0.331-0.084)	0.015 (-0.016-0.071)	7	8	4	4	6	2
	PA-824 1200 mg	12	7.1 (3.1-10.2)	0.031 (0.005-0.069)	0.003 (-0.028-0.034)	7	5	5	0	5	0
	Rifafour	8	6.2 (2.7-10.0)	0.048 (0.024-0.100)	0.003 (-0.031-0.019)	3	5	5	0	4	1
	Total	62	6.1 (2.0-11.0)	0.014 (-0.331-0.100)	0.006 (-0.111-0.071)	31	31	20	11	26	5

Note: TTP: Time to positivity. N = Total number of patients. n = Number of patients with complete profiles and no censored log(TTP) values. n_L = Number of linearly increasing profiles ($|\beta_2| \leq 0.02$). n_B = Number of biphasic profiles ($|\beta_2| > 0.02$). n_{BFS} = Number of biphasic profiles which initial rate of increase is fast, followed by slower rate of increase ($\beta_2 < -0.02$). n_{BSF} = Number of biphasic profiles which initial rate of increase is slow, followed by a faster rate of increase ($\beta_2 > 0.02$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of increase ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of increase ($\gamma \geq 1$).

Table 5.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	κ	λ_1	λ_2	n_L	n_B	n_{BFS}	n_{BSF}	n_{BI}	n_{BM}
CL010	PA-824 50 mg	13	6.6 (2.0-11.0)	0.004 (-0.032-0.031)	0.009 (-0.028-0.033)	11	2	1	1	2	0
	PA-824 100 mg	14	6.2 (2.0-11.0)	0.008 (-0.053-0.034)	0.014 (-0.018-0.038)	12	2	0	2	2	0
	PA-824 150 mg	15	6.3 (2.3-11.0)	0.011 (-0.010-0.038)	0.013 (-0.029-0.035)	14	1	1	0	1	0
	PA-824 200 mg	16	8.4 (2.0-11.0)	0.016 (-0.079-0.052)	0.008 (-0.047-0.052)	11	5	3	2	5	0
	Rifafour	8	5.3 (2.0-9.6)	0.075 (0.015-0.145)	0.015 (-0.007-0.043)	4	4	4	0	4	0
	Total	66	6.7 (2.0-11.0)	0.018 (-0.079-0.145)	0.011 (-0.047-0.052)	52	14	9	5	14	0
NC001	J	14	7.6 (2.0-11.0)	0.006 (-0.080-0.046)	0.022 (-0.027-0.077)	11	3	1	2	3	0
	J-Z	14	6.9 (3.0-11.0)	0.039 (0.007-0.071)	-0.000 (-0.117-0.027)	8	6	6	0	4	2
	J-Pa	13	7.7 (4.3-10.9)	0.023 (-0.001-0.036)	0.008 (-0.048-0.076)	10	3	2	1	3	0
	Pa-Z	14	7.0 (2.0-11.0)	0.034 (-0.026-0.137)	0.006 (-0.051-0.038)	9	5	4	1	4	1
	Pa-Z-M	11	6.1 (2.0-11.0)	0.070 (0.008-0.150)	0.003 (-0.091-0.027)	4	7	7	0	3	4
	Rifafour	10	3.3 (2.0-9.2)	0.107 (0.019-0.210)	0.014 (0.003-0.026)	2	8	8	0	5	3
	Total	76	6.6 (2.0-11.0)	0.043 (-0.080-0.210)	0.009 (-0.117-0.077)	44	32	28	4	22	10

Note: TTP: Time to positivity. N = Total number of patients. n = Number of patients with complete profiles and no censored log(TTP) values. n_L = Number of linearly increasing profiles ($|\beta_2| \leq 0.02$). n_B = Number of biphasic profiles ($|\beta_2| > 0.02$). n_{BFS} = Number of biphasic profiles which initial rate of increase is fast, followed by slower rate of increase ($\beta_2 < -0.02$). n_{BSF} = Number of biphasic profiles which initial rate of increase is slow, followed by a faster rate of increase ($\beta_2 > 0.02$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of increase ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of increase ($\gamma \geq 1$).

Table 5.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	$\boldsymbol{\kappa}$	$\boldsymbol{\lambda_1}$	$\boldsymbol{\lambda_2}$	$\mathbf{n_L}$	$\mathbf{n_B}$	$\mathbf{n_{BFS}}$	$\mathbf{n_{BSF}}$	$\mathbf{n_{BI}}$	$\mathbf{n_{BM}}$
NC002 (EBA)	M-PA100-Z	11	6.4 (2.8-10.2)	0.058 (0.004-0.152)	0.027 (-0.006-0.073)	4	7	4	3	4	3
	M-PA200-Z	10	5.2 (2.0-8.6)	0.067 (-0.013-0.151)	0.012 (-0.025-0.034)	3	7	6	1	5	2
	M-PA200-Z-MDR	6	5.4 (2.2-8.5)	0.089 (0.055-0.157)	0.008 (0.001-0.020)	0	6	6	0	5	1
	Rifafour	9	4.6 (2.2-10.5)	0.082 (0.003-0.145)	0.008 (-0.007-0.015)	1	8	8	0	5	3
	Total	36	5.5 (2.0-10.5)	0.072 (-0.013-0.157)	0.015 (-0.025-0.073)	8	28	24	4	19	9
NC002 ("SSCC")	M-PA100-Z	15	6.4 (2.9-11.0)	0.525 (0.146-1.187)	0.043 (-0.116-0.130)	0	15	15	0	11	4
	M-PA200-Z	13	3.9 (2.9-11.0)	0.568 (0.235-0.916)	0.064 (0.023-0.162)	0	13	13	0	9	4
	M-PA200-Z-MDR	3	4.9 (3.4-7.9)	0.612 (0.349-0.764)	0.059 (0.036-0.080)	0	3	3	0	3	0
	Rifafour	21	4.8 (2.9-11.0)	0.583 (0.192-0.994)	0.053 (-0.060-0.111)	0	21	21	0	17	4
	Total	52	5.0 (2.9-11.0)	0.564 (0.146-1.187)	0.053 (-0.116-0.162)	0	52	52	0	40	12

Note: TTP: Time to positivity. N = Total number of patients. n = Number of patients with complete profiles and no censored log(TTP) values. n_L = Number of linearly increasing profiles ($|\beta_2| \leq 0.02$). n_B = Number of biphasic profiles ($|\beta_2| > 0.02$). n_{BFS} = Number of biphasic profiles which initial rate of increase is fast, followed by slower rate of increase ($\beta_2 < -0.02$). n_{BSF} = Number of biphasic profiles which initial rate of increase is slow, followed by a faster rate of increase ($\beta_2 > 0.02$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of increase ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of increase ($\gamma \geq 1$).

Table 5.2: By-Patient Regression Model Parameter Estimates for Empirical Study

			Mean (Range)								
Clinical Trial	**Treatment Group**	**n**	$\boldsymbol{\kappa}$	$\boldsymbol{\lambda_1}$	$\boldsymbol{\lambda_2}$	$\mathbf{n_L}$	$\mathbf{n_B}$	$\mathbf{n_{BFS}}$	$\mathbf{n_{BSF}}$	$\mathbf{n_{BI}}$	$\mathbf{n_{BM}}$
NC003	J-Pa-Z-C	13	7.0 (3.8-11.0)	0.045 (0.017-0.088)	0.005 (-0.060-0.028)	9	4	4	0	3	1
	J-Pa-Z	12	5.2 (2.0-11.0)	0.062 (-0.104-0.234)	0.012 (-0.053-0.033)	5	7	6	1	5	2
	J-Pa-C	12	6.8 (2.4-11.0)	0.024 (0.006-0.043)	0.012 (-0.009-0.025)	11	1	1	0	1	0
	J-Z-C	14	5.6 (2.0-11.0)	0.040 (-0.011-0.122)	0.009 (-0.050-0.036)	9	5	5	0	3	2
	Z	14	6.4 (2.0-9.0)	0.023 (-0.006-0.097)	0.001 (-0.034-0.018)	11	3	3	0	3	0
	C	13	6.8 (2.0-11.0)	-0.001 (-0.051-0.067)	-0.004 (-0.051-0.020)	10	3	2	1	3	0
	Rifafour	13	4.6 (2.0-11.0)	0.071 (0.014-0.145)	0.018 (-0.057-0.061)	4	9	8	1	6	3
	Total	91	6.0 (2.0-11.0)	0.037 (-0.104-0.234)	0.007 (-0.060-0.061)	59	32	29	3	24	8
Total	Total	437	6.1 (2.0-11.0)	0.096 (-0.331-1.187)	0.015 (-0.117-0.162)	230	207	174	33	159	48

Note: TTP: Time to positivity. N = Total number of patients. n = Number of patients with complete profiles and no censored log(TTP) values. n_L = Number of linearly increasing profiles ($|\beta_2| \leq 0.02$). n_B = Number of biphasic profiles ($|\beta_2| > 0.02$). n_{BFS} = Number of biphasic profiles which initial rate of increase is fast, followed by slower rate of increase ($\beta_2 < -0.02$). n_{BSF} = Number of biphasic profiles which initial rate of increase is slow, followed by a faster rate of increase ($\beta_2 > 0.02$). n_{BI} = Number of bilinear profiles with abrupt transition between the two rates of increase ($\gamma < 1$). n_{BM} = Number of biphasic profiles with smooth transition between the two rates of increase ($\gamma \geq 1$).

5.6 NC001 Trial

This section provides results from the reanalysis of the TTP data of the NC001 trial (see Table 5.1).

Results from the fit of the following mixed effects regression models are presented: Model 1.1, Model 1.5 and Model 2.2. None of the outliers were excluded from the joint Bayesian NLME analyses.

Figure 5.5 shows nested plots of the observed log(TTP) by treatment group.

Plots of the observed log(TTP) together with by-patient and joint Bayesian NLME fits of the regression model are included in Figure D.14 through Figure D.19 of Appendix D for each patient for Model 1.1.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table 5.3 for Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(TTP) versus time profiles are shown in Figure 5.6 by study day and treatment group for Model 1.1.

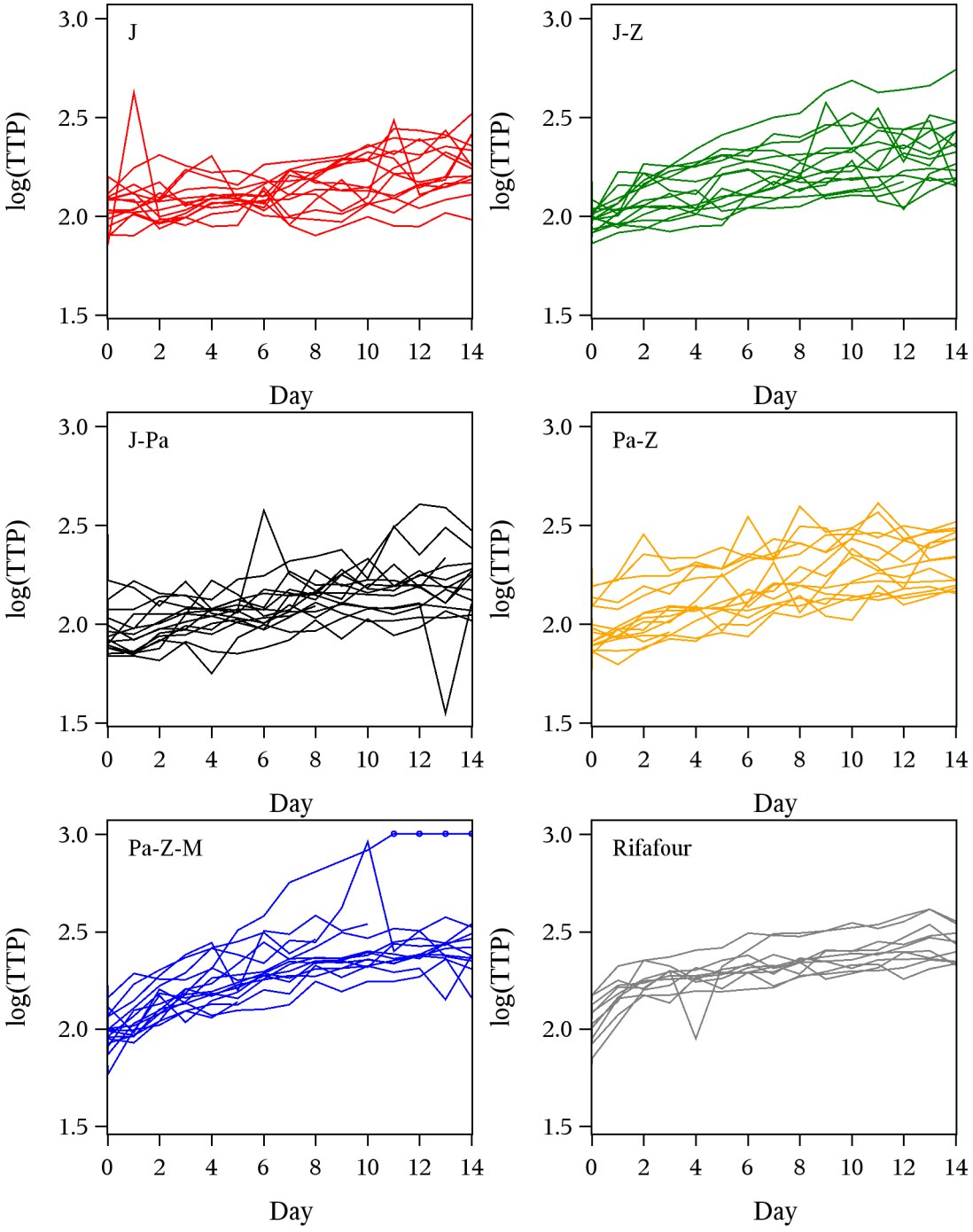
Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$ are shown in Figure 5.7, Figure 5.8 and Figure 5.9 by treatment group and model. The linear model (Model 2.2) yields results substantially different to those of other models.

Model comparison statistics for the various Bayesian NLME regression models fitted are provided in Table 5.4.

The DIC favors differential hyperbolic tangent regression models, followed by the linear regression model.

Bayes factors (marginal likelihoods) favor the linear regression model, followed by differential hyperbolic tangent regression models.

Figure 5.5: Observed log(TTP) Over Time



Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

The ICPOs suggest the models fit the data reasonably well.

Table 5.3: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Percentage Versus Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	1.497	[0.740; 2.239]	−1.238	[-2.281; -0.199]
	J-Z (N=15)	15	2.387	[1.454; 3.291]	−0.372	[-1.531; 0.795]
	J-Pa (N=15)	15	1.705	[1.015; 2.374]	−1.035	[-2.031; -0.034]
	Pa-Z (N=15)	15	2.434	[1.651; 3.197]	−0.327	[-1.391; 0.739]
	Pa-Z-M (N=15)	15	3.096	[0.930; 5.121]	0.317	[-1.909; 2.432]
	Rifafour (N=10)	10	2.771	[1.996; 3.549]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	1.058	[-0.212; 2.301]	−6.896	[-9.758; -4.236]
	J-Z (N=15)	15	3.592	[2.314; 4.983]	−4.561	[-7.449; -1.786]
	J-Pa (N=15)	15	2.041	[0.636; 3.444]	−5.989	[-8.908; -3.244]
	Pa-Z (N=15)	15	3.264	[2.087; 4.451]	−4.863	[-7.743; -2.163]
	Pa-Z-M (N=15)	15	6.643	[4.446; 9.051]	−1.750	[-5.160; 1.614]
	Rifafour (N=10)	10	8.563	[5.813; 11.720]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	1.571	[0.828; 2.352]	−0.261	[-1.416; 0.937]
	J-Z (N=15)	15	2.189	[1.101; 3.117]	0.346	[-1.050; 1.660]
	J-Pa (N=15)	15	1.650	[0.832; 2.420]	−0.182	[-1.368; 1.019]
	Pa-Z (N=15)	15	2.296	[1.423; 3.057]	0.452	[-0.768; 1.660]
	Pa-Z-M (N=15)	15	2.518	[-0.022; 4.814]	0.670	[-1.964; 3.120]
	Rifafour (N=10)	10	1.838	[0.902; 2.775]		

Note: BCI: Bayesian credibility interval; $\text{EBA}(t_1 - t_2)$: Daily percentage change in TTP from Day t_1 to Day t_2; TTP: Time to positivity. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure 5.6: Posterior Estimates and Corresponding 95% BCIs for Mean log(TTP) Over Time

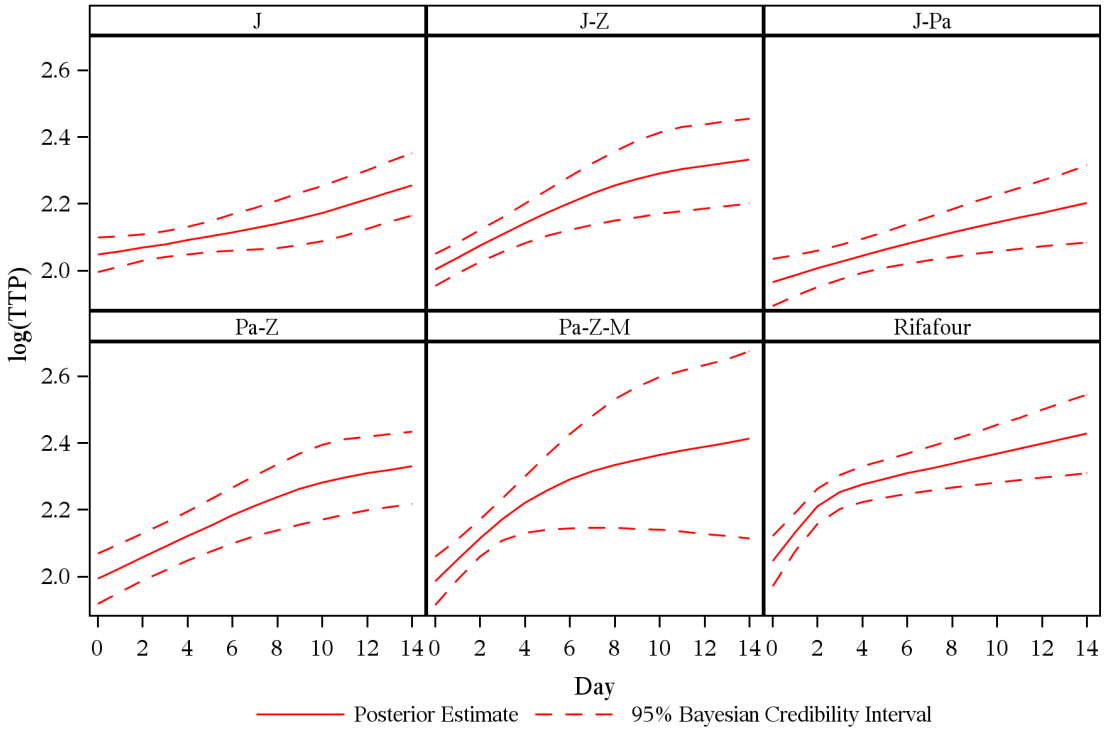
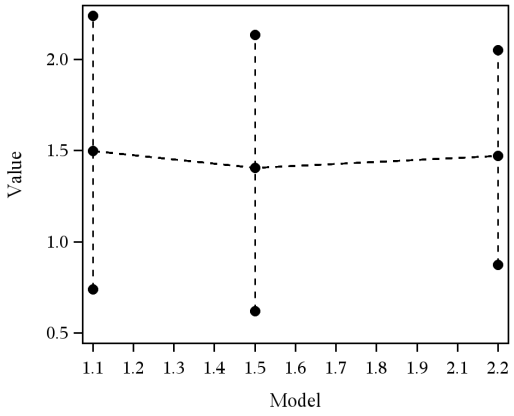


Table 5.4: Comparison of Bayesian NLME Regression Models

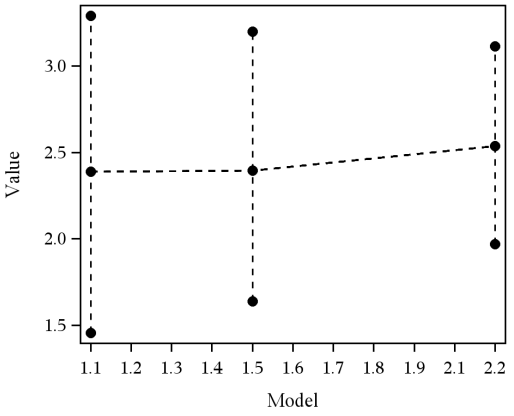
		DIC					% ICPO $< x$		
Regression Function	**Model**	$\overline{\mathbf{D}(\boldsymbol{\theta_m}, \boldsymbol{M})}$	$\mathbf{D}(\bar{\boldsymbol{\theta}}_{\boldsymbol{m}}, \boldsymbol{M})$	$\boldsymbol{p_m}$	**DIC**$(\boldsymbol{M})$	$\ln(\hat{\boldsymbol{f}}(\boldsymbol{y}\|\boldsymbol{M}))$	$\boldsymbol{x = 40}$	$\boldsymbol{x = 70}$	$\boldsymbol{x = 100}$
Differential hyperbolic tangent	Model 1.1	-3487.00	-3670.00	183.60	-3303.00	874.11	98.91	98.99	98.99
	Model 1.5	-3985.00	-4202.00	217.30	-3768.00	1022.18	99.22	99.46	99.46
Linear	Model 2.2	-3350.00	-3517.00	167.10	-3183.00	1084.56	99.15	99.46	99.61

Note: CPO: Conditional posterior ordinate; ICPO: Reciprocal of CPO; DIC: Deviance information criterion; NLME: Nonlinear mixed effects. See Table 3.1 for the specifications of each Bayesian mixed effects regression model.

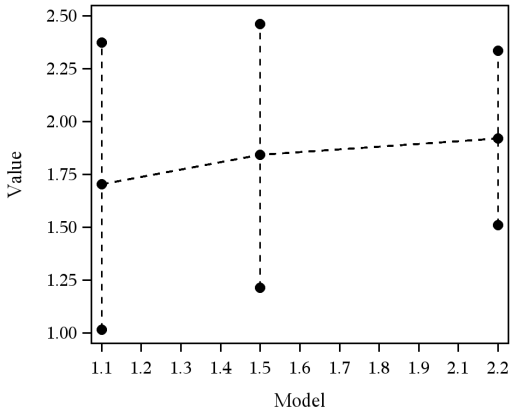
Figure 5.7: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-14)$ by Treatment Group and Model



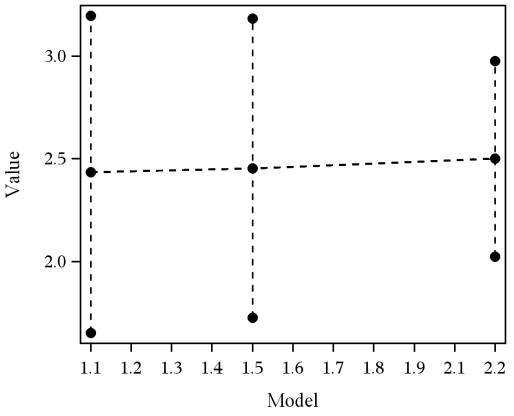
(a) J



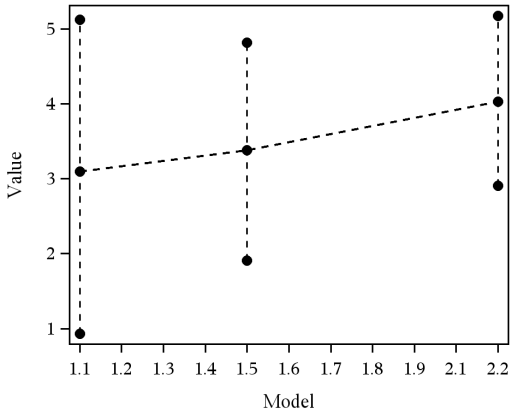
(b) J-Z



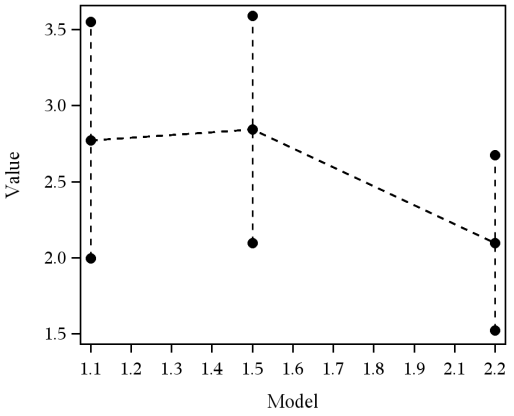
(c) J-Pa



(d) Pa-Z

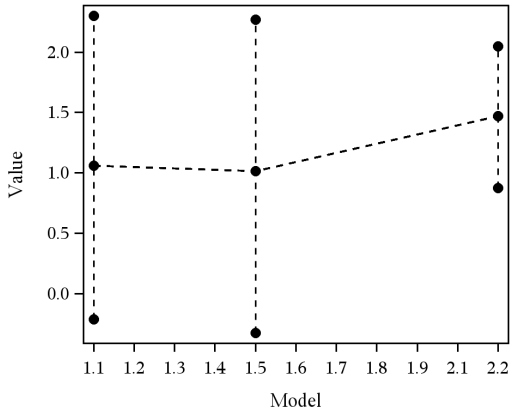


(e) Pa-Z-M

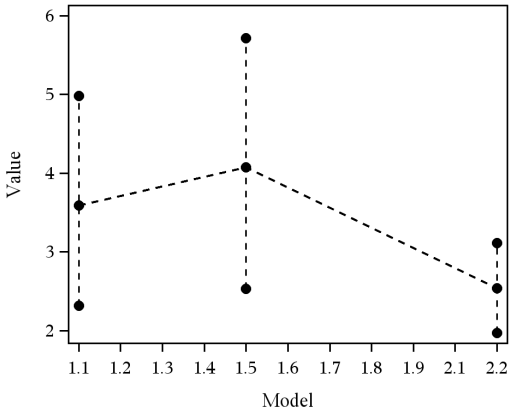


(f) Rifafour

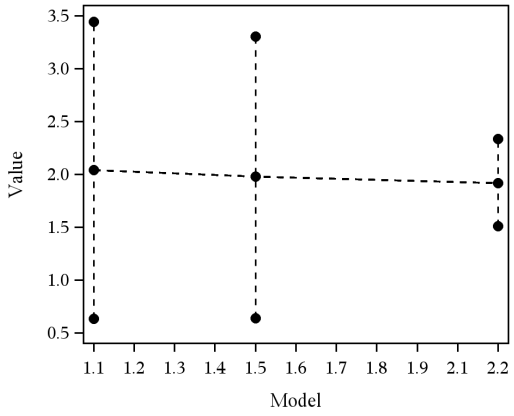
Figure 5.8: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-2)$ by Treatment Group and Model



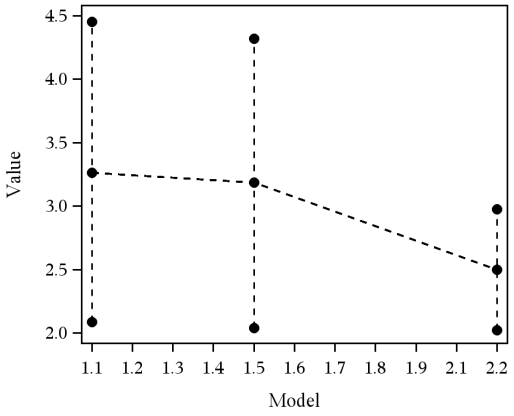
(a) J



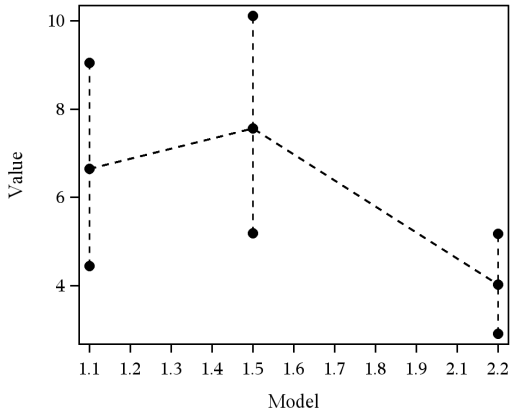
(b) J-Z



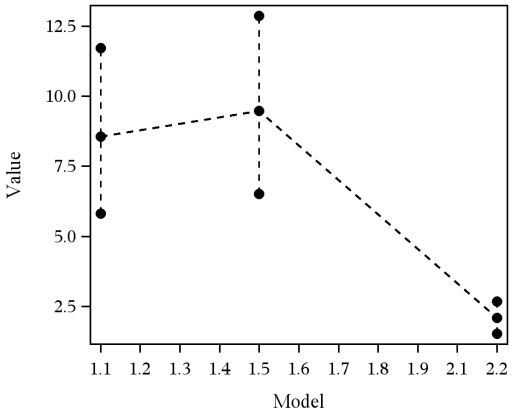
(c) J-Pa



(d) Pa-Z

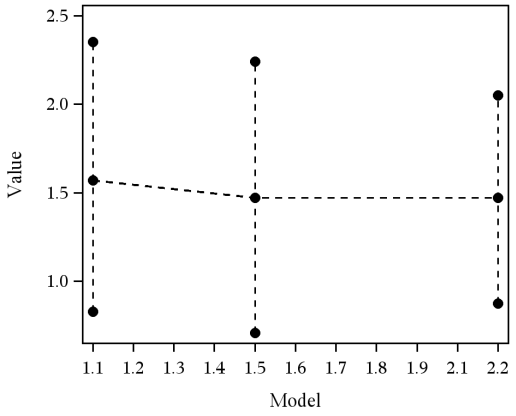


(e) Pa-Z-M

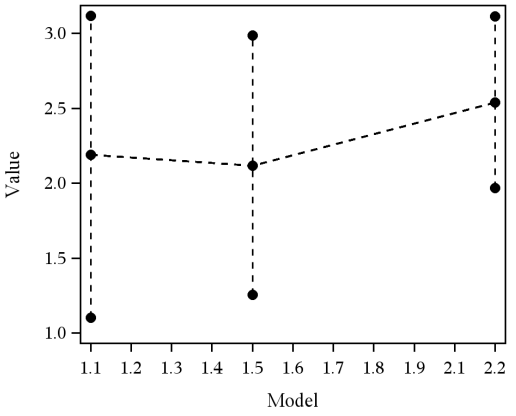


(f) Rifafour

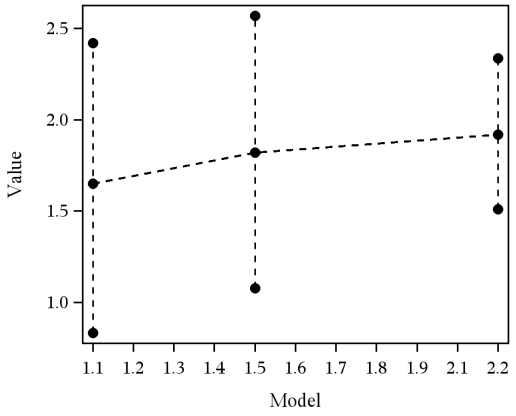
Figure 5.9: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(2-14)$ by Treatment Group and Model



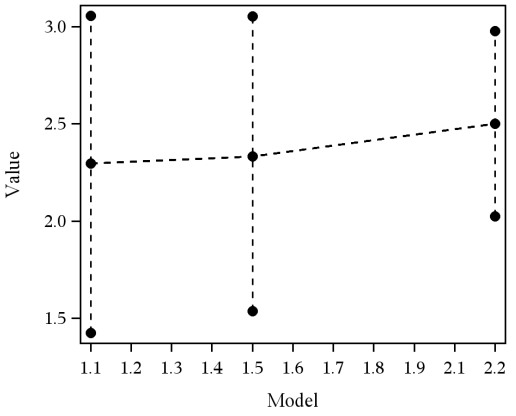
(a) J



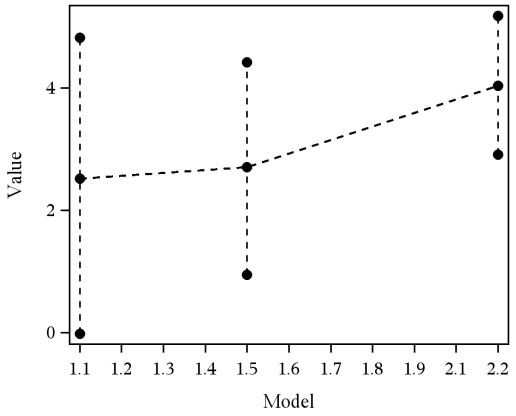
(b) J-Z



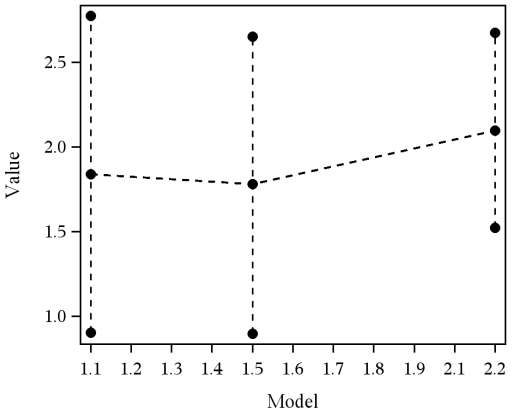
(c) J-Pa



(d) Pa-Z



(e) Pa-Z-M



(f) Rifafour

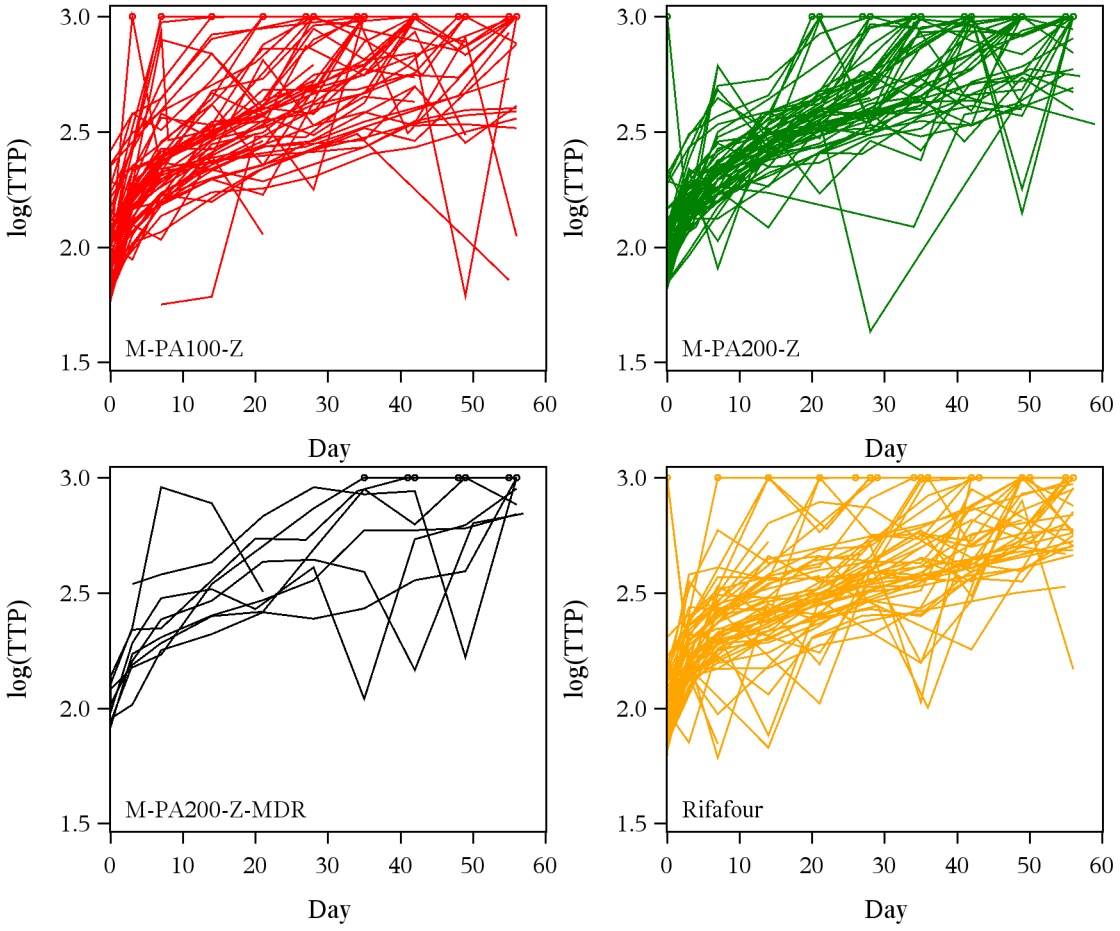
5.7 NC002 ("SSCC") Trial

This section provides results from the reanalysis of the TTP data of the NC002 ("SSCC") trial (see Table 5.1).

Results from the fit of the following mixed effects regression models are presented: Model 1.3 and Model 1.6. None of the outliers were excluded from the joint Bayesian NLME analyses.

Figure 5.10 shows nested plots of the observed log(TTP) by treatment group.

Figure 5.10: Observed log(TTP) Over Time



Posterior estimates and corresponding 95% BCIs for $\text{BA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table 5.5 for Model 1.3.

Posterior estimates and corresponding 95% BCIs for the mean log(TTP) versus time profiles are shown in Figure 5.11 by study day and treatment group for Model 1.3.

Table 5.5: Posterior Estimates and Corresponding 95% BCIs for $\text{BA}_j(t_1 - t_2)$

					Percentage Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{BA_j(0-56)}$	M-PA100-Z (N=60)	55	1.852	[1.528; 2.184]	0.269	[-0.135; 0.673]
	M-PA200-Z (N=61)	57	1.915	[1.668; 2.161]	0.331	[-0.010; 0.676]
	M-PA200-Z-MDR (N=26)	9	1.567	[0.792; 2.297]	−0.012	[-0.819; 0.742]
	Rifafour (N=59)	58	1.579	[1.335; 1.827]		
$\mathbf{BA_j(7-56)}$	M-PA100-Z (N=60)	55	1.453	[1.116; 1.819]	0.200	[-0.224; 0.631]
	M-PA200-Z (N=61)	57	1.605	[1.345; 1.886]	0.350	[-0.009; 0.717]
	M-PA200-Z-MDR (N=26)	9	1.155	[0.249; 1.981]	−0.095	[-1.015; 0.743]
	Rifafour (N=59)	58	1.251	[1.005; 1.515]		

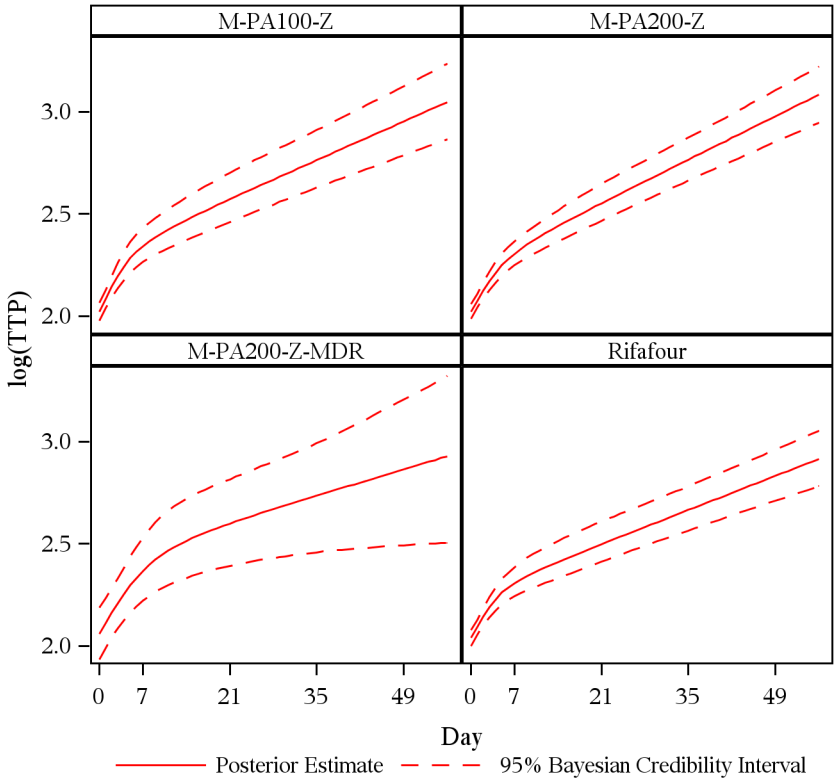
Note: BCI: Bayesian credibility interval; $\text{BA}(t_1 - t_2)$: Daily percentage change in TTP from Day t_1 to Day t_2; TTP: Time to positivity. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

The DIC, marginal likelihood and ICPO < 40 for the model with normally distributed residuals are respectively -863.60, -27.48 and 97.87%, and for the model with Student t distributed residuals are respectively -1899.00, 267.03 and 97.19%.

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

The ICPOs suggest the models fit the data reasonably well.

Figure 5.11: Posterior Estimates and Corresponding 95% BCIs for Mean log(TTP) Over Time



5.8 NC003 Trial

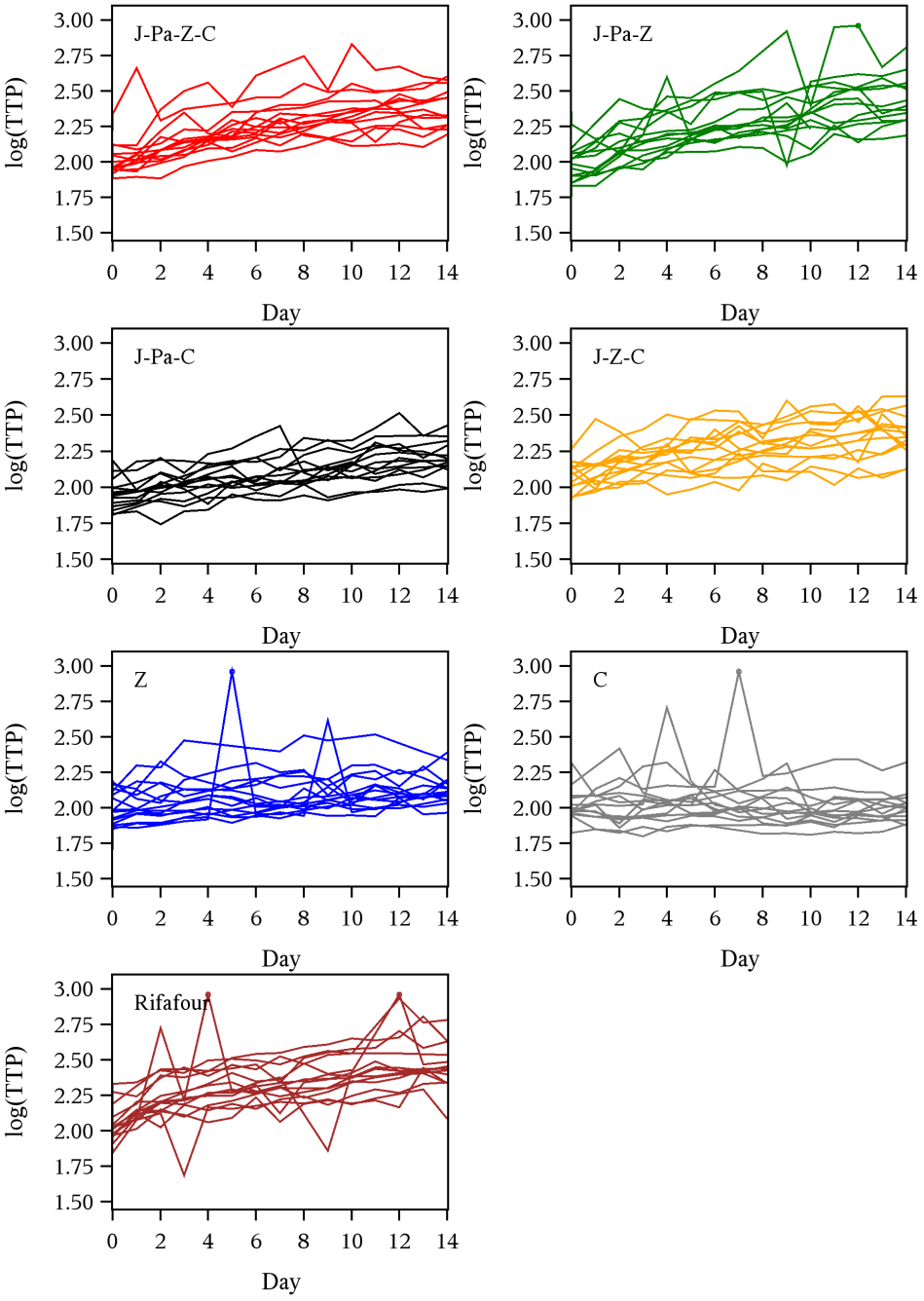
This section provides results from the reanalysis of the TTP data of the NC003 trial (see Table 5.1).

Results from the fit of the following mixed effects regression models are presented: Model 1.1, Model 1.5 and Model 2.2. None of the outliers were excluded from the joint Bayesian NLME analyses.

Figure 5.12 shows nested plots of the observed log(TTP) by treatment group.

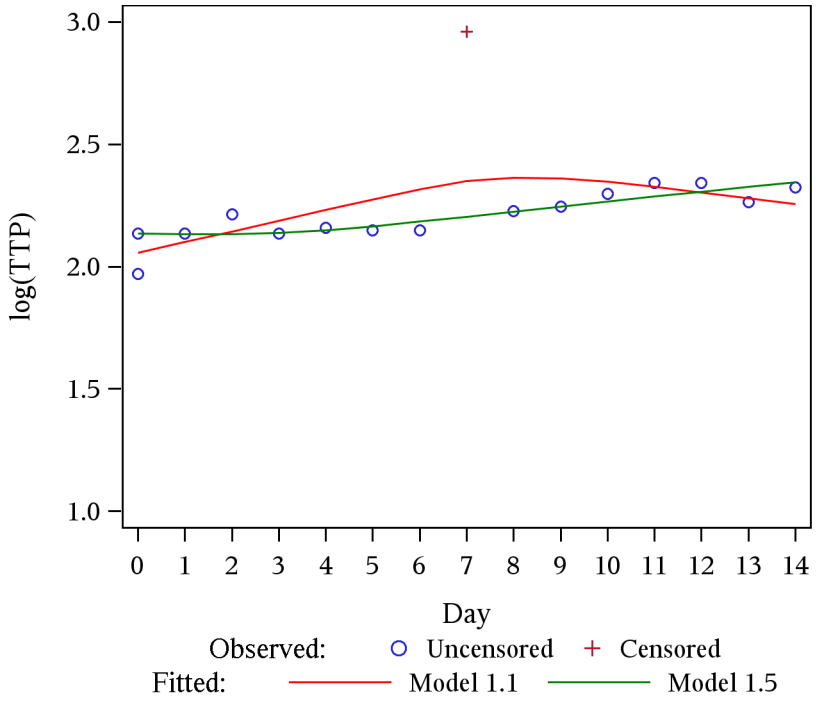
Plots of the observed log(TTP) together with by-patient and joint Bayesian NLME fits of the regression model are included in Figure D.20 through Figure D.26 of Appendix D for each patient for Model 1.1.

Figure 5.12: Observed log(TTP) Over Time



A plot of observed log(TTP) for Patient 001038067 together with joint Bayesian NLME fits calculated from Model 1.1 and Model 1.5 are included in Figure 5.13. This plot is an example of how the Student t distribution (for residuals) is associated with more robust fits than the normal distribution.

Figure 5.13: log(TTP) Versus Time Profile: Model 1.1 Versus Model 1.5



Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table 5.6 for Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(TTP) versus time profiles are shown in Figure 5.14 by study day and treatment group for Model 1.1.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$ are shown in Figure 5.15, Figure 5.16 and Figure 5.17 by treatment group and model. The linear model (Model 2.2) yields results substantially different to those of other models.

Model comparison statistics for the various Bayesian NLME regression models fitted are provided in Table 5.7.

The DIC favors differential hyperbolic tangent regression models, followed by the linear regression model.

Table 5.6: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Percentage Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J-Pa-Z-C (N=14)	14	2.660	[1.613; 3.695]	−0.147	[-1.550; 1.246]
	J-Pa-Z (N=14)	14	3.085	[1.837; 4.414]	0.267	[-1.274; 1.904]
	J-Pa-C (N=15)	15	1.809	[1.156; 2.471]	−0.974	[-2.139; 0.220]
	J-Z-C (N=14)	14	1.949	[1.042; 2.912]	−0.838	[-2.146; 0.522]
	Z (N=15)	15	0.856	[-0.034; 1.760]	−1.901	[-3.200; -0.556]
	C (N=15)	14	−0.152	[-1.094; 0.759]	−2.882	[-4.188; -1.563]
	Rifafour (N=15)	15	2.813	[1.777; 3.820]		
$\mathbf{EBA_j(0-2)}$	J-Pa-Z-C (N=14)	14	4.442	[2.990; 5.968]	−1.925	[-5.042; 1.096]
	J-Pa-Z (N=14)	14	6.317	[3.704; 9.226]	−0.164	[-3.930; 3.583]
	J-Pa-C (N=15)	15	2.266	[1.094; 3.408]	−3.969	[-6.917; -1.170]
	J-Z-C (N=14)	14	3.717	[2.093; 5.552]	−2.606	[-5.774; 0.573]
	Z (N=15)	15	1.778	[0.196; 3.469]	−4.427	[-7.512; -1.428]
	C (N=15)	14	0.730	[-0.999; 2.565]	−5.411	[-8.526; -2.350]
	Rifafour (N=15)	15	6.513	[3.699; 9.631]		
$\mathbf{EBA_j(2-14)}$	J-Pa-Z-C (N=14)	14	2.366	[1.126; 3.482]	0.155	[-1.530; 1.795]
	J-Pa-Z (N=14)	14	2.558	[1.103; 4.005]	0.342	[-1.497; 2.221]
	J-Pa-C (N=15)	15	1.733	[1.022; 2.406]	−0.464	[-1.829; 0.957]
	J-Z-C (N=14)	14	1.658	[0.634; 2.699]	−0.538	[-2.057; 1.060]
	Z (N=15)	15	0.704	[-0.363; 1.653]	−1.471	[-3.004; 0.069]
	C (N=15)	14	−0.298	[-1.455; 0.704]	−2.451	[-4.042; -0.883]
	Rifafour (N=15)	15	2.211	[0.948; 3.449]		

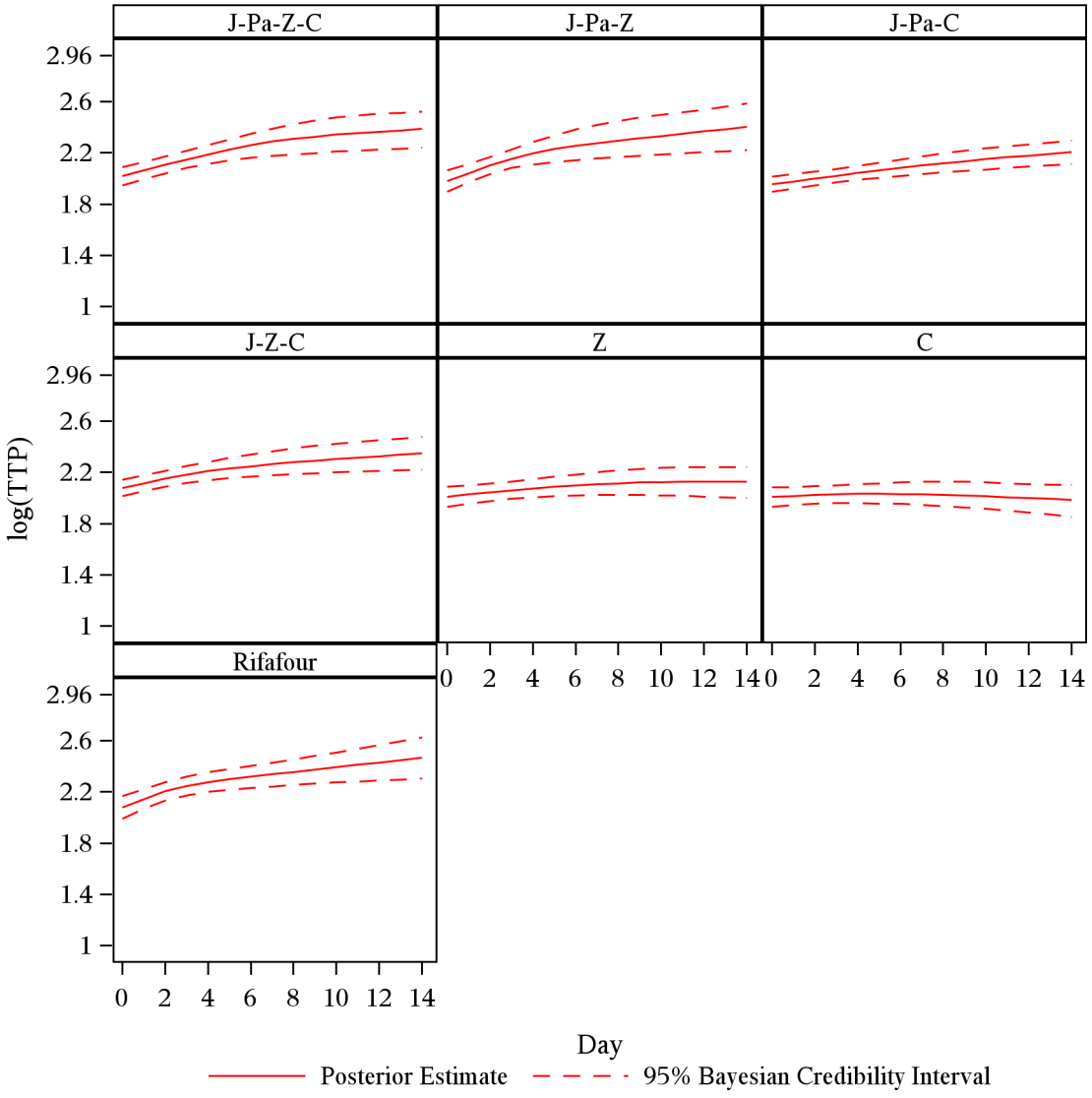
Note: BCI: Bayesian credibility interval; $\text{EBA}(t_1 - t_2)$: Daily percentage change in TTP from Day t_1 to Day t_2; TTP: Time to positivity. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table 5.7: Comparison of Bayesian NLME Regression Models

		DIC					% ICPO $< x$		
Regression Function	Model	$\overline{D(\theta_m, M)}$	$D(\bar{\theta}_m, M)$	p_m	DIC(M)	$\ln(\hat{f}(y\|M))$	$x = 40$	$x = 70$	$x = 100$
Differential hyperbolic	Model 1.1	NE	NE	NE	NE	837.14	98.64	98.77	98.90
tangent	Model 1.5	-4909.00	-5166.00	256.40	-4653.00	1239.65	99.03	99.09	99.16
Linear	Model 2.2	-4248.00	-4452.00	203.60	-4044.00	1376.72	98.97	99.22	99.29

Note: CPO: Conditional posterior ordinate; ICPO: Reciprocal of CPO; DIC: Deviance information criterion; NE: Not estimable; NLME: Nonlinear mixed effects. See Table 3.1 for the specifications of each Bayesian mixed effects regression model.

Figure 5.14: Posterior Estimates and Corresponding 95% BCIs for Mean log(TTP) Over Time

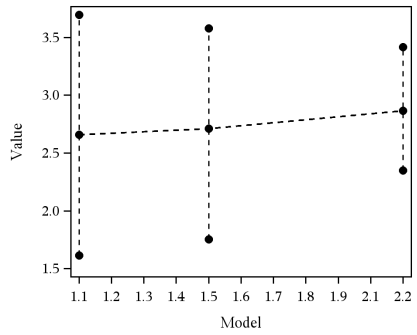


Bayes factors (marginal likelihoods) favor the linear regression model, followed by differential hyperbolic tangent regression models.

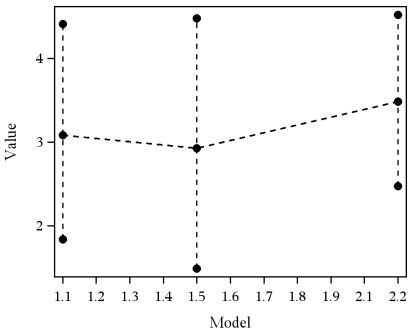
Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

The ICPOs suggest the models fit the data reasonably well.

Figure 5.15: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-14)$ by Treatment Group and Model



(a) J-Pa-Z-C



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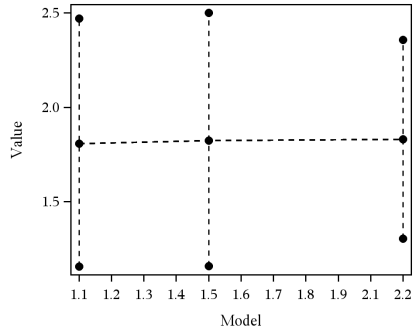
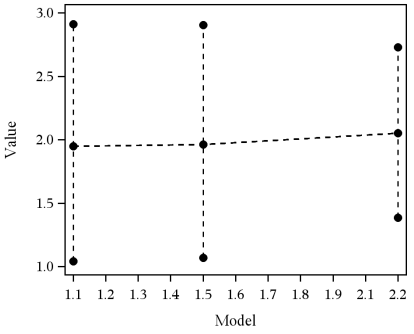
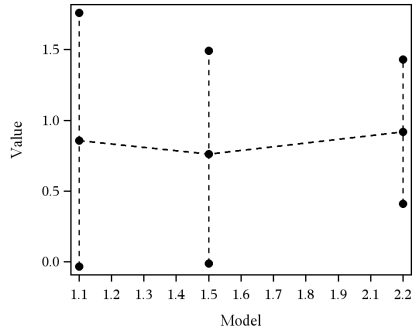


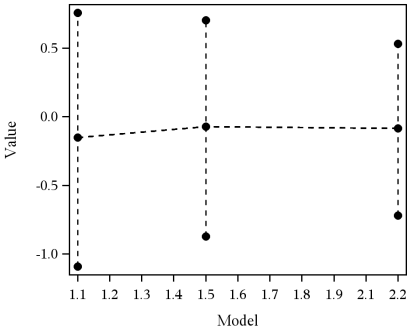
(c) J-Pa-C



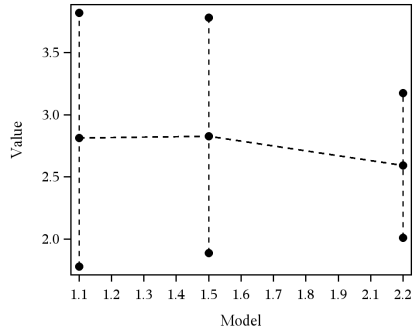
(d) J-Z-C



(e) Z

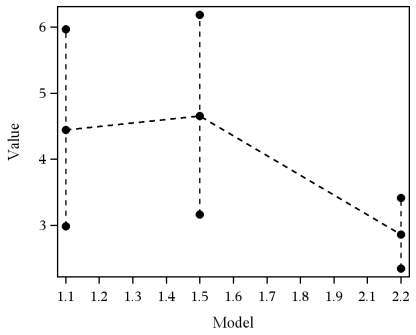


(f) C

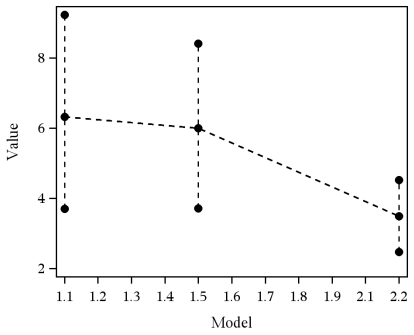


(g) Rifafour

Figure 5.16: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-2)$ by Treatment Group and Model



(a) J-Pa-Z-C



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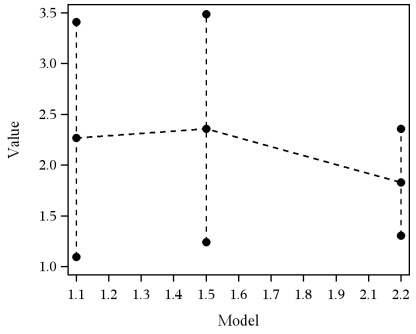
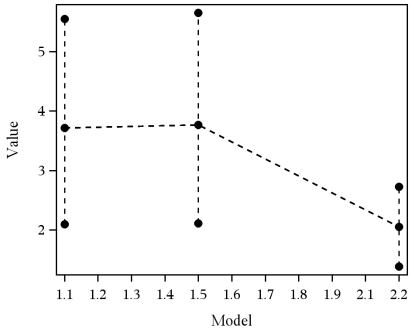


(c) J-Pa-C



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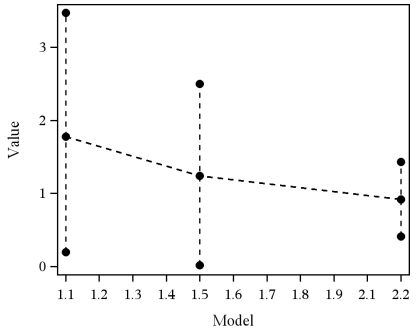

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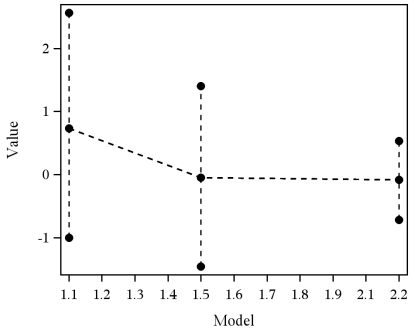

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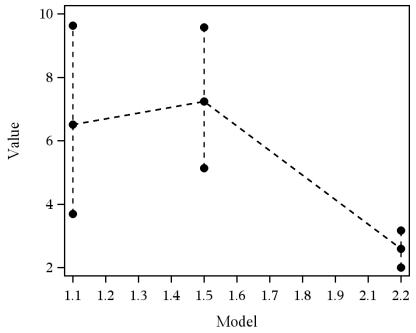
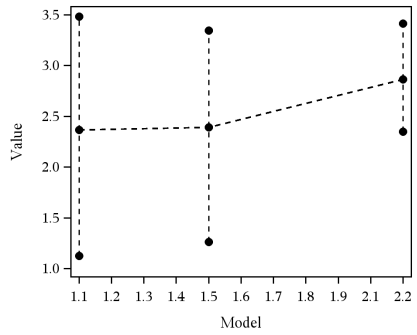


(g) Rifafour

Figure 5.17: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(2-14)$ by Treatment Group and Model



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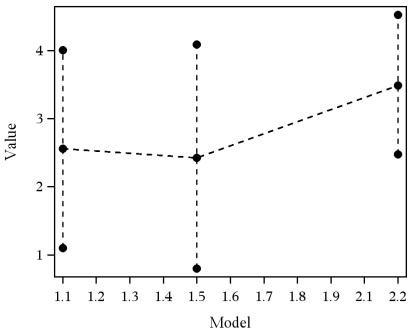
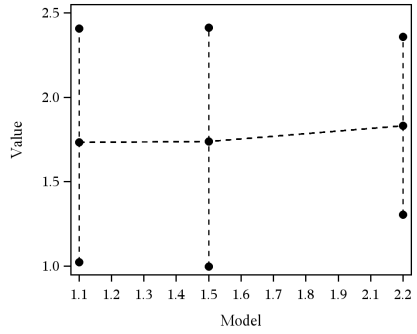
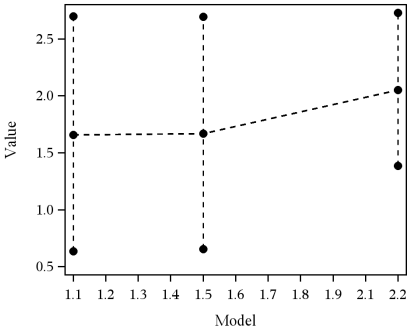


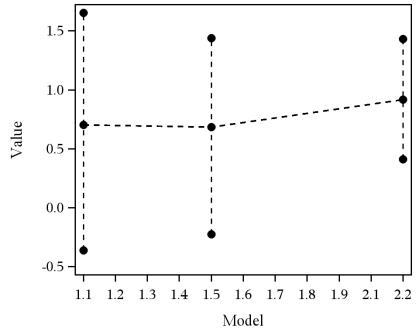
(b) J-Pa-Z



(c) J-Pa-C



(d) J-Z-C



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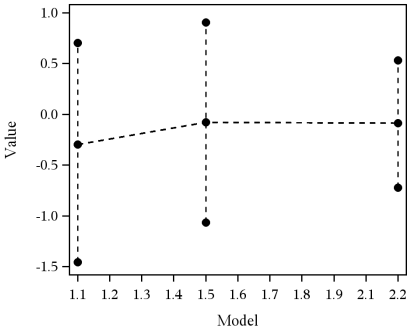
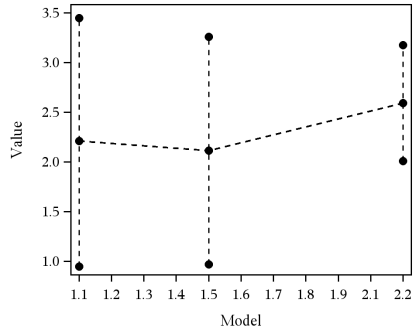


(f) C



(g) Rifafour

Chapter 6

Discussion and Conclusions

Section 6.1 and Section 6.4 of this chapter respectively provide a discussion and conclusions (including recommendations) based on this thesis. Section 6.2 mentions possible shortcomings of the research, and Section 6.3 lists topics for possible future research.

6.1 Discussion

An EBA trial of TB treatments assesses the decline, during the first few days to weeks of treatment, in CFU count of *Mycobacterium tuberculosis* in the sputum of patients with smear-microscopy-positive pulmonary TB. EBA trials are a mainstay of the early clinical development of TB treatment regimens, and thus are frequently performed.

The research reported in this thesis was motivated by the need for a general and flexible regression model for CFU versus time data. Such data have conventionally been modeled using linear, bilinear or bi-exponential regression. Most researchers fitted models to such data on a by-patient basis, and implementation of NLME regression models (in particular, the bi-exponential mixed effects regression model) using frequentist methods has been introduced only recently. Linear regression, while potentially appropriate for some individual profiles, is not generally adequate

since many data profiles are clearly biphasic, at least for treatment and observation periods longer than 2 to 7 days. Both bilinear and bi-exponential models seem adequate for many individual profiles, but the former do not allow for a smooth transition between the initial and terminal phase of decline of CFU counts, while the latter cannot account for drugs and individual profiles which are associated with terminal rates of decline that are faster than initial rates of decline. Such terminal rates of decline have in fact been described recently for a new anti-TB drug, namely TMC207.

In this thesis, a biphasic nonlinear regression model (called the "differential hyperbolic tangent regression model") for CFU data has been proposed; the model comprises linear and bilinear regression models as special cases, and is more flexible than bi-exponential regression models. The model consists of an intercept, two slopes (characterizing the rate of change over time), node (or inflection point) at which transition from one slope to another occurs, and a "smoothness" parameter governing the "speed" of transition. An extensive empirical study of a large number of CFU versus time profiles from a database of six 2-week EBA trials suggests that the proposed model fits well virtually all individual profiles. The model has been implemented as a Bayesian NLME regression model, fitted jointly to the data of all patients from each of the six trial. Zero counts were treated as left censored values.

One advantage of the mixed effects implementation of the model is that for patients with incomplete and sparse profiles (due to missing data), model fits generally remain plausible since "strength is borrowed" from the remainder of the data, which manifests as random effects estimates shrunken towards the overall mean. In particular, mixed effects regression modeling provides improved precision of estimates of random effects relative to their fixed effects counterparts, with more appropriate fixed effects estimates and SEs, and may reduce the bias caused by missing data. In addition, one important advantage of Bayesian inference is that it does not rely on asymptotic approximations, as classical inference methods do for complex models. The implementation of the model using frequentist methods such as SAS® procedure NLMIXED causes convergence issues, and therefore, makes the Bayesian implementation thereof (as an alternative) more attractive.

Statistical inference about the mean EBA of TB treatments, including the mean log(CFU) versus time profile, is based on the Bayesian NLME regression model. The posterior predictive distribution of relevant slope parameters of the Bayesian NLME regression model provides insight into the nature of the EBA of TB treatments; specifically, the posterior predictive distribution of slope parameters allows one to judge whether treatments are associated with mono-linear or bilinear decline of log(CFU) count, and whether log(CFU) count initially decreases fast, followed by a slower rate of decrease, or *vice versa*. In this regard, the reanalysis of data from previously published trials confirms that TMC207, somewhat unusually among anti-TB treatments, is a drug associated with a terminal rate of decline in CFU count that is faster than the initial rate of decline.

The primary Bayesian implementation of the regression model was based on vague prior distributions, normal distribution, and the so-called "default" Wishart prior for the covariance matrix of the random intercept and slope parameters. However, the fit of alternative specifications of residuals, random effects and prior distributions was also explored. The conventional normal regression models for log(CFU) versus time profiles were adapted to offer a more robust approach to accommodate outliers caused by laboratory error, and especially for those isolated cases where zero CFU counts were reported. These models, in particular, specified the Student t distribution for random coefficients and residuals which allows for heavier tails than the normal distribution. These models were further adapted to allow for the modeling of potential skewness. Compared to the conventional normal models, the generalized (heavy tailed) models yielded EBA estimates of smaller magnitude for treatment regimens which appear to contain such outliers. Furthermore, joint Bayesian NLME fits of data profiles containing outliers, based on the Student t distribution, seem more plausible than fits based on the normal distribution. Therefore it seems that the Student t distribution better accommodates occasional outliers seen in the data. Some degree of negative skewness in the distribution of residuals was observed for some treatment regimens.

The Bayesian NLME regression model fitted to CFU data of 2-week EBA trials was extended and fitted to those of an 8-week "SSCC" trial.

DIC statistics and compound Laplace-Metropolis Bayes factors were calculated to discriminate between the various mixed effects regression models investigated. The calculation of the former, especially with regards to the associated multidimensional integrals, is known to be challenging and cumbersome. This thesis describes a workaround whereby marginal likelihoods are calculated relatively easily using an adapted approach in SAS® and the R project.

The DICs favor bilinear models slightly over biphasic models, followed by linear models, whereas the Bayes factors favor linear models, followed by biphasic and bilinear models. Both model comparison statistics prefer the (conventional) Student t distributed models over normal models. Given the different verdicts, it should be noted that the DIC compares models conditional on their model parameters (for which their random effects are likely to enhance model fit), whereas the Bayes factors compare models on a marginal basis. With the analyses, the Bayes factors prefer the most simple model (i.e. linear) over the more refined models (i.e. biphasic and bilinear), whereas the DICs prefer the latter. Note, however, that the linear model cannot establish to which extent the bactericidal activity between initial and later phases of treatment differs, and investigation of this difference is a crucial aspect of EBA studies. Thus the linear model might provide an adequate overall fit to the data in many cases, but does not address one of the important research questions to be answered by EBA studies.

According to previous literature, TTP data (which is an important substitute for CFU data) have only been fitted on a by-patient basis. A large empirical study of TTP data suggests that TTP versus time profiles increase linearly or bilinearly over time. The methodology for modeling of CFU data has therefore been extended to the analysis of TTP data. The conclusions drawn for the modeling of TTP data are similar to those of CFU data.

In summary, the biphasic model proposed here empirically fits well all individual data profiles studied and, according to the marginal likelihood (Bayes factor) criterion, is favored over the bilinear model. Furthermore, the biphasic model allows one to quantify differences in early and late rates of decline of CFU counts, which is of some importance in characterizing the mode of action of anti-TB treatments.

6.2 Possible Shortcomings

The following is a list of possible shortcomings of the methods developed in this PhD thesis:

- The DIC statistics for Bayesian regression models have been obtained directly from OpenBUGS. The DICs for specialized models which implement heavy tailed distributions are conditional also on the nuisance parameters, and have therefore not been reported. Only Bayes factors have been calculated to discriminate between these and remainder models. In future research, the associated DIC statistics will be calculated outside OpenBUGS.

- Posterior samples of the parameters of the bi-exponential mixed effects regression model unexpectedly failed to converge for the 8-week "SSCC" study. Alternative MCMC sampling techniques and reparameterizations of the model will be looked into for any possible future research.

- With the proposed model, the random effects describing the inflection points (or nodes) follow truncated normal distributions. The OpenBUGS software does not have the functionality to model correlation between parameters with truncated distributions. In possible future research, multivariate truncated distributions will be implemented once available with future releases of OpenBUGS. However, modeling correlation between the node parameter and the intercept and slope parameters would further add parameters to a model that is already relatively "parameter-rich".

- Due to long MCMC sampling periods, simulation studies to assess the coverage probability of the associated models have not been carried out. In possible future research, simultaneous MCMC sampling on multiple computers will be used to speed up the simulation process. In addition, more sophisticated simulation techniques can be explored once available with future releases of OpenBUGS.

6.3 Topics for Possible Future Research

The following is a (non-exhaustive) list of possible research extensions to the methods developed in this PhD thesis:

- **Covariate adjustments**: The proposed NLME regression model can be extended to adjust for important factors (interaction terms) and covariates such as HIV status, CD4 count and other baseline characteristics.
- **Nonlinear Poisson regression for CFU data**: As an alternative to performing "normal" nonlinear regression of log(CFU) count against time, treating zero counts as censored values, one can fit overdispersed NLME Poisson regression models.
- **Nonlinear gamma regression for TTP data**: The gamma distribution might be a useful alternative to the log-normal distribution for TTP data.
- **Relationship and correlation of EBA characteristics based on CFU and TTP data, respectively**: The research may include the investigation of the relationship and correlation of EBA characteristics based on CFU and TTP data, respectively. Furthermore, it seems worthwhile to investigate which of the two types of data is associated with the highest statistical power to discriminate between treatment regimens.
- **Surrogacy (short term versus long term outcomes)**: The proposed NLME regression model can be extended to assess how short term outcomes in Phase II trials (e.g. bactericidal activity during the first 8 weeks of treatment) predict long term (binary) outcomes in Phase II trials, using logistic regression modeling.

Further research beyond the scope of EBA TB drug development includes the following Bayesian methodologies, specific to linear and nonlinear random effects models:

- **Bayesian model selection**: The use of compound Laplace-Metropolis Bayes factors in mixed models can be compared with alternative techniques for the estimation of Bayes factors.

- **Robust Bayesian models**: Random effects in mixed models are usually specified to follow a normal distribution. The investigation of heavy tailed and skew distributions (i.e. "robust" regression modeling) that are robust to occasional outliers seen in data can be extended.

6.4 Conclusions and Recommendations

This thesis proposes a new biphasic nonlinear regression model (called the "differential hyperbolic tangent regression model") for CFU data that comprises linear and bilinear regression models as special cases, and is more flexible than biexponential regression models.

The following conclusions and recommendations are listed below for practitioners who need to analyze CFU and TTP data of EBA TB trials:

- The biphasic regression model should be implemented as a Bayesian NLME regression model, fitted jointly to the data of all patients from a given trial, is more appropriate than by-patient regression modeling. Fits of Bayesian mixed effects regression models are plausible since they:
  - Are associated with shrunken random effects estimates which may accommodate incomplete and sparse profiles more appropriately.
  - Provide improved precision of model parameter estimates.
  - Do not rely on asymptotic approximations (like classical inference methods).
  - Are associated with less convergence issues when fitted using the OpenBUGS software.

- The so-called "default" Wishart prior for the covariance matrix of the random intercept and slope parameters should be specified to accommodate small variances in the latter.
- The posterior predictive distribution of relevant slope parameters should be calculated, to provide insight into the nature of the EBA of TB treatments.
- Heavy tailed distributions (in particular, the Student t distribution) better accommodate occasional outliers seen in the data. Thus the Student t model should routinely be fitted.
- DIC statistics and compound Laplace-Metropolis Bayes factors should be calculated to discriminate between models (with alternative specifications of residuals, random effects and prior distributions).
- The biphasic model should be fitted to TTP data in the same way as for CFU data.

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Appendix A

Differential Hyperbolic Tangent Regression Model: Posterior Distributions

Full Likelihood

$$L\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \boldsymbol{\mu_j}, \kappa_j, \gamma_j, \Omega_{\boldsymbol{\mu}j}, \sigma^2_{\kappa j}, \sigma^2_{\gamma j}, \sigma^2_{\varepsilon j}, i = 1, \ldots, N, j = 1, \ldots, J, k = 1, \ldots, K_{ij} | \boldsymbol{y}\right) \tag{A.1}$$

$$= \left(\prod_{i=1}^{N} \prod_{\substack{j=1 \\ i \in \{j\}}}^{J} L\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \sigma^2_{\varepsilon j}, k = 1, \ldots, K_{ij} | \boldsymbol{y_{ij}}\right) \right) \cdot \prod_{i=1}^{N} \prod_{\substack{j=1 \\ i \in \{j\}}}^{J} \left(P\left[\boldsymbol{\mu_{ij}} | \boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}\right] \cdot P\left[\kappa_{ij} | \kappa_j, \sigma^2_{\kappa j}\right] \cdot P\left[\gamma_{ij} | \gamma_j, \sigma^2_{\gamma j}\right] \right)$$

$$\propto \left(\prod_{j=1}^{J}\left(\sigma_{\varepsilon_j}^2\right)^{-\frac{1}{2}T_j}\right)\cdot\exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\sum_{k=1}^{K_{ij}}\left[\frac{\log(y_{ijk})-\left(\alpha_{ij}-\beta_{1ij}\cdot t_{ijk}-\beta_{2ij}\cdot\gamma_{ij}\cdot\log\left[\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}+e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}}+e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right]\right)}{\sigma_{\varepsilon_j}}\right]^2\right)\cdot$$

$$\prod_{i=1}^{N}\prod_{\substack{j=1\\ i\in\{j\}}}^{J}\left(|\Omega_{\boldsymbol{\mu}j}|^{-\frac{1}{2}}\cdot\exp\left[-\frac{1}{2}\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)'\cdot\Omega_{\boldsymbol{\mu}j}^{-1}\cdot\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)\right]\cdot\frac{\left(\sigma_{\kappa_j}^2\right)^{-\frac{1}{2}}\cdot I\left(L_\kappa\leq\kappa_{ij}\leq U_\kappa\right)}{F_N\left(\frac{U_\kappa-\kappa_j}{\sigma_{\kappa_j}}\right)-F_N\left(\frac{L_\kappa-\kappa_j}{\sigma_{\kappa_j}}\right)}\cdot\exp\left[-\frac{1}{2}\left[\frac{\kappa_{ij}-\kappa_j}{\sigma_{\kappa_j}}\right]^2\right]\right)\cdot$$

$$\prod_{i=1}^{N}\prod_{\substack{j=1\\ i\in\{j\}}}^{J}\left(\frac{\left(\sigma_{\gamma_j}^2\right)^{-\frac{1}{2}}\cdot I\left(L_\gamma\leq\gamma_{ij}\leq U_\gamma\right)}{F_N\left(\frac{U_\gamma-\gamma_j}{\sigma_{\gamma_j}}\right)-F_N\left(\frac{L_\gamma-\gamma_j}{\sigma_{\gamma_j}}\right)}\cdot\exp\left[-\frac{1}{2}\left[\frac{\gamma_{ij}-\gamma_j}{\sigma_{\gamma_j}}\right]^2\right]\right)$$

Joint Prior Distribution

$$\begin{aligned}
&P\left(\boldsymbol{\mu_j},\kappa_j,\gamma_j,\Omega_{\boldsymbol{\mu}j},\sigma_{\kappa j}^2,\sigma_{\gamma j}^2,\sigma_{\varepsilon j}^2,j=1,\ldots,J\right) \qquad \text{(A.2)}\\
=&\prod_{j=1}^{J}\left(P\left[\boldsymbol{\mu_j}\right]\cdot P\left[\kappa_j\right]\cdot P\left[\gamma_j\right]\cdot P\left[\Omega_{\boldsymbol{\mu}j}^{-1}\right]\cdot P\left[\sigma_{\kappa j}^2\right]\cdot P\left[\sigma_{\gamma j}^2\right]\cdot P\left[\sigma_{\varepsilon j}^{-2}\right]\right)\\
\propto&\prod_{j=1}^{J}\left(\exp\left[-\frac{1}{2}\boldsymbol{\mu_j}'\cdot\frac{1}{10^4}\cdot\boldsymbol{\mu_j}\right]\cdot I\left(L_\kappa\leq\kappa_j\leq U_\kappa\right)\cdot I\left(L_\gamma\leq\gamma_j\leq U_\gamma\right)\cdot|\Omega_{\boldsymbol{\mu}j}^{-1}|^{-\frac{1}{2}}\cdot\operatorname{etr}\left[-\frac{3}{2}\cdot R_j\cdot\Omega_{\boldsymbol{\mu}j}^{-1}\right]\cdot I\left[L_{\sigma_\kappa^2}\leq\sigma_{\kappa_j}^2\leq U_{\sigma_\kappa^2}\right]\right)\cdot\\
&\prod_{j=1}^{J}\left(I\left[L_{\sigma_\gamma^2}\leq\sigma_{\gamma_j}^2\leq U_{\sigma_\gamma^2}\right]\cdot\left(\sigma_{\varepsilon j}^{-2}\right)^{\left(10^{-4}-1\right)}\cdot\exp\left(-10^{-4}\cdot\sigma_{\varepsilon j}^{-2}\right)\right)
\end{aligned}$$

Joint Posterior Distribution

$$
\begin{aligned}
&P\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \boldsymbol{\mu_j}, \kappa_j, \gamma_j, \Omega_{\boldsymbol{\mu}j}, \sigma^2_{\kappa j}, \sigma^2_{\gamma j}, \sigma^2_{\varepsilon j}, i = 1, \ldots, N, j = 1, \ldots, J, k = 1, \ldots, K_{ij} | \boldsymbol{y}\right) \qquad \text{(A.3)}\\
&\propto L\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \boldsymbol{\mu_j}, \kappa_j, \gamma_j, \Omega_{\boldsymbol{\mu}j}, \sigma^2_{\kappa j}, \sigma^2_{\gamma j}, \sigma^2_{\varepsilon j}, i = 1, \ldots, N, j = 1, \ldots, J, k = 1, \ldots, K_{ij} | \boldsymbol{y}\right) \cdot P\left(\boldsymbol{\mu_j}, \kappa_j, \gamma_j, \Omega_{\boldsymbol{\mu}j}, \sigma^2_{\kappa j}, \sigma^2_{\gamma j}, \sigma^2_{\varepsilon j}, j = 1, \ldots, J\right)\\
&\propto \left(\prod_{j=1}^{J} \left(\sigma^2_{\varepsilon_j}\right)^{-\frac{1}{2}T_j}\right) \cdot \exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\sum_{k=1}^{K_{ij}}\left[\frac{\log(y_{ijk}) - \left(\alpha_{ij} - \beta_{1ij}\cdot t_{ijk} - \beta_{2ij}\cdot\gamma_{ij}\cdot\log\left[\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right]\right)}{\sigma_{\varepsilon_j}}\right]^2\right) \cdot\\
&\left(\prod_{j=1}^{J} |\Omega_{\boldsymbol{\mu}j}|^{-\frac{1}{2}N_j}\right) \cdot \exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}(\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})' \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})\right) \cdot \frac{\left(\prod_{j=1}^{J}\left(\sigma^2_{\kappa_j}\right)^{-\frac{1}{2}N_j}\right) \cdot \left(\prod_{i=1}^{N}\prod_{\substack{j=1\\ i\in\{j\}}}^{J} I\left(L_\kappa \le \kappa_{ij} \le U_\kappa\right)\right)}{\prod_{j=1}^{J}\left(F_N\left[\frac{U_\kappa - \kappa_j}{\sigma_{\kappa_j}}\right] - F_N\left[\frac{L_\kappa - \kappa_j}{\sigma_{\kappa_j}}\right]\right)^{N_j}} \cdot\\
&\exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\left(\frac{\kappa_{ij} - \kappa_j}{\sigma_{\kappa_j}}\right)^2\right) \cdot \frac{\left(\prod_{j=1}^{J}\left(\sigma^2_{\gamma_j}\right)^{-\frac{1}{2}N_j}\right) \cdot \left(\prod_{i=1}^{N}\prod_{\substack{j=1\\ i\in\{j\}}}^{J} I\left(L_\gamma \le \gamma_{ij} \le U_\gamma\right)\right)}{\prod_{j=1}^{J}\left(F_N\left[\frac{U_\gamma - \gamma_j}{\sigma_{\gamma_j}}\right] - F_N\left[\frac{L_\gamma - \gamma_j}{\sigma_{\gamma_j}}\right]\right)^{N_j}} \cdot \exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\left(\frac{\gamma_{ij} - \gamma_j}{\sigma_{\gamma_j}}\right)^2\right) \cdot\\
&\exp\left(-\frac{1}{2}\sum_{j=1}^{J}\left[\boldsymbol{\mu_j'} \cdot \frac{1}{10^4} \cdot \boldsymbol{\mu_j}\right]\right) \cdot \left(\prod_{j=1}^{J} I\left(L_\kappa \le \kappa_j \le U_\kappa\right)\right) \cdot \left(\prod_{j=1}^{J} I\left(L_\gamma \le \gamma_j \le U_\gamma\right)\right) \cdot \left(\prod_{j=1}^{J} |\Omega^{-1}_{\boldsymbol{\mu}j}|^{-\frac{1}{2}}\right) \cdot \operatorname{etr}\left(-\frac{3}{2} \cdot \cdot \sum_{j=1}^{J} R_j \cdot \Omega^{-1}_{\boldsymbol{\mu}j}\right) \cdot\\
&\left(\prod_{j=1}^{J} I\left(L_{\sigma^2_\kappa} \le \sigma^2_{\kappa j} \le U_{\sigma^2_\kappa}\right)\right) \cdot \left(\prod_{j=1}^{J} I\left(L_{\sigma^2_\gamma} \le \sigma^2_{\gamma j} \le U_{\sigma^2_\gamma}\right)\right) \cdot \left(\prod_{j=1}^{J}\left(\sigma^{-2}_{\varepsilon j}\right)^{\left(10^{-4}-1\right)}\right) \cdot \exp\left(-10^{-4} \cdot \sum_{j=1}^{J}\sigma^{-2}_{\varepsilon j}\right)
\end{aligned}
$$

Conditional Posterior Distributions

$$P\left(\boldsymbol{\mu_{ij}}|\kappa_{ij},\gamma_{ij},\boldsymbol{\mu_j},\Omega_{\boldsymbol{\mu}j},\sigma^2_{\varepsilon j},\boldsymbol{y}\right) \tag{A.4}$$
$$\propto\exp\left(-\frac{1}{2}\sum_{k=1}^{K_{ij}}\left[\frac{\log(y_{ijk})-\left(\alpha_{ij}-\beta_{1ij}\cdot t_{ijk}-\beta_{2ij}\cdot\gamma_{ij}\cdot\log\left[\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}+e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}}+e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right]\right)}{\sigma_{\varepsilon_j}}\right]^2\right)\cdot\exp\left(-\frac{1}{2}\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)'\cdot\Omega^{-1}_{\boldsymbol{\mu}j}\cdot\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)\right)$$

$$L\left(\boldsymbol{\mu_{ij}},\kappa_{ij},\gamma_{ij},\sigma^2_{\varepsilon j},k=1,\ldots,K_{ij}|\boldsymbol{y_{ij}}\right) \tag{A.5}$$
$$\propto\exp\left(-\frac{1}{2}\sum_{k=1}^{K_{ij}}\left[\frac{\log(y_{ijk})-\left(\alpha_{ij}-\beta_{1ij}\cdot t_{ijk}-\beta_{2ij}\cdot\gamma_{ij}\cdot\log\left[\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}+e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}}+e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right]\right)}{\sigma_{\varepsilon_j}}\right]^2\right)$$
$$\propto\exp\left(-\frac{1}{2\cdot\sigma^2_{\varepsilon_j}}\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)'\cdot\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)\right)$$

where X_{ij} is a $K_{ij} \times 3$ matrix as follows:

$$X_{ij} = \begin{bmatrix} 1 & -t_{ij1} & -\gamma_{ij} \cdot \log\left(\frac{e^{\frac{t_{ij1}-\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{t_{ij1}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right) \\ \vdots & \vdots & \vdots \\ 1 & -t_{ijk} & -\gamma_{ij} \cdot \log\left(\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right) \\ \vdots & \vdots & \vdots \\ 1 & -t_{ijK_{ij}} & -\gamma_{ij} \cdot \log\left(\frac{e^{\frac{t_{ijK_{ij}}-\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{t_{ijK_{ij}}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right) \end{bmatrix}$$

Define $\boldsymbol{B_{ij}}$ and s_{ij} as follows:

$$\boldsymbol{B_{ij}} = \left(X_{ij}^{'} \cdot X_{ij}\right)^{-1} \cdot X_{ij}^{'} \cdot \boldsymbol{y_{ij}} \tag{A.6}$$

$$s_{ij} = (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{B_{ij}})' \cdot (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{B_{ij}}) \tag{A.7}$$

Making use of the following algebraic identity for Equation (A.5):

$$\begin{aligned} & (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{\mu_{ij}})' \cdot (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{\mu_{ij}}) \\ =& (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{B_{ij}} - X_{ij} \cdot [\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}}])' \cdot (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{B_{ij}} - X_{ij} \cdot [\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}}]) \\ =& (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{B_{ij}})' \cdot (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{B_{ij}}) + (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot X_{ij}^{'} \cdot X_{ij} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}}) \\ =& s_{ij} + (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot X_{ij}^{'} \cdot X_{ij} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}}) \end{aligned} \tag{A.8}$$

since the crossproduct terms equals:

$$
\begin{aligned}
&(\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot X_{ij}^{'} \cdot (\boldsymbol{y_{ij}} - X_{ij} \cdot \boldsymbol{B_{ij}}) \\
=&(\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot \left(X_{ij}^{'} \cdot \boldsymbol{y_{ij}} - X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} \right) \\
=&(\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot \left(X_{ij}^{'} \cdot \boldsymbol{y_{ij}} - X_{ij}^{'} \cdot X_{ij} \cdot \left[X_{ij}^{'} \cdot X_{ij} \right]^{-1} \cdot X_{ij}^{'} \cdot \boldsymbol{y_{ij}} \right) \\
=&(\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot \left(X_{ij}^{'} \cdot \boldsymbol{y_{ij}} - X_{ij}^{'} \cdot \boldsymbol{y_{ij}} \right) \\
=&\mathbf{0}
\end{aligned}
\tag{A.9}
$$

Finally, from Equation (A.8), Equation (A.5) can be written as follows:

$$
\begin{aligned}
&L\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \sigma_{\varepsilon j}^2, k = 1, \ldots, K_{ij} | \boldsymbol{y_{ij}}\right) \\
\propto &\exp\left(-\frac{1}{2 \cdot \sigma_{\varepsilon_j}^2} \left[s_{ij} + (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot X_{ij}^{'} \cdot X_{ij} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}}) \right] \right)
\end{aligned}
\tag{A.10}
$$

$$
\begin{aligned}
&P\left(\boldsymbol{\mu_{ij}} | \kappa_{ij}, \gamma_{ij}, \boldsymbol{\mu_j}, \Omega_{\mu j}, \sigma_{\varepsilon j}^2, \boldsymbol{y}\right) \\
\propto &L\left(\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \sigma_{\varepsilon j}^2, k = 1, \ldots, K_{ij} | \boldsymbol{y_{ij}}\right) \cdot \exp\left(-\frac{1}{2} (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})' \cdot \Omega_{\boldsymbol{\mu} j}^{-1} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}) \right) \\
\propto &\exp\left(-\frac{1}{2 \cdot \sigma_{\varepsilon_j}^2} \left[s_{ij} + (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot X_{ij}^{'} \cdot X_{ij} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}}) \right] \right) \cdot \exp\left(-\frac{1}{2} (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})' \cdot \Omega_{\boldsymbol{\mu} j}^{-1} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}) \right)
\end{aligned}
\tag{A.11}
$$

Completing the square inside $\exp\left(-\frac{1}{2}[.]\right)$ of Equation (A.11):

$$
\begin{aligned}
&\frac{1}{\sigma^2_{\varepsilon_j}} \cdot \Big((\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}})' \cdot X_{ij}^{'} \cdot X_{ij} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{B_{ij}}) \Big) + (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})' \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}) \\
=&\frac{1}{\sigma^2_{\varepsilon_j}} \cdot \Big(\boldsymbol{\mu_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{\mu_{ij}} - \boldsymbol{\mu_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} - \boldsymbol{B_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{\mu_{ij}} + \boldsymbol{B_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} \Big) + \\
&\boldsymbol{\mu_{ij}^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_{ij}} - \boldsymbol{\mu_{ij}^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} - \boldsymbol{\mu_j^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_{ij}} + \boldsymbol{\mu_j^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} \\
=&\boldsymbol{\mu_{ij}^{'}} \cdot \left(\frac{1}{\sigma^2_{\varepsilon_j}} \cdot X_{ij}^{'} \cdot X_{ij} + \Omega^{-1}_{\boldsymbol{\mu}j} \right) \cdot \boldsymbol{\mu_{ij}} - \boldsymbol{\mu_{ij}^{'}} \left(\frac{1}{\sigma^2_{\varepsilon_j}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} + \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} \right) - \left(\frac{1}{\sigma^2_{\varepsilon_j}} \cdot \boldsymbol{B_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} + \boldsymbol{\mu_j^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \right) \cdot \boldsymbol{\mu_{ij}} + \\
&\frac{1}{\sigma^2_{\varepsilon_j}} \cdot \boldsymbol{B_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} + \boldsymbol{\mu_j^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} \\
=&\boldsymbol{\mu_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{\mu_{ij}} - \boldsymbol{\mu_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{O_{ij}} - \boldsymbol{O_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{\mu_{ij}} + \frac{1}{\sigma^2_{\varepsilon_j}} \cdot \boldsymbol{B_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} + \boldsymbol{\mu_j^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} \\
=&\boldsymbol{\mu_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{\mu_{ij}} - \boldsymbol{\mu_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{O_{ij}} - \boldsymbol{O_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{\mu_{ij}} + \boldsymbol{O_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{O_{ij}} - \boldsymbol{O_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{O_{ij}} + \frac{1}{\sigma^2_{\varepsilon_j}} \cdot \boldsymbol{B_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} + \boldsymbol{\mu_j^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} \\
=&(\boldsymbol{\mu_{ij}} - \boldsymbol{O_{ij}})' \cdot V_{ij}^{-1} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{O_{ij}}) - \boldsymbol{O_{ij}^{'}} \cdot V_{ij}^{-1} \cdot \boldsymbol{O_{ij}} + \frac{1}{\sigma^2_{\varepsilon_j}} \cdot \boldsymbol{B_{ij}^{'}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} + \boldsymbol{\mu_j^{'}} \cdot \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j}
\end{aligned}
$$

where $V_{ij} = \left(\frac{1}{\sigma^2_{\varepsilon_j}} \cdot X_{ij}^{'} \cdot X_{ij} + \Omega^{-1}_{\boldsymbol{\mu}j} \right)^{-1}$ and $\boldsymbol{O_{ij}} = V_{ij} \cdot \left(\frac{1}{\sigma^2_{\varepsilon_j}} \cdot X_{ij}^{'} \cdot X_{ij} \cdot \boldsymbol{B_{ij}} + \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} \right) = V_{ij} \cdot \left(\frac{1}{\sigma^2_{\varepsilon_j}} \cdot X_{ij}^{'} \cdot \boldsymbol{y_{ij}} + \Omega^{-1}_{\boldsymbol{\mu}j} \cdot \boldsymbol{\mu_j} \right)$.

Thus, the conditional posterior distribution of $\boldsymbol{\mu_{ij}} | \kappa_{ij}, \gamma_{ij}, \boldsymbol{\mu_j}, \Omega^{-1}_{\mu j}, \sigma^2_{\varepsilon j}, \boldsymbol{y}$ is given by:

$$
P\left(\boldsymbol{\mu_{ij}} | \kappa_{ij}, \gamma_{ij}, \boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}, \sigma^2_{\varepsilon j}, \boldsymbol{y} \right) \propto \exp\left(-\frac{1}{2} (\boldsymbol{\mu_{ij}} - \boldsymbol{O_{ij}})' \cdot V_{ij}^{-1} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{O_{ij}}) \right) \tag{A.12}
$$

From Equation (A.12), the posterior distribution of $\boldsymbol{\mu_{ij}}|\kappa_{ij},\gamma_{ij},\boldsymbol{\mu_j},\Omega_{\mu j}^{-1},\sigma_{\varepsilon j}^2,\boldsymbol{y}$ is therefore as follows:

$$\begin{aligned}\boldsymbol{\mu_{ij}}|\kappa_{ij},\gamma_{ij},\boldsymbol{\mu_j},\Omega_{\mu j}^{-1},\sigma_{\varepsilon j}^2,\boldsymbol{y} \sim & N\left(\boldsymbol{O_{ij}},V_{ij}\right) \\ & N\left(\left[\frac{1}{\sigma_{\varepsilon_j}^2}\cdot X_{ij}^{'}\cdot X_{ij}+\Omega_{\boldsymbol{\mu j}}^{-1}\right]^{-1}\cdot\left[\frac{1}{\sigma_{\varepsilon_j}^2}\cdot X_{ij}^{'}\cdot \boldsymbol{y_{ij}}+\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_j}\right],\left[\frac{1}{\sigma_{\varepsilon_j}^2}\cdot X_{ij}^{'}\cdot X_{ij}+\Omega_{\boldsymbol{\mu j}}^{-1}\right]^{-1}\right)\end{aligned} \tag{A.13}$$

$$\begin{aligned}& P\left(\boldsymbol{\mu_j}|\boldsymbol{\mu_{ij}},\Omega_{\boldsymbol{\mu} j},\boldsymbol{y},i[i\in\{j\}]=1,\ldots,N\right) \\ \propto & \exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)'\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)\right)\cdot\exp\left(-\frac{1}{2}\sum_{j=1}^{J}\left[\boldsymbol{\mu_j^{'}}\cdot\frac{1}{10^4}\cdot\boldsymbol{\mu_j}\right]\right)\end{aligned} \tag{A.14}$$

Completing the square inside $\exp\left(-\frac{1}{2}[.]\right)$ of Equation (A.14):

$$\begin{aligned}& \sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)'\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\left(\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_j}\right)+\sum_{j=1}^{J}\left(\boldsymbol{\mu_j^{'}}\cdot\frac{1}{10^4}\cdot\boldsymbol{\mu_j}\right) \\ = & \sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\left(\boldsymbol{\mu_{ij}^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_{ij}}-\boldsymbol{\mu_{ij}^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_j}-\boldsymbol{\mu_j^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_{ij}}+\boldsymbol{\mu_j^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_j}\right)+\sum_{j=1}^{J}\left(\boldsymbol{\mu_j^{'}}\cdot\frac{1}{10^4}\cdot\boldsymbol{\mu_j}\right) \\ = & \sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\boldsymbol{\mu_{ij}^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_{ij}}-2\cdot\sum_{j=1}^{J}\boldsymbol{\mu_j^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\sum_{\substack{i=1\\ i\in\{j\}}}^{N}\boldsymbol{\mu_{ij}}+\sum_{j=1}^{J}N_j\cdot\boldsymbol{\mu_j^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_j}+\sum_{j=1}^{J}\boldsymbol{\mu_j^{'}}\cdot\frac{1}{10^4}\cdot\boldsymbol{\mu_j} \\ = & \sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\boldsymbol{\mu_{ij}^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\boldsymbol{\mu_{ij}}+\sum_{j=1}^{J}\boldsymbol{\mu_j^{'}}\left(N_j\cdot\Omega_{\boldsymbol{\mu j}}^{-1}+\frac{1}{10^4}\right)\cdot\boldsymbol{\mu_j}-2\cdot\sum_{j=1}^{J}\boldsymbol{\mu_j^{'}}\cdot\Omega_{\boldsymbol{\mu j}}^{-1}\cdot\sum_{\substack{i=1\\ i\in\{j\}}}^{N}\boldsymbol{\mu_{ij}}\end{aligned}$$

$$
\begin{aligned}
&= \sum_{i=1}^{N} \sum_{\substack{j=1 \\ i \in \{j\}}}^{J} \boldsymbol{\mu_{ij}'} \cdot \Omega_{\boldsymbol{\mu j}}^{-1} \cdot \boldsymbol{\mu_{ij}} + \sum_{j=1}^{J} \boldsymbol{\mu_j'} \cdot D_j^{-1} \cdot \boldsymbol{\mu_j} - 2 \cdot \sum_{j=1}^{J} \boldsymbol{\mu_j'} \cdot D_j^{-1} \cdot \boldsymbol{E_j} \\
&= \sum_{i=1}^{N} \sum_{\substack{j=1 \\ i \in \{j\}}}^{J} \boldsymbol{\mu_{ij}'} \cdot \Omega_{\boldsymbol{\mu j}}^{-1} \cdot \boldsymbol{\mu_{ij}} + \sum_{j=1}^{J} \boldsymbol{\mu_j'} \cdot D_j^{-1} \cdot \boldsymbol{\mu_j} - 2 \cdot \sum_{j=1}^{J} \boldsymbol{\mu_j'} \cdot D_j^{-1} \cdot \boldsymbol{E_j} + \sum_{j=1}^{J} \boldsymbol{E_j'} \cdot D_j^{-1} \cdot \boldsymbol{E_j} - \sum_{j=1}^{J} \boldsymbol{E_j'} \cdot D_j^{-1} \cdot \boldsymbol{E_j} \\
&= \sum_{i=1}^{N} \sum_{\substack{j=1 \\ i \in \{j\}}}^{J} \boldsymbol{\mu_{ij}'} \cdot \Omega_{\boldsymbol{\mu j}}^{-1} \cdot \boldsymbol{\mu_{ij}} + \sum_{j=1}^{J} (\boldsymbol{\mu_j} - \boldsymbol{E_j})' \cdot D_j^{-1} \cdot (\boldsymbol{\mu_j} - \boldsymbol{E_j}) - \sum_{j=1}^{J} \boldsymbol{E_j'} \cdot D_j^{-1} \cdot \boldsymbol{E_j}
\end{aligned}
$$

where $D_j = \left(N_j \cdot \Omega_{\boldsymbol{\mu j}}^{-1} + \frac{1}{10^4}\right)^{-1}$ and $\boldsymbol{E_j} = D_j \cdot \Omega_{\boldsymbol{\mu j}}^{-1} \cdot \sum_{\substack{i=1 \\ i \in \{j\}}}^{N} \boldsymbol{\mu_{ij}}$.

Thus, the conditional posterior distribution of $\boldsymbol{\mu_j} | \boldsymbol{\mu_{ij}}, \Omega_{\boldsymbol{\mu j}}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N$ is given by:

$$
P\left(\boldsymbol{\mu_j} | \boldsymbol{\mu_{ij}}, \Omega_{\boldsymbol{\mu j}}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N\right) \propto \exp\left(-\frac{1}{2} \left(\boldsymbol{\mu_j} - \boldsymbol{E_j}\right)' \cdot D_j^{-1} \cdot \left(\boldsymbol{\mu_j} - \boldsymbol{E_j}\right)\right) \tag{A.15}
$$

From Equation (A.15), the posterior distribution of $\boldsymbol{\mu_j} | \boldsymbol{\mu_{ij}}, \Omega_{\boldsymbol{\mu j}}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N$ is therefore as follows:

$$
\begin{aligned}
\boldsymbol{\mu_j} | \boldsymbol{\mu_{ij}}, \Omega_{\boldsymbol{\mu j}}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N \sim & N\left(\boldsymbol{E_j}, D_j\right) \\
& N\left(\left(N_j \cdot \Omega_{\boldsymbol{\mu j}}^{-1} + \frac{1}{10^4}\right)^{-1} \cdot \left[\Omega_{\boldsymbol{\mu j}}^{-1} \cdot \sum_{\substack{i=1 \\ i \in \{j\}}}^{N} \boldsymbol{\mu_{ij}}\right], \left(N_j \cdot \Omega_{\boldsymbol{\mu j}}^{-1} + \frac{1}{10^4}\right)^{-1}\right)
\end{aligned} \tag{A.16}
$$

$$
\begin{aligned}
&P\left(\Omega_{\boldsymbol{\mu j}}^{-1}|\boldsymbol{\mu_{ij}}, \boldsymbol{\mu_j}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N\right) \\
&\propto \left(\prod_{j=1}^{J} |\Omega_{\boldsymbol{\mu j}}|^{-\frac{1}{2}N_j}\right) \cdot \exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1 \\ i\in\{j\}}}^{J} (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})' \cdot \Omega_{\boldsymbol{\mu j}}^{-1} \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})\right) \left(\prod_{j=1}^{J} |\Omega_{\boldsymbol{\mu j}}^{-1}|^{-\frac{1}{2}}\right) \cdot \operatorname{etr}\left(-\frac{3}{2} \cdot R_j \cdot \sum_{j=1}^{J} \Omega_{\boldsymbol{\mu j}}^{-1}\right) \\
&\propto \left(\prod_{j=1}^{J} |\Omega_{\boldsymbol{\mu j}}^{-1}|^{\frac{1}{2}(N_j-1)}\right) \cdot \operatorname{etr}\left(-\frac{1}{2}\left[\sum_{i=1}^{N}\sum_{\substack{j=1 \\ i\in\{j\}}}^{J} (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}) \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})' \cdot \Omega_{\boldsymbol{\mu j}}^{-1} + 3 \cdot \cdot \sum_{j=1}^{J} R_j \cdot \Omega_{\boldsymbol{\mu j}}^{-1}\right]\right)
\end{aligned}
\tag{A.17}
$$

From Equation (A.17), the posterior distribution of $\Omega_{\boldsymbol{\mu j}}^{-1}|\boldsymbol{\mu_{ij}}, \boldsymbol{\mu_j}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N$ is therefore as follows:

$$
\Omega_{\boldsymbol{\mu j}}^{-1}|\boldsymbol{\mu_{ij}}, \boldsymbol{\mu_j}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N \sim W_3\left(N_j + 3, \left[\sum_{\substack{i=1 \\ i\in\{j\}}}^{N} (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j}) \cdot (\boldsymbol{\mu_{ij}} - \boldsymbol{\mu_j})' + 3 \cdot R_j\right]^{-1}\right) \tag{A.18}
$$

$$
\begin{aligned}
&P\left(\sigma_{\varepsilon j}^{-2}|\boldsymbol{\mu_{ij}}, \kappa_{ij}, \gamma_{ij}, \boldsymbol{y}, i[i \in \{j\}] = 1, \ldots, N\right) \\
&\propto \left(\prod_{j=1}^{J} \left(\sigma_{\varepsilon_j}^2\right)^{-\frac{1}{2}\cdot T_j}\right) \cdot \exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1 \\ i\in\{j\}}}^{J}\sum_{k=1}^{K_{ij}} \left[\frac{\log(y_{ijk}) - \left(\alpha_{ij} - \beta_{1ij} \cdot t_{ijk} - \beta_{2ij} \cdot \gamma_{ij} \cdot \log\left[\frac{e^{\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{t_{ijk}-\kappa_{ij}}{\gamma_{ij}}}}{e^{\frac{\kappa_{ij}}{\gamma_{ij}}} + e^{-\frac{\kappa_{ij}}{\gamma_{ij}}}}\right]\right)}{\sigma_{\varepsilon_j}}\right]^2\right) \cdot \\
&\left(\prod_{j=1}^{J} \left(\sigma_{\varepsilon j}^{-2}\right)^{\left(10^{-4}-1\right)}\right) \cdot \exp\left(-10^{-4} \cdot \sum_{j=1}^{J} \sigma_{\varepsilon j}^{-2}\right)
\end{aligned}
\tag{A.19}
$$

$$\propto \left(\prod_{j=1}^{J}\left(\sigma_{\varepsilon_j}^2\right)^{-\frac{1}{2}\cdot T_j}\right)\cdot\exp\left(-\frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ i\in\{j\}}}^{J}\frac{1}{\sigma_{\varepsilon_j}^2}\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)'\cdot\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)\right)\cdot\left(\prod_{j=1}^{J}\left(\sigma_{\varepsilon j}^{-2}\right)^{\left(10^{-4}-1\right)}\right)\cdot\exp\left(-10^{-4}\cdot\sum_{j=1}^{J}\sigma_{\varepsilon j}^{-2}\right)$$

$$\propto \left(\prod_{j=1}^{J}\left(\sigma_{\varepsilon_j}^{-2}\right)^{\frac{1}{2}\cdot T_j+10^{-4}-1}\right)\cdot\exp\left(-\sum_{j=1}^{J}\sigma_{\varepsilon_j}^{-2}\left[\frac{1}{2}\sum_{\substack{i=1\\ i\in\{j\}}}^{N}\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)'\cdot\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)+10^{-4}\right]\right)$$

From Equation (A.19), the posterior distribution of $\sigma_{\varepsilon j}^{-2}|\boldsymbol{\mu_{ij}},\kappa_{ij},\gamma_{ij},\boldsymbol{y},i[i\in\{j\}]=1,\ldots,N$ is therefore as follows:

$$\sigma_{\varepsilon j}^{-2}|\boldsymbol{\mu_{ij}},\kappa_{ij},\gamma_{ij},\boldsymbol{y},i[i\in\{j\}]=1,\ldots,N\sim G\left(\frac{1}{2}\cdot T_j+10^{-4},\frac{1}{2}\sum_{\substack{i=1\\ i\in\{j\}}}^{N}\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)'\cdot\left(\boldsymbol{y_{ij}}-X_{ij}\cdot\boldsymbol{\mu_{ij}}\right)+10^{-4}\right) \tag{A.20}$$

Appendix B

Programming Code

B.1 SAS® Procedure NLMIXED (By-Patient Analysis)

```
proc nlmixed data = NC001D03 seed = 1;
    bounds 2 <= SKAPPA <= 11;
    bounds 0.1 <= SGAMMA <= 2;
    parms SALPHA = 6 SBETA1 = 0.2 SBETA2 = 0 SKAPPA = 7 SGAMMA = 0.5 S2 = 0.2;
    MLOGCFU = SALPHA - SBETA1*TIME - SBETA2*SGAMMA*log((exp((TIME - SKAPPA)/SGAMMA) +
              exp(-(TIME - SKAPPA)/SGAMMA))/(exp((SKAPPA)/SGAMMA) + exp(-(SKAPPA)/SGAMMA)));
    PD = pdf('Normal', LOGCFUA, MLOGCFU, S2);
    CD = cdf('Normal', LOGCFUA, MLOGCFU, S2);
    LL = (CENSOR = 0)*log(PD) + (CENSOR = 1)*log(CD);
    model LOGCFUA ~ general(LL);
```

```
estimate 'MEBA002' SBETA1 + SBETA2*SGAMMA*(log(exp((2 - SKAPPA)/SGAMMA) +
                   exp(-(2 - SKAPPA)/SGAMMA)) - log(exp((0 - SKAPPA)/SGAMMA) + exp(-(0 - SKAPPA)/SGAMMA)))/2;
estimate 'MEBA007' SBETA1 + SBETA2*SGAMMA*(log(exp((7 - SKAPPA)/SGAMMA) +
                   exp(-(7 - SKAPPA)/SGAMMA)) - log(exp((0 - SKAPPA)/SGAMMA) + exp(-(0 - SKAPPA)/SGAMMA)))/7;
estimate 'MEBA014' SBETA1 + SBETA2*SGAMMA*(log(exp((14 - SKAPPA)/SGAMMA) +
                   exp(-(14 - SKAPPA)/SGAMMA)) - log(exp((0 - SKAPPA)/SGAMMA) + exp(-(0 - SKAPPA)/SGAMMA)))/14;
estimate 'MEBA214' SBETA1 + SBETA2*SGAMMA*(log(exp((14 - SKAPPA)/SGAMMA) +
                   exp(-(14 - SKAPPA)/SGAMMA)) - log(exp((2 - SKAPPA)/SGAMMA) + exp(-(2 - SKAPPA)/SGAMMA)))/12;
estimate 'MEBA714' SBETA1 + SBETA2*SGAMMA*(log(exp((14 - SKAPPA)/SGAMMA) +
                   exp(-(14 - SKAPPA)/SGAMMA)) - log(exp((7 - SKAPPA)/SGAMMA) + exp(-(7 - SKAPPA)/SGAMMA)))/7;
predict MLOGCFU out = NC001D04;
ods output PARAMETERESTIMATES = NC001D05;
ods output ADDITIONALESTIMATES = NC001D06;
by NSUBJID USUBJID KVTRTN MEBA: OKVTRTN;
run;
```

B.2 SAS® Example Code: Prior for Covariance Matrix

B.2.1 "Default" Wishart

```
data NC001W01 (drop = KAPPA GAMMA PRED);
    set NC001D04; /*SEE PROC NLMIXED CODE*/
    by KVTRTN NSUBJID;
    if CENSOR = 1 then LOGCFU = -2;
    KAPPA = (11 + 2)/2;
    GAMMA = (2 + 0.1)/2;
    if LOGCFU ne . then do; /*DESIGN MATRIX*/
        TIMEH1 = 1;
        TIMEH2 = -TIME;
        TIMEH3 = -GAMMA*log((exp((TIME - KAPPA)/GAMMA) + exp(-(TIME - KAPPA)/GAMMA))/(exp((KAPPA)/GAMMA) + exp(-(KAPPA)/GAMMA)));
    end;
    if first.KVTRTN then TSUBJID = .;
    if first.NSUBJID then TSUBJID + 1;
run;

data NC001W01; /*POOLED DATA (ALL TREATMENT GROUPS)*/
    set NC001W01 NC001W01 (in = x);
    if x then do;
        KVTRTN = &NTRT. + 1 /*CATEGORY: NUMBER OF TREATMENT GROUPS PLUS ONE*/; TSUBJID = NSUBJID;
        call symput("TSUBJ" || trim(left(put(&NTRT. + 1, BEST.))), trim(left(put(&NSUBJ.,  BEST.)))); /*NUMBER OF PATIENTS*/
    end;
run;
```

```
proc mixed data = NC001W01;
    by KVTRTN;
    model LOGCFU = TIMEH1 TIMEH2 TIMEH3 / noint solution outpred = NC001W02;
    ods output COVPARMS = NC001W03; /*RESIDUAL VARIANCE*/
run;

proc sort data = NC001W01;
    by KVTRTN TIME;
run;

data NC001W04;
    merge NC001W02 NC001W03;
    by KVTRTN;
    if LOGCFU ne . then SIGMAR = ESTIMATE;
run;

data _NULL_;
    set NC001W03;
    call symput("SIGMAR" || trim(left(put(KVTRTN, BEST.))), trim(left(put(ESTIMATE, BEST.))));
run;

%put &SIGMAR1.;

/*CALCULATE Z*/

proc transpose data = NC001W04 out = NC001W05 (rename = (_NAME_ = Z)) prefix = TP;
    by KVTRTN NSUBJID TSUBJID;
    var TIMEH1 TIMEH2 TIMEH3;
    id TP;
run;
```

```
data NCO01W06;
    set NCO01W05;
    array ZTP TP:;
    length ZMATRIX $999.;
    do i = 1 to dim(ZTP);
        if i = 1 then ZMATRIX = trim(left(put(ZTP(i), BEST.))); else
                      ZMATRIX = trim(left(ZMATRIX)) || " " || trim(left(put(ZTP(i), BEST.)));
    end;
run;

proc transpose data = NCO01W06 out = NCO01W07;
    by KVTRTN NSUBJID TSUBJID;
    var ZMATRIX;
    id Z;
run;

%let IFACT = 2.5;

%macro RMAT ();

    %do i = 1 %to %eval(&NTRT. + 1);

        data NCO01W08;
            length ZMATRIX $9999.;
            set NCO01W07 (where = (KVTRTN = &i.));
            ZMATRIX = compbl("{" || trim(left(TIMEH1)) || ", " || trim(left(TIMEH2)) || ", " || trim(left(TIMEH3)) || "}");
            call symput("ZMATRIX" || trim(left(put(TSUBJID, BEST.))), trim(left(ZMATRIX)));
        run;

        %put &&ZMATRIX&i..;
```

```
    proc iml;
        R&i. = (%do j = 1 %to %eval(&&TSUBJ&i.. - 1);
                (1/&&SIGMAR&i..)*&&ZMATRIX&j..*&&ZMATRIX&j..' +
            %end; (1/&&SIGMAR&i..)*&&&&ZMATRIX&&TSUBJ&i...*&&&&ZMATRIX&&TSUBJ&i...')/&&TSUBJ&i..;
        R&i. = &WDF.*&IFACT.*inv(R&i.); /*WDF IS THE DEGREES OF FREEDOM*/
        print R&i.;
        create NCO01W09T&i. var {R&i.};
        append;
          close NCO01W09T&i.;
        quit;

    %end;

%mend;

%RMAT ();

data NCO01W10 (drop = i);
   merge NCO01W09:;
   array R R:;
   do i = 1 to %eval(&NTRT. + 1);
      if _N_ = 1 then call symput("WAT" || trim(left(put(i, BEST.))), trim(left(put(R(i), BEST.)))); /*R ENTRY FOR ALPHA VARIANCE*/
      if _N_ = 2 then call symput("WAB1T" || trim(left(put(i, BEST.))), trim(left(put(R(i), BEST.)))); /*R ENTRY FOR ALPHA & BETA1 COVARIANCE*/
      if _N_ = 3 then call symput("WAB2T" || trim(left(put(i, BEST.))), trim(left(put(R(i), BEST.)))); /*R ENTRY FOR ALPHA & BETA2 COVARIANCE*/
      if _N_ = 5 then call symput("WB1T" || trim(left(put(i, BEST.))), trim(left(put(R(i), BEST.)))); /*R ENTRY FOR BETA1 VARIANCE*/
      if _N_ = 6 then call symput("WB1B2T" || trim(left(put(i, BEST.))), trim(left(put(R(i), BEST.)))); /*R ENTRY FOR BETA1 & BETA2 COVARIANCE*/
      if _N_ = 9 then call symput("WB2T" || trim(left(put(i, BEST.))), trim(left(put(R(i), BEST.)))); /*R ENTRY FOR BETA2 VARIANCE*/
   end;
run;
```

B.2.2 "Frequentist" Wishart

```
data NC001W01 (drop = KAPPA GAMMA);
    set NC001D03;
    by KVTRTN NSUBJID;
    KAPPA = (11 + 2)/2;
    GAMMA = (2 + 0.1)/2;
    if LOGCFU ne . then do; /*DESIGN MATRIX*/
        TIMEH1 = 1;
        TIMEH2 = -TIME;
        TIMEH3 = -GAMMA*log((exp((TIME - KAPPA)/GAMMA) + exp(-(TIME - KAPPA)/GAMMA))/(exp((KAPPA)/GAMMA) + exp(-(KAPPA)/GAMMA)));
    end;
    if first.KVTRTN then TSUBJID = .;
    if first.NSUBJID then TSUBJID + 1;
run;

data NC001W01; /*POOLED DATA (ALL TREATMENT GROUPS)*/
    set NC001W01 NC001W01 (in = x);
    if x then do;
        KVTRTN = &NTRT. + 1 /*CATEGORY: NUMBER OF TREATMENT GROUPS PLUS ONE*/; TSUBJID = NSUBJID;
        call symput("TSUBJ" || trim(left(put(&NTRT. + 1, BEST.))), trim(left(put(&NSUBJ.,  BEST.)))); /*NUMBER OF PATIENTS*/
    end;
proc sort;
    by KVTRTN NSUBJID;
run;
```

```
proc nlmixed data = NC001W01 (where = (KVTRTN <= &NTRT.)) seed = 1 method = GAUSS tech = DBLDOG; /*BY TREATMENT GROUP*/
    bounds G22 G33 > 0;
    parms ALPHA = 6.5 BETA1 = 0.2 BETA2 = 0 S2 = 0.45 G22 = 0.1 G33 = 0.05;
    SBETA1 = BETA1 + SB1; /*RANDOM EFFECTS*/
    SBETA2 = BETA2 + SB2;
    MLOGCFU = ALPHA*TIMEH1 + SBETA1*TIMEH2 + SBETA2*TIMEH3;
    PD = pdf('Normal', LOGCFU, MLOGCFU, S2);
    CD = cdf('Normal', LOGCFU, MLOGCFU, S2);
    LL = (CENSOR = 0)*log(PD) + (CENSOR = 1)*log(CD);
    model LOGCFU ~ general(LL);
    random SB1 SB2 ~ normal([0, 0], [G22, 0, G33]) subject = USUBJID;
    predict MLOGCFU out = NC001W02;
    ods output PARAMETERESTIMATES = NC001W03;
    by KVTRTN;
run;

proc nlmixed data = NC001W01 (where = (KVTRTN = &NTRT. + 1)) seed = 1 method = GAUSS tech = DBLDOG; /*ALL TREATMENT GROUPS POOLED*/
    bounds G11 G22 G33 > 0;
    parms ALPHA = 6.5 BETA1 = 0.2 BETA2 = 0 S2 = 0.45 G11 = 0.5 G22 = 0.1 G33 = 0.05;
    SALPHA = ALPHA + SA;
    SBETA1 = BETA1 + SB1;
    SBETA2 = BETA2 + SB2;
    MLOGCFU = SALPHA*TIMEH1 + SBETA1*TIMEH2 + SBETA2*TIMEH3;
    PD = pdf('Normal', LOGCFU, MLOGCFU, S2);
    CD = cdf('Normal', LOGCFU, MLOGCFU, S2);
    LL = (CENSOR = 0)*log(PD) + (CENSOR = 1)*log(CD);
    model LOGCFU ~ general(LL);
    random SA SB1 SB2 ~ normal([0, 0, 0], [G11, 0, G22, 0, 0, G33]) subject = USUBJID;
    predict MLOGCFU out = NC001W04;
    ods output PARAMETERESTIMATES = NC001W05;
    by KVTRTN;
run;
```

```
data NC001W06 (drop = i);
    set NC001W03 NC001W05;
    ESTIMATE = ESTIMATE*&WDF.; /*WDF IS THE DEGREES OF FREEDOM*/
    do i = 1 to %eval(&NTRT. + 1); /*SEE CODE FOR "DEFAULT" WISHART*/
        if PARAMETER = "G11" and KVTRTN = &NTRT. + 1 then call symput("WAT" || trim(left(put(i, BEST.))), trim(left(put(ESTIMATE, BEST.))));
        call symput("WAB1T" || trim(left(put(i, BEST.))), trim(left(put(0, BEST.)))); /*DIAGONAL ELEMENTS: ZERO*/
        call symput("WAB2T" || trim(left(put(i, BEST.))), trim(left(put(0, BEST.))));
        call symput("WB1B2T" || trim(left(put(i, BEST.))), trim(left(put(0, BEST.))));
    end;
    if PARAMETER = "G22" then call symput("WB1T" || trim(left(put(KVTRTN, BEST.))), trim(left(put(ESTIMATE, BEST.))));
    if PARAMETER = "G33" then call symput("WB2T" || trim(left(put(KVTRTN, BEST.))), trim(left(put(ESTIMATE, BEST.))));
run;
```

B.3 Bayesian Mixed Effects Regression Models

B.3.1 Differential Hyperbolic Tangent Regression Model

Model 1.1: Residuals: Normal
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS (FILE);

    data _NULL_;
        file "&FILE." linesize = 600;
        put "model { #THE MODEL";
        put "    for (i in 1:&NCNSNOBS.) { #UNCENSORED DATA";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]]) #DATA";
        put "        X[i] <- density(LOGCFU[i], DATA[i]) #LIKELIHOOD (DENSITY (PDF))";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) { CENSORED DATA";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]])C(, C[i]) #CENSORED DATA";
        put "        X[i] <- cumulative(LOGCFU[i], C[i]) #LIKELIHOOD (CUMULATIVE (CDF))";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] - SMU[NSUBJID[i], 3]*SGAMMA[NSUBJID[i]]*";
        put "                   log((exp((TIME[i] - SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(TIME[i] - SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]]))/(exp((SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]])))";
```

```
put "    PPO[i] <- X[i] #USED FOR CALCULATION OF CPO";
put "  }";
put "  for (i in 1:&NSUBJ.) { #RANDOM EFFECTS";
put "    SALPHA[i] <- SMU[i, 1]";
put "    SBETA1[i] <- SMU[i, 2]";
put "    SBETA2[i] <- SMU[i, 3]";
put "    SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
put "    SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "    SMU[i, 1:3] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3])";
put "    SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "    SGAMMA[i] ~ dnorm(MGAMMA[OKVTRTN[1 + &NTP.*(i - 1)]], GAMINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(0.1, 2)";
put "    SEBA002[i] <- SBETA1[i] + SBETA2[i]*SGAMMA[i]*(log(exp((2 - SKAPPA[i])/SGAMMA[i]) + exp(-(2 - SKAPPA[i])/SGAMMA[i])) -";
put "                  log(exp((0 - SKAPPA[i])/SGAMMA[i]) + exp(-(0 - SKAPPA[i])/SGAMMA[i])))/2";
put "    SEBA007[i] <- SBETA1[i] + SBETA2[i]*SGAMMA[i]*(log(exp((7 - SKAPPA[i])/SGAMMA[i]) + exp(-(7 - SKAPPA[i])/SGAMMA[i])) -";
put "                  log(exp((0 - SKAPPA[i])/SGAMMA[i]) + exp(-(0 - SKAPPA[i])/SGAMMA[i])))/7";
put "    SEBA014[i] <- SBETA1[i] + SBETA2[i]*SGAMMA[i]*(log(exp((14 - SKAPPA[i])/SGAMMA[i]) + exp(-(14 - SKAPPA[i])/SGAMMA[i])) -";
put "                  log(exp((0 - SKAPPA[i])/SGAMMA[i]) + exp(-(0 - SKAPPA[i])/SGAMMA[i])))/14";
put "    SEBA214[i] <- SBETA1[i] + SBETA2[i]*SGAMMA[i]*(log(exp((14 - SKAPPA[i])/SGAMMA[i]) + exp(-(14 - SKAPPA[i])/SGAMMA[i])) -";
put "                  log(exp((2 - SKAPPA[i])/SGAMMA[i]) + exp(-(2 - SKAPPA[i])/SGAMMA[i])))/12";
put "    SEBA714[i] <- SBETA1[i] + SBETA2[i]*SGAMMA[i]*(log(exp((14 - SKAPPA[i])/SGAMMA[i]) + exp(-(14 - SKAPPA[i])/SGAMMA[i])) -";
put "                  log(exp((7 - SKAPPA[i])/SGAMMA[i]) + exp(-(7 - SKAPPA[i])/SGAMMA[i])))/7";
put "  }";
put "  for (i in 1:&NTRT.) { #PRIORS";
put "    MALPHA[i] <- MMU[i, 1]";
put "    MBETA1[i] <- MMU[i, 2]";
put "    MBETA2[i] <- MMU[i, 3]";
put "    MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "    MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "    MMU[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "    MKAPPA[i] ~ dunif(2, 11)";
put "    MGAMMA[i] ~ dunif(0.1, 2)";
put "    INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "    SIGSQ[i] <- 1/INVSIGSQ[i]";
```

```
put "    KAPSIGSQ[i] ~ dunif(0.01, 30)";
put "    KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "    GAMSIGSQ[i] ~ dunif(0.01, 5)";
put "    GAMINVSQ[i] <- 1/GAMSIGSQ[i]";
put "    SMUTILDA[i, 1:3] ~ dmnorm(MMU[i, 1:3], MOMGINV[i, 1:3, 1:3]) #PREDICTIVE DISTRIBUTIONS (FOR FUTURE SLOPES)";
put "    SKAPPATILDA[i] ~ dnorm(MKAPPA[i], KAPINVSQ[i])T(2, 11)";
put "    SGAMMATILDA[i] ~ dnorm(MGAMMA[i], GAMINVSQ[i])T(0.1, 2)";
put "    SALPHATILDA[i] <- SMUTILDA[i, 1]";
put "    SBETA1TILDA[i] <- SMUTILDA[i, 2]";
put "    SBETA2TILDA[i] <- SMUTILDA[i, 3]";
put "    MEBA002[i] <- MBETA1[i] + MBETA2[i]*MGAMMA[i]*(log(exp((2 - MKAPPA[i])/MGAMMA[i]) + exp(-(2 - MKAPPA[i])/MGAMMA[i])) -";
put "                  log(exp((0 - MKAPPA[i])/MGAMMA[i]) + exp(-(0 - MKAPPA[i])/MGAMMA[i])))/2";
put "    MEBA007[i] <- MBETA1[i] + MBETA2[i]*MGAMMA[i]*(log(exp((7 - MKAPPA[i])/MGAMMA[i]) + exp(-(7 - MKAPPA[i])/MGAMMA[i])) -";
put "                  log(exp((0 - MKAPPA[i])/MGAMMA[i]) + exp(-(0 - MKAPPA[i])/MGAMMA[i])))/7";
put "    MEBA014[i] <- MBETA1[i] + MBETA2[i]*MGAMMA[i]*(log(exp((14 - MKAPPA[i])/MGAMMA[i]) + exp(-(14 - MKAPPA[i])/MGAMMA[i])) -";
put "                  log(exp((0 - MKAPPA[i])/MGAMMA[i]) + exp(-(0 - MKAPPA[i])/MGAMMA[i])))/14";
put "    MEBA214[i] <- MBETA1[i] + MBETA2[i]*MGAMMA[i]*(log(exp((14 - MKAPPA[i])/MGAMMA[i]) + exp(-(14 - MKAPPA[i])/MGAMMA[i])) -";
put "                  log(exp((2 - MKAPPA[i])/MGAMMA[i]) + exp(-(2 - MKAPPA[i])/MGAMMA[i])))/12";
put "    MEBA714[i] <- MBETA1[i] + MBETA2[i]*MGAMMA[i]*(log(exp((14 - MKAPPA[i])/MGAMMA[i]) + exp(-(14 - MKAPPA[i])/MGAMMA[i])) -";
put "                  log(exp((7 - MKAPPA[i])/MGAMMA[i]) + exp(-(7 - MKAPPA[i])/MGAMMA[i])))/7";
put "    for (j in 0:14) { #MEAN LOG(CFU) COUNT";
put "        MPLOT[i, j + 1] <- MMU[i, 1] - MMU[i, 2]*j - MMU[i, 3]*MGAMMA[i]*log((exp((j - MKAPPA[i])/MGAMMA[i]) +";
put "                           exp(-(j - MKAPPA[i])/MGAMMA[i]))/(exp((MKAPPA[i])/MGAMMA[i]) + exp(-(MKAPPA[i])/MGAMMA[i])))";
put "    }";
put "  }";
put "  for (i in 1:&NTRT.) { #DIFFERENCE VERSUS CONTROL";
put "    MEBAD002[i] <-  MEBA002[i] -  MEBA002[&NTRT.]";
put "    MEBAD007[i] <-  MEBA007[i] -  MEBA007[&NTRT.]";
put "    MEBAD014[i] <-  MEBA014[i] -  MEBA014[&NTRT.]";
put "    MEBAD214[i] <-  MEBA214[i] -  MEBA214[&NTRT.]";
put "    MEBAD714[i] <-  MEBA714[i] -  MEBA714[&NTRT.]";
put "  }";
```

```
put "   for (i in 1:&NTRT.) { #DIFFERENCE VERSUS CONTROL";
put "      for (j in 0:14) {";
put "         MPLOTD[i, j + 1] <- MPLOT[i, j + 1] - MPLOT[&NTRT., j + 1]";
put "         MPLOTDTILDA[i, j + 1] <- MPLOTTILDA[i, j + 1] - MPLOTTILDA[&NTRT., j + 1]";
put "      }";
put "   }";
put "   D[1] <- 0";
put "   D[2] <- 0";
put "   D[3] <- 0";
put "   IDENX[1, 1] <- 0.0001";
put "   IDENX[1, 2] <- 0";
put "   IDENX[1, 3] <- 0";
put "   IDENX[2, 1] <- IDENX[1, 2]";
put "   IDENX[2, 2] <- 0.0001";
put "   IDENX[2, 3] <- 0";
put "   IDENX[3, 1] <- IDENX[1, 3]";
put "   IDENX[3, 2] <- IDENX[2, 3]";
put "   IDENX[3, 3] <- 0.0001";
put "   for (i in 1:&NTRT.) {";
put "      MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
put "      MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
put "      ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
put "      BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
put "      BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
put "      ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
put "      ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
put "      BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
```

```
    put "      LM1SIGSQ[i] <- BT1SIGSQ[i] + BT2SIGSQ[i] - 2*BT1BT2SIGSQ[i]";
    put "      LM2SIGSQ[i] <- BT1SIGSQ[i] + BT2SIGSQ[i] + 2*BT1BT2SIGSQ[i]";
    put "      ALPLM1RHO[i] <- (ALPBT1SIGSQ[i] - ALPBT2SIGSQ[i])/sqrt(ALPSIGSQ[i]*(BT1SIGSQ[i] + BT2SIGSQ[i] - 2*BT1BT2SIGSQ[i]))";
    put "      ALPLM2RHO[i] <- (ALPBT1SIGSQ[i] + ALPBT2SIGSQ[i])/sqrt(ALPSIGSQ[i]*(BT1SIGSQ[i] + BT2SIGSQ[i] + 2*BT1BT2SIGSQ[i]))";
    put "      LM1LM2RHO[i] <- (BT1SIGSQ[i] - BT2SIGSQ[i])/sqrt((BT1SIGSQ[i] + BT2SIGSQ[i] - 2*BT1BT2SIGSQ[i])*(BT1SIGSQ[i] + BT2SIGSQ[i] +";
    put "                     2*BT1BT2SIGSQ[i]))";
    put "   }";
    %do i = 1 %to &NTRT.;
        put "   IDEN[&i., 1, 1] <- &&WAT&i.. #R MATRIX FROM 'DEFAULT' WISHART PRIOR";
        put "   IDEN[&i., 1, 2] <- &&WAB1T&i..";
        put "   IDEN[&i., 1, 3] <- &&WAB2T&i..";
        put "   IDEN[&i., 2, 1] <- IDEN[&i., 1, 2]";
        put "   IDEN[&i., 2, 2] <- &&WB1T&i..";
        put "   IDEN[&i., 2, 3] <- &&WB1B2T&i..";
        put "   IDEN[&i., 3, 1] <- IDEN[&i., 1, 3]";
        put "   IDEN[&i., 3, 2] <- IDEN[&i., 2, 3]";
        put "   IDEN[&i., 3, 3] <- &&WB2T&i..";
    %end;
    put "}";
run;

%mend;
```

SAS® and R Example Code: Bayes Factors

```
%macro DWISHART (); /*WISHART PACKAGE IN R (FOR CALCULATION OF DISTRIBUTION)*/

    put 'library("colorspace")';
    put 'library("mixAK")';
    put 'library("Matrix")';
    put 'dWishart <- function(W, df, S, log = FALSE) {';
    put 'thispackage <- "mixAK"';
    put 'if (is.null(dim(S))) wdim <- 1';
    put 'else{';
    put 'wdim <- nrow(S)';
    put 'if (ncol(S) != wdim) stop("S must be a square matrix")}';
    put 'lW <- (wdim*(wdim + 1))/2';
    put 'if (df <= wdim - 1) stop(paste("df must be > ", wdim - 1, sep = ""))';
    put 'Si <- chol(S)';
    put 'Si <- chol2inv(Si)';
    put 'Sitri <- Si[lower.tri(Si, diag = TRUE)]';
    put 'if (is.null(dim(W))){';
    put 'if (wdim == 1) n <- length(W)';
    put 'else stop("W must be a matrix")}';
    put 'else {';
    put 'if (nrow(W) == wdim & ncol(W) == wdim){';
    put 'n <- 1';
    put 'W <- W[lower.tri(W, diag = TRUE)]}';
    put 'else {';
    put 'if (ncol(W) != lW) stop(paste("W must have ", lW, " columns (lower triangles of sampled W form rows of the argument W)", sep = ""))';
    put 'n <- nrow(W)';
    put 'W <- as.numeric(t(W))}} ';
    put '## Compute log-density';
    put 'lDens <- .C("ldWishart_R", ldens = double(n),';
    put 'W.L = double(n*lW),';
    put 'log.sqrt.detW  = double(n), ';
```

```
    put 'log.const = double(1),';
    put 'invS.L = double(1W),';
    put 'log.sqrt.detinvS = double(1),';
    put 'err = as.integer(0),';
    put 'W = as.double(W),';
    put 'nu = as.double(df),';
    put 'invS = as.double(Sitri),';
    put 'dim = as.integer(wdim),';
    put 'npoints = as.integer(n),';
    put 'PACKAGE = thispackage)';
    put 'if (!log) lDens$ldens <- exp(lDens$ldens)';
    put 'return(lDens$ldens)';
    put '}';
%mend;

%macro MTCNTOBS (DATA = _LAST_); /*PROVIDING THE NUMBER OF OBSERVATIONS WITHIN A GIVEN DATASET*/

    %local DSID ANOBS WHSTMT COUNTED RC;

    %let DSID = %sysfunc(open(&DATA., IS));

    %if &DSID = 0 %then %do;

        %put %sysfunc(sysmsg());

        %let COUNTED = .;

        %goto MEXIT;

    %end;
```

```
%else %do;

    %let ANOBS = %sysfunc(attrn(&DSID, ANOBS));
    %let WHSTMT = %sysfunc(attrn(&DSID, WHSTMT));

%end;

%if &ANOBS = 1 & &WHSTMT = 0 %then %let COUNTED = %sysfunc(attrn(&DSID, NLOBS));

%else %do;

    %if %sysfunc(getoption(msglevel)) = I %then %put INFO: Observations in "&DATA." must be counted by iteration.;

    %let COUNTED = 0;

    %do %while (%sysfunc(fetch(&DSID)) = 0);

        %let COUNTED = %eval(&COUNTED. + 1);

    %end;

%end;

%let RC = %sysfunc(close(&DSID));

%MEXIT:

%put &COUNTED.;
%global NOBS;

%let NOBS = &COUNTED.;

%mend MTCNTOBS;
```

```
proc sort data = NC001P09; /*DATASET CONTAINING SUMMARY STATISTICS FOR EACH MODEL PARAMETER*/
    by KVTRTN;
run;

proc transpose data = NC001P09 (where = (KVTRTN ne .)) out = NC001CMP01;
    by KVTRTN;
    id IVAR;
    var MEAN; /*POSTERIOR MEANS USED FOR CALCULATION OF BAYES FACTORS*/
run;

proc sort data = NC001D15;
    by KVTRTN;
run;

data NC001CMP02;
    merge NC001D15 NC001CMP01;
    by KVTRTN;
proc sort;
    by NSUBJID;
run;

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do;
        LIKER = "dnorm(" || trim(left(put(LOGCFU, BEST.))) ||
                ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" ||
                trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))), " || "sd = " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end; else
```

```
    if CENSOR = 1 then do;
       LIKER = "pnorm(" || trim(left(put(C, BEST.))) ||
               ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" ||
               trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
               " - x[4])/x[5])))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))), " || "sd = " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end;
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = trim(left(TOTALLIKER)) || "*dmnorm(cbind(x[1], x[2], x[3]), c(" || trim(left(put(MALPHA, BEST.))) || ", " ||
                 trim(left(put(MBETA1, BEST.))) || ", " || trim(left(put(MBETA2, BEST.))) || "), SIGMA <- matrix(c(" ||
                 trim(left(put(ALPSIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3))*dtruncnorm(x[4], a = 2, b = 11, mean = " ||
                 trim(left(put(MKAPPA, BEST.))) || ", sd = " || trim(left(put(sqrt(KAPSIGSQ), BEST.))) ||
                 ")*dtruncnorm(x[5], a = 0.1, b = 2, mean = " || trim(left(put(MGAMMA, BEST.))) || ", sd = " ||
                 trim(left(put(sqrt(GAMSIGSQ), BEST.))) || ")";
       call symput("TOTALLIKER" || trim(left(put(NSUBJID, BEST.))), trim(left(TOTALLIKER)));
    run;

    %put &TOTALLIKER1.;

    data _NULL_;
       call symput("SETWD", "setwd('" || "&OPENBUGS." || "')");
    run;

    %put &SETWD.;
```

```
%macro LOG;

    data RLOG&i.;
        infile "&OPENBGSF.\RP&i..txt" length = LEN;
        input VAR1 $VARYING8192. LEN;
    run;

    data RLOG&i. (where = (LOGLIKL ne .)); /*ASSESSES WHETHER INTEGRAL EXISTS AND CONVERGED*/
        length LOGLIKE $200.;
        set RLOG&i.;
        where index(VAR1, "integral:");
        LOGLIKE = trim(left(tranwrd(VAR1, "integral: ", "")));
        LOGLIKE = substr(LOGLIKE, 1, index(LOGLIKE, " "));
        LOGLIKL = input(LOGLIKE, BEST32.);
    run;

%mend;

%macro DOINTLIKE; /*CHOOSEING FEASIBLE INTEGRATION BOUNDS (INFINITY CAUSES R TO BOMB OUT WITH THE SUAVE PACKAGE BELOW)*/

    %do i = 1 %to &NSUBJ.;

        data _NULL_;
            set NCO01P09 (where = (NSUBJID = &i.));
            if IVAR = "SALPHA" then do;
                call symput("ALPLOW", strip(put(MIN - 2*RANGE, BEST.)));
                call symput("ALPHIH", strip(put(MAX + 2*RANGE, BEST.)));
            end;
            if IVAR = "SBETA1" then do;
                call symput("BT1LOW", strip(put(MIN - 2*RANGE, BEST.)));
                call symput("BT1HIH", strip(put(MAX + 2*RANGE, BEST.)));
            end;
```

```
    if IVAR = "SBETA2" then do;
        call symput("BT2LOW", strip(put(MIN - 2*RANGE, BEST.)));
        call symput("BT2HIH", strip(put(MAX + 2*RANGE, BEST.)));
    end;
run;

%put &ALPLOW. &ALPHIH.;
%put &BT1LOW. &BT1HIH.;
%put &BT2LOW. &BT2HIH.;

%macro INTNNEW (NNEW);

    data _NULL_;
        file "&OPENBUGS./RP&i..r" linesize = 32767;
        put "&SETWD.";
        put 'library("grDevices")';
        put 'library("R2Cuba")';
        put 'library("mnormt")';
        put 'library("stats4")';
        put 'library("numDeriv")';
        put 'library("sn")';
        put 'library("truncnorm")';
        put 'integrand <- function(x) {';
        put "&&TOTALLIKER&i.."; /*CALL LIKELIHOOD PER PATIENT*/
        put '}';
        put "suave(ndim = 5, ncomp = 1, integrand, lower = c(&ALPLOW., &BT1LOW., &BT2LOW., 2, 0.1),";
        put "upper = c(&ALPHIH., &BT1HIH., &BT2HIH., 11, 2), rel.tol = 1e-3, abs.tol = 5e-6,";
        put "flags = list(verbose = 1, final = 1, pseudo.random = 0, mersenne.seed = NULL),";
        put "min.eval = 1e5, max.eval = 1e6, nnew = &NNEW., flatness = 50)";
        put "q()";
    run;
```

```
    data _NULL_; /*CALL R VIA SAS*/
        file "&OPENSHRT./RunR.bat";
        put "CD &OPENSHRT.";
        put "&RSHORT./R.exe CMD BATCH --vanilla --quiet &OPENSHRT./RP&i..r &OPENSHRT./RP&i..txt";
        put "EXIT";
    run;

    data _NULL_;
        X "&OPENSHRT./RunR.bat";
    run; quit;

%mend;

%INTNNEW (NNEW = 1000); /*FIRST TRY*/
%LOG;
%MTCNTOBS (DATA = RLOG&i.);
%put &NOBS.;

%if "&NOBS." = "0" %then %do;

    %INTNNEW (NNEW = 100); /*SECOND TRY WITH FEWER ITERATIONS*/
    %LOG;

%end;

%MTCNTOBS (DATA = RLOG&i.);
%put &NOBS.;
```

```
    %if "&NOBS." = "0" %then %do;

        %INTNNEW (NNEW = 10); /*THIRD TRY WITH FEWER ITERATIONS*/
        %LOG;

    %end;

%end;

%mend;

%DOINTLIKE;

data NCO01CMP04 (drop = VAR1 LOGLIKE); set RLOG1 - RLOG&NSUBJ.; run;

%macro DOMATRIX ();

    data NCO01CMP05; /*R CODE FOR PRIORS EVALUATED AT POSTERIOR MEAN*/
        length PMMU PMKAPPA PMGAMMA PMOMGINV PKAPSIGSQ PGAMSIGSQ PINVSIGSQ $9999.;
        set NCO01CMP01;
        %do i = 1 %to &NTRT.;
            if KVTRTN = &i. then do; /*SEE CODE FOR "DEFAULT WISHART" PRIOR*/
                WA = &&WAT&i..; WAB1 = &&WAB1T&i..; WAB2 = &&WAB2T&i..; WB1 = &&WB1T&i..; WB1B2 = &&WB1B2T&i..; WB2 = &&WB2T&i..;
            end;
        %end; /*WDF IS THE DEGREES OF FREEDOM*/
        PMMU = "dmnorm(cbind(" || trim(left(put(MALPHA, BEST.))) || ", " || trim(left(put(MBETA1, BEST.))) || ", " ||
            trim(left(put(MBETA2, BEST.))) || "), c(0, 0, 0), SIGMA <- 10^4*matrix(c(1, 0, 0, 0, 1, 0, 0, 0, 1), 3, 3))";
        PMKAPPA = "dunif(" || trim(left(put(MKAPPA, BEST.))) || ", min = 2, max = 11)";
        PMGAMMA = "dunif(" || trim(left(put(MGAMMA, BEST.))) || ", min = 0.1, max = 2)";
        PMOMGINV = "dWishart(solve(matrix(c(" || trim(left(put(ALPSIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) ||
            "," || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
            trim(left(put(BT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
            trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
```

```
        trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3)), &WDF., S <- solve(matrix(c(" || trim(left(put(WA, BEST.))) ||
        "," || trim(left(put(WAB1, BEST.))) || ", " || trim(left(put(WAB2, BEST.))) || ", " ||
        trim(left(put(WAB1, BEST.))) || ", " || trim(left(put(WB1, BEST.))) || ", " || trim(left(put(WB1B2, BEST.))) || "," ||
        trim(left(put(WAB2, BEST.))) || ", " || trim(left(put(WB1B2, BEST.))) || ", " || trim(left(put(WB2, BEST.))) || "), 3, 3)))";
    PKAPSIGSQ = "dunif(" || trim(left(put(KAPSIGSQ, BEST.))) || ", min = 0.01, max = 30)";
    PGAMSIGSQ = "dunif(" || trim(left(put(GAMSIGSQ, BEST.))) || ", min = 0.01, max = 5)";
    PINVSIGSQ = "dgamma(" || trim(left(put(1/SIGSQ, BEST.))) || ", 0.0001, 0.0001)";
run;

%mend;

%DOMATRIX;

%macro PRIORLIKE (PARAMETER); /*CALLING R VIA SAS*/

  %do i = 1 %to &NTRT.;

    data _NULL_;
        set NC001CMP05;
        if KVTRTN = &i.;
        call symput("&PARAMETER." || trim(left(put(KVTRTN, BEST.))), trim(left(&PARAMETER.)));
    run;

    %put &&&PARAMETER&i..;

    data _NULL_;
        file "&OPENBUGS./PT&i..r" linesize = 32767;
        put "&SETWD.";
        put 'library("grDevices")';
        put 'library("mnormt")';
        %if "&PARAMETER." = "PMOMGINV" %then %do;
            %DWISHART;
        %end;
```

```
    put "&&&PARAMETER&i..";
    put "q()";
  run;

  data _NULL_;
    file "&OPENSHRT./RunR.bat";
    put "CD &OPENSHRT.";
    put "&RSHORT./R.exe CMD BATCH --vanilla --quiet &OPENSHRT./PT&i..r &OPENSHRT./PT&i..txt";
    put "EXIT";
  run;

  data _NULL_;
    X "&OPENSHRT./RunR.bat";
  run; quit;

  data &PARAMETER.&i.;
    infile "&OPENBGSF.\PT&i..txt" length = LEN;
    input VAR1 $VARYING8192. LEN;
  run;

  data &PARAMETER.&i. (drop = VAR1);
    set &PARAMETER.&i.;
    KVTRTN = &i.;
    if index(VAR1, "[1]");
    &PARAMETER. = input(substr(VAR1, 4), BEST32.);
  run;

%end;
```

```
    data &PARAMETER.;
        set &PARAMETER.::;
    run;

%mend;

%PRIORLIKE (PARAMETER = PMMU);
%PRIORLIKE (PARAMETER = PMKAPPA);
%PRIORLIKE (PARAMETER = PMGAMMA);
%PRIORLIKE (PARAMETER = PMOMGINV);
%PRIORLIKE (PARAMETER = PKAPSIGSQ);
%PRIORLIKE (PARAMETER = PGAMSIGSQ);
%PRIORLIKE (PARAMETER = PINVSIGSQ);

data _NULL_; /*NUMBER OF PARAMETERS ASSOCIATED WITH EACH MATRIX TIMES TREATMENT GROUP*/
    PMMU = 3;
    PMKAPPA = 1;
    PMGAMMA = 1;
    PMOMGINV = 6;
    PKAPSIGSQ = 1;
    PGAMSIGSQ = 1;
    PINVSIGSQ = 1;
    call symput("BFPRMSN", trim(left(put(&NTRT.*sum(of _ALL_), BEST.))));
run;

%put &BFPRMSN.;

data NCO01CMP05;
    merge PMMU PMKAPPA PMGAMMA PMOMGINV PKAPSIGSQ PGAMSIGSQ PINVSIGSQ;
    by KVTRTN;
run;
```

```
proc datasets;
   delete PMMU: PMKAPPA: PMGAMMA: PMOMGINV: PKAPSIGSQ: PGAMSIGSQ: PINVSIGSQ:;
run;

proc transpose data = NC001CMP05 out = NC001CMP06 (where = (_NAME_ ne 'KVTRTN'));
   by KVTRTN;
   var _ALL_;
run;

data _NULL_;
   set NC001CMP06;
   call symput("NPRMSFIXV", trim(left(put(_N_, BEST.))));
run;

%put &NPRMSFIXV.;

data NC001CMP07;
   set NC001CMP04 (in = x) NC001CMP06 (in = y rename = (COL1 = LOGLIKL));
   if x then PTYPE = "DATA"; else
   if y then PTYPE = "PARM";
   LPROB = log(LOGLIKL);
run;

proc means data = NC001CMP07 noprint;
   var LPROB; output out = NC001CMP08 sum = LSPRB;
run;

proc corr data = NC001P10_ (keep = MALPHA: MBETA1: MBETA2: MKAPPA: MGAMMA: SIGSQ:) out = NC001CMP09 (rename = (_NAME_ = VARNAME));
   var _ALL_; /*CALCULATION OF DET(R)*/
proc sort;
   by _TYPE_;
run;
```

```
data NCO01CMP10;
    set NCO01CMP09 (where = (_TYPE_ = "CORR"));
run;

data NCO01CMP11;
    set NCO01CMP10 (drop = _TYPE_ VARNAME);
    array MTRX _ALL_;
    call symput("NPRMSFIX", trim(left(put(dim(MTRX), BEST.))));
    length DMATRIX $32767.;
    do i = 1 to dim(MTRX);
        if i = 1 then DMATRIX = trim(left(put(MTRX(i), BEST.))); else
                      DMATRIX = trim(left(DMATRIX)) || " " || trim(left(put(MTRX(i), BEST.)));
    end;
    call symput("MTRX" || trim(left(put(_N_, BEST.))), trim(left(DMATRIX)));
run;

%put &MTRX1.;
%put &NPRMSFIX.;

ods listing;

%macro DETR ();

    proc iml;
        M = {%do i = 1 %to %eval(&NPRMSFIX. - 1); &&MTRX&i.. , %end; &&MTRX&NPRMSFIX.};
        DETM = det(M);
        print DETM;
        create NCO01CMP11 var {DETM};
        append;
        close NCO01CMP11;
    quit;

%mend;
```

```
%DETR ();

/*STANDARD DEVIATIONS OF POSTERIOR DISTRIBUTIONS*/

data NC001CMP13;
    set NC001CMP09 (where = (_TYPE_ = "STD"));
run;

data NC001CMP14;
    set NC001CMP13 (drop = _TYPE_ VARNAME);
    array LSTD _ALL_;
    do i = 1 to dim(LSTD);
       LSTD(i) = log(LSTD(i));
    end; LSTDP = sum(of _ALL_);
run;

/*LAPLACE ESTIMATE*/

data NC001CMP15;
    merge NC001CMP08 (drop = _FREQ_ _TYPE_) NC001CMP11 NC001CMP14 (keep = LSTDP);
    MARGINAL = 0.5*&BFPRMSN.*log(2*3.141592654) + 0.5*log(DETM) + LSTDP + LSPRB;
run;
```

Model 1.2: Residuals: Normal
Random Coefficients: Normal, Fixed Smoothness
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS ();

    data _NULL_;
        file "&OPENBUGS./NC001 &TYPE1. Model.txt";
        put "model {";
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]])";
        put "        X[i] <- density(LOGCFU[i], DATA[i])";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]])C(, C[i])";
        put "        X[i] <- cumulative(LOGCFU[i], C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] - SMU[NSUBJID[i], 3]*MGAMMA[KVTRTN[i]]*";
        put "                   log((exp((TIME[i] - SKAPPA[NSUBJID[i]])/MGAMMA[KVTRTN[i]]) + exp(-(TIME[i] - SKAPPA[NSUBJID[i]])/";
        put "                   MGAMMA[KVTRTN[i]]))/(exp((SKAPPA[NSUBJID[i]])/MGAMMA[KVTRTN[i]]) + exp(-(SKAPPA[NSUBJID[i]])/";
        put "                   MGAMMA[KVTRTN[i]])))";
        put "        PPO[i] <- X[i]";
        put "    }";
        put "    for (i in 1:&NSUBJ.) {";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
        put "        SBETA2[i] <- SMU[i, 3]";
        put "        SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
```

```
put "    SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "    SMU[i, 1:3] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3])";
put "    SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "    SEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "  }";
put "  for (i in 1:&NTRT.) {";
put "    MALPHA[i] <- MMU[i, 1]";
put "    MBETA1[i] <- MMU[i, 2]";
put "    MBETA2[i] <- MMU[i, 3]";
put "    MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "    MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "    MMU[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "    MKAPPA[i] ~ dunif(2, 11)";
put "    MGAMMA[i] ~ dunif(0.1, 2)";
put "    INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "    SIGSQ[i] <- 1/INVSIGSQ[i]";
put "    KAPSIGSQ[i] ~ dunif(0.01, 30)";
put "    KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "    SMUTILDA[i, 1:3] ~ dmnorm(MMU[i, 1:3], MOMGINV[i, 1:3, 1:3])";
put "    SALPHATILDA[i] <- SMUTILDA[i, 1]";
put "    SBETA1TILDA[i] <- SMUTILDA[i, 2]";
put "    SBETA2TILDA[i] <- SMUTILDA[i, 3]";
put "    MEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "    for (j in 0:14) {";
put "      MPLOT[i, j + 1] <- <SEE MODEL 1.1>";
put "    }";
put "  }";
```

```
    put "   for (i in 1:&NTRT.) {";
    put "       MEBAD002[i] <- <SEE MODEL 1.1>";
    put "         ...";
    put "   }";
    put "   D[1] <- 0";
    put "   D[2] <- 0";
    put "   D[3] <- 0";
    put "   IDENX[1, 1] <- 0.0001";
    put "   IDENX[1, 2] <- 0";
    put "   IDENX[1, 3] <- 0";
    put "   IDENX[2, 1] <- IDENX[1, 2]";
    put "   IDENX[2, 2] <- 0.0001";
    put "   IDENX[2, 3] <- 0";
    put "   IDENX[3, 1] <- IDENX[1, 3]";
    put "   IDENX[3, 2] <- IDENX[2, 3]";
    put "   IDENX[3, 3] <- 0.0001";
    put "   for (i in 1:&NTRT.) {";
    put "       MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
    put "   MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
    put "       ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "       BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "       BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
    put "       ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "       ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
    put "       BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "   }";
    %do i = 1 %to &NTRT.;
       put "<SEE MODEL 1.1>";
    %end;
       put "}";
run;
%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.1, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do;
        LIKER = "dnorm(" || trim(left(put(LOGCFU, BEST.))) ||
                ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*" || trim(left(put(MGAMMA, BEST.))) || "*log((exp((" ||
                trim(left(put(TIME, BEST.))) || " - x[4])/" || trim(left(put(MGAMMA, BEST.))) || ") + exp(-(" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/" || trim(left(put(MGAMMA, BEST.))) || "))/(exp(x[4]/" || trim(left(put(MGAMMA, BEST.))) || ") + exp(-x[4]/" ||
                trim(left(put(MGAMMA, BEST.))) || "))), " || "sd = " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end; else
    if CENSOR = 1 then do;
        LIKER = "pnorm(" || trim(left(put(C, BEST.))) ||
                ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*" || trim(left(put(MGAMMA, BEST.))) || "*log((exp((" ||
                trim(left(put(TIME, BEST.))) || " - x[4])/" || trim(left(put(MGAMMA, BEST.))) || ") + exp(-(" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/" || trim(left(put(MGAMMA, BEST.))) || "))/(exp(x[4]/" || trim(left(put(MGAMMA, BEST.))) || ") + exp(-x[4]/" ||
                trim(left(put(MGAMMA, BEST.))) || "))), " || "sd = " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end;
```

```
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = trim(left(TOTALLIKER)) || "*dmnorm(cbind(x[1], x[2], x[3]), c(" || trim(left(put(MALPHA, BEST.))) || ", "  ||
                 trim(left(put(MBETA1, BEST.))) || ", " || trim(left(put(MBETA2, BEST.))) || "), SIGMA <- matrix(c(" ||
                 trim(left(put(ALPSIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3))*dtruncnorm(x[4], a = 2, b = 11, mean = " ||
                 trim(left(put(MKAPPA, BEST.))) || ", sd = " || trim(left(put(sqrt(KAPSIGSQ), BEST.))) || ")";
    call symput("TOTALLIKER" || trim(left(put(NSUBJID, BEST.))), trim(left(TOTALLIKER)));
run;
```

Model 1.4: Residuals: Skew Normal
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS (FILE);

    data _NULL_;
        file "&FILE." linesize = 600;
        put "model { #THE MODEL";
        put "    PI <- 3.14159265358979";
        put "    ADJMEAN <- pow(2/PI, 0.5)";
        put "    for (i in 1:&NCNSNOBS.) { #MIXTURE";
        put "        LOGCFU[i] ~ dnorm(NMEAN[i], INVSIGSQ[KVTRTN[i]]) #DATA";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFU[i] ~ dnorm(NMEAN[i], INVSIGSQ[KVTRTN[i]])C(, C[i]) #CENSORED DATA";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] -";
        put "                   SMU[NSUBJID[i], 3]*SGAMMA[NSUBJID[i]]*log((exp((TIME[i] - SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]]) + exp(-(TIME[i] - SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]))/";
        put "                   (exp((SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + ";
        put "                   exp(-(SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]])))";
        put "        NMEAN[i] <- MEAN[i] - ADJMEAN*D[KVTRTN[i]] + D[KVTRTN[i]]*U[i]";
        put "        U[i] ~ dnorm(0, 1)T(0, ) #NUISANCE PARAMETER";
        put "    }";
        put "    for (i in 1:&NSUBJ.) { #RANDOM EFFECTS";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
```

```
    put "      SBETA2[i] <- SMU[i, 3]";
    put "      SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
    put "      SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
    put "      SMU[i, 1:3] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3])";
    put "      SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
    put "      SGAMMA[i] ~ dnorm(MGAMMA[OKVTRTN[1 + &NTP.*(i - 1)]], GAMINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(0.1, 2)";
    put "      SEBAOO2[i] <- <SEE MODEL 1.1>";
    put "      ...";
    put "   }";
    put "   for (i in 1:&NTRT.) { #PRIORS";
    put "      D[i] ~ dnorm(0, 0.0001)";
    put "      MALPHA[i] <- MMU[i, 1]";
    put "      MBETA1[i] <- MMU[i, 2]";
    put "      MBETA2[i] <- MMU[i, 3]";
    put "      MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
    put "      MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
    put "      MMU[i, 1:3] ~ dmnorm(I[1:3], IDENX[1:3, 1:3])";
    put "      MKAPPA[i] ~ dunif(2, 11)";
    put "      MGAMMA[i] ~ dunif(0.1, 2)";
    put "      INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
    put "      SIGSQ[i] <- 1/INVSIGSQ[i]";
    put "      KAPSIGSQ[i] ~ dunif(0.01, 30)";
    put "      KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
    put "      GAMSIGSQ[i] ~ dunif(0.01, 5)";
    put "      GAMINVSQ[i] <- 1/GAMSIGSQ[i]";
    put "      MEBAOO2[i] <- <SEE MODEL 1.1>";
    put "      ...";
    put "      for (j in 0:14) {";
    put "         MPLOT[i, j + 1] <- <SEE MODEL 1.1>";
    put "      }";
    put "   }";
```

```
    put "   for (i in 1:&NTRT.) {";
    put "      MEBAD002[i] <- <SEE MODEL 1.1>";
    put "         ...";
    put "   }";
    put "   I[1] <- 0";
    put "   I[2] <- 0";
    put "   I[3] <- 0";
    put "   IDENX[1, 1] <- 0.0001";
    put "   IDENX[1, 2] <- 0";
    put "   IDENX[1, 3] <- 0";
    put "   IDENX[2, 1] <- IDENX[1, 2]";
    put "   IDENX[2, 2] <- 0.0001";
    put "   IDENX[2, 3] <- 0";
    put "   IDENX[3, 1] <- IDENX[1, 3]";
    put "   IDENX[3, 2] <- IDENX[2, 3]";
    put "   IDENX[3, 3] <- 0.0001";
    put "   for (i in 1:&NTRT.) {";
    put "      MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
    put "      MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
    put "      ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "      BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "      BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
    put "      ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "      ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
    put "      BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "   }";
    %do i = 1 %to &NTRT.;
       put "<SEE MODEL 1.1>";
    %end;
    put "}";
 run;
%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.1, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do;
        LIKER = "2*(" || trim(left(put(SIGSQ, BEST.))) || " + " || trim(left(put(D**2, BEST.))) || ")^(-0.5)*dnorm((" ||
                trim(left(put(LOGCFU, BEST.))) || " - (" || "x[1] - x[2]*" || trim(left(put(TIME, BEST.))) ||
                " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" ||
                trim(left(put(TIME, BEST.))) || " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5])))" ||
                " - (((2/3.141592654)^0.5)*" || trim(left(put(D, BEST.))) || ")))*(" || trim(left(put(SIGSQ, BEST.))) ||
                " + " || trim(left(put(D**2, BEST.))) || ")^(-0.5), 0, 1)*pnorm((" || trim(left(put(D, BEST.))) || "/" ||
                trim(left(put(sqrt(SIGSQ), BEST.))) || ")*(" || trim(left(put(LOGCFU, BEST.))) || " - (x[1] - x[2]*" ||
                trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) || " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5])))" ||
                " - (((2/3.141592654)^0.5)*" || trim(left(put(D, BEST.))) || ")))*(" || trim(left(put(SIGSQ, BEST.))) || " + " ||
                trim(left(put(D**2, BEST.))) || ")^(-0.5), 0, 1)";
    end; else
```

```
    if CENSOR = 1 then do;
       LIKER = "integrate(function(y) {2*(" || trim(left(put(SIGSQ, BEST.))) || " + " ||
               trim(left(put(D**2, BEST.))) || ")^(-0.5)*dnorm((y - (x[1] - x[2]*" || trim(left(put(TIME, BEST.))) ||
               " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" ||
               trim(left(put(TIME, BEST.))) || " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5])))" ||
               " - (((2/3.141592654)^0.5)*" || trim(left(put(D, BEST.))) || ")))*(" || trim(left(put(SIGSQ, BEST.))) ||
               " + " || trim(left(put(D**2, BEST.))) || ")^(-0.5), 0, 1)*pnorm((" || trim(left(put(D, BEST.))) || "/" ||
               trim(left(put(sqrt(SIGSQ), BEST.))) || ")*(y - (x[1] - x[2]*" || trim(left(put(TIME, BEST.))) ||
               " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" ||
               trim(left(put(TIME, BEST.))) || " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5])))" ||
               " - (((2/3.141592654)^0.5)*" || trim(left(put(D, BEST.))) || ")))*(" || trim(left(put(SIGSQ, BEST.))) ||
               " + " || trim(left(put(D**2, BEST.))) || ")^(-0.5), 0, 1)}, lower = -Inf, upper = " ||  trim(left(put(C, BEST.))) || ")$value";
    end;
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = ... ;
      call symput("TOTALLIKER" || trim(left(put(NSUBJID, BEST.))), trim(left(TOTALLIKER)));
run;

      ...
```

Model 1.5: Residuals: Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS (FILE);

    data _NULL_;
        file "&FILE." linesize = 600;
        put "model {"
                                        ;
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])";
        put "        LOGCFUC[i] ~ dunif(0, 1)";
        put "        X[i] <- density(LOGCFU[i], DATA[i])";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFUC[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])C(, C[i])";
        put "        X[i] <- cumulative(LOGCFUC[i], C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] - SMU[NSUBJID[i], 3]*SGAMMA[NSUBJID[i]]*";
        put "                   log((exp((TIME[i] - SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(TIME[i] - SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]]))/(exp((SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]])))";
        put "        PPO[i] <- X[i]";
        put "    }";
        put "    for (i in 1:&NSUBJ.) {";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
```

```
put "    SBETA2[i] <- SMU[i, 3]";
put "    SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
put "    SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "    SMU[i, 1:3] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3])";
put "    SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "    SGAMMA[i] ~ dnorm(MGAMMA[OKVTRTN[1 + &NTP.*(i - 1)]], GAMINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(0.1, 2)";
put "    SEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "  }";
put "  for (i in 1:&NTRT.) {";
put "    V[i] ~ dunif(2, 100)";
put "    MALPHA[i] <- MMU[i, 1]";
put "    MBETA1[i] <- MMU[i, 2]";
put "    MBETA2[i] <- MMU[i, 3]";
put "    MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "    MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "    MMU[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "    MKAPPA[i] ~ dunif(2, 11)";
put "    MGAMMA[i] ~ dunif(0.1, 2)";
put "    INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "    SIGSQ[i] <- 1/INVSIGSQ[i]";
put "    KAPSIGSQ[i] ~ dunif(0.01, 30)";
put "    KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "    GAMSIGSQ[i] ~ dunif(0.01, 5)";
put "    GAMINVSQ[i] <- 1/GAMSIGSQ[i]";
put "    MEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "    for (j in 0:14) {";
put "      MPLOT[i, j + 1] <- <SEE MODEL 1.1>";
put "    }";
put "  }";
```

```
    put "   for (i in 1:&NTRT.) {";
    put "      MEBAD002[i] <- <SEE MODEL 1.1>";
    put "        ...";
    put "   }";
    put "   D[1] <- 0";
    put "   D[2] <- 0";
    put "   D[3] <- 0";
    put "   IDENX[1, 1] <- 0.0001";
    put "   IDENX[1, 2] <- 0";
    put "   IDENX[1, 3] <- 0";
    put "   IDENX[2, 1] <- IDENX[1, 2]";
    put "   IDENX[2, 2] <- 0.0001";
    put "   IDENX[2, 3] <- 0";
    put "   IDENX[3, 1] <- IDENX[1, 3]";
    put "   IDENX[3, 2] <- IDENX[2, 3]";
    put "   IDENX[3, 3] <- 0.0001";
    put "   for (i in 1:&NTRT.) {";
    put "      MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
    put "      MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
    put "      ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "      BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "      BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
    put "      ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "      ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
    put "      BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "   }";
    %do i = 1 %to &NTRT.;
       put "<SEE MODEL 1.1>";
    %end;
    put "}";
run;
%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.1, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do;
        LIKER = "dst(" || trim(left(put(LOGCFU, BEST.))) ||
                ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" ||
                trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))), " ||
                trim(left(put(sqrt(SIGSQ), BEST.))) || ", 0, " || trim(left(put(V, BEST.))) || ")";
    end; else
    if CENSOR = 1 then do;
        LIKER = "pst(" || trim(left(put(C, BEST.))) ||
                ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" ||
                trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))), " ||
                trim(left(put(sqrt(SIGSQ), BEST.))) || ", 0, " || trim(left(put(V, BEST.))) || ")";
    end;
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = ... ;
run;

...
```

Model 1.7: Residuals: Student t
Random Coefficients: Student t
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS ();

    data _NULL_;
        file "&OPENBUGS./NC001 &TYPE1. Model.txt";
        put "model {";
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])";
        put "        LOGCFUC[i] ~ dunif(0, 1)";
        put "        X[i] <- density(LOGCFU[i], DATA[i])";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFUC[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])C(, C[i])";
        put "        X[i] <- cumulative(LOGCFUC[i], C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] - SMU[NSUBJID[i], 3]*SGAMMA[NSUBJID[i]]*";
        put "                   log((exp((TIME[i] - SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(TIME[i] - SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]]))/(exp((SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]])))";
        put "        PPO[i] <- X[i]";
        put "    }";
        put "    for (i in 1:&NSUBJ.) {";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
        put "        SBETA2[i] <- SMU[i, 3]";
```

```
put "    SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
put "    SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "    SMU[i, 1:3] ~ dmt(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3], ";
put "                     RVS[OKVTRTN[1 + &NTP.*(i - 1)]])";
put "    SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "    SGAMMA[i] ~ dnorm(MGAMMA[OKVTRTN[1 + &NTP.*(i - 1)]], GAMINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(0.1, 2)";
put "    SEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "  }";
put "  for (i in 1:&NTRT.) {";
put "    V[i] ~ dunif(2, 100)";
put "    RVS[i] ~ dunif(2, 100)";
put "    MALPHA[i] <- MMU[i, 1]";
put "    MBETA1[i] <- MMU[i, 2]";
put "    MBETA2[i] <- MMU[i, 3]";
put "    MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "    MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "    MMU[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "    MKAPPA[i] ~ dunif(2, 11)";
put "    MGAMMA[i] ~ dunif(0.1, 2)";
put "    INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "    SIGSQ[i] <- 1/INVSIGSQ[i]";
put "    KAPSIGSQ[i] ~ dunif(0.01, 30)";
put "    KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "    GAMSIGSQ[i] ~ dunif(0.01, 5)";
put "    GAMINVSQ[i] <- 1/GAMSIGSQ[i]";
put "    MEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "    for (j in 0:14) {";
put "      MPLOT[i, j + 1] <- <SEE MODEL 1.1>";
put "    }";
put "  }";
```

```
    put "   for (i in 1:&NTRT.) {";
    put "       MEBAD002[i] <- <SEE MODEL 1.1>";
    put "         ...";
    put "   }";
    put "   D[1] <- 0";
    put "   D[2] <- 0";
    put "   D[3] <- 0";
    put "   IDENX[1, 1] <- 0.0001";
    put "   IDENX[1, 2] <- 0";
    put "   IDENX[1, 3] <- 0";
    put "   IDENX[2, 1] <- IDENX[1, 2]";
    put "   IDENX[2, 2] <- 0.0001";
    put "   IDENX[2, 3] <- 0";
    put "   IDENX[3, 1] <- IDENX[1, 3]";
    put "   IDENX[3, 2] <- IDENX[2, 3]";
    put "   IDENX[3, 3] <- 0.0001";
    put "   for (i in 1:&NTRT.) {";
    put "       MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
    put "   MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
    put "       ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "       BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "       BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
    put "       ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "       ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
    put "       BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "   }";
    %do i = 1 %to &NTRT.;
       put "<SEE MODEL 1.1>";
    %end;
       put "}";
run;
%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.5, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do; LIKER = ... ; end; else if CENSOR = 1 then do; LIKER = ... ; end;
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = trim(left(TOTALLIKER)) || "*dmst(cbind(x[1], x[2], x[3]), c(" || trim(left(put(MALPHA, BEST.))) || ", "  ||
                 trim(left(put(MBETA1, BEST.))) || ", " || trim(left(put(MBETA2, BEST.))) || "), matrix(c(" ||
                 trim(left(put(ALPSIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3), c(0, 0, 0), " || trim(left(put(RVS, BEST.))) ||
                 ")*dtruncnorm(x[4], a = 2, b = 11, mean = " || trim(left(put(MKAPPA, BEST.))) || ", sd = " ||
                 trim(left(put(sqrt(KAPSIGSQ), BEST.))) || ")*dtruncnorm(x[5], a = 0.1, b = 2, mean = " ||
                 trim(left(put(MGAMMA, BEST.))) || ", sd = " || trim(left(put(sqrt(GAMSIGSQ), BEST.))) || ")";
    call symput("TOTALLIKER" || trim(left(put(NSUBJID, BEST.))), trim(left(TOTALLIKER)));
run;

...
```

Model 1.8: Residuals: Student t
Random Coefficients: Skew Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS ();

    data _NULL_;
       file "&OPENBUGS./NC001 &TYPE1. Model.txt";
        put "model {";
        put "    PI <- 3.14159265358979";
        put "    ADJMU <-pow(2/PI, 0.5)";
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])";
        put "        LOGCFUC[i] ~ dunif(0, 1)";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFUC[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])C(, C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] - SMU[NSUBJID[i], 3]*SGAMMA[NSUBJID[i]]*";
        put "                   log((exp((TIME[i] - SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(TIME[i] - SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]]))/(exp((SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]])))";
        put "    }";
        put "    for (i in 1:&NSUBJ.) {";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
        put "        SBETA2[i] <- SMU[i, 3]";
        put "        SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
```

```
put "    SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "    NMMU[i, 1] <- MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1] - ADJMU*DM[OKVTRTN[1 + &NTP.*(i - 1)], 1] + ";
put "                  DM[OKVTRTN[1 + &NTP.*(i - 1)], 1]*U[i, 1]";
put "    NMMU[i, 2] <- MMU[OKVTRTN[1 + &NTP.*(i - 1)], 2] - ADJMU*DM[OKVTRTN[1 + &NTP.*(i - 1)], 2] + ";
put "                  DM[OKVTRTN[1 + &NTP.*(i - 1)], 2]*U[i, 2]";
put "    NMMU[i, 3] <- MMU[OKVTRTN[1 + &NTP.*(i - 1)], 3] - ADJMU*DM[OKVTRTN[1 + &NTP.*(i - 1)], 3] + ";
put "                  DM[OKVTRTN[1 + &NTP.*(i - 1)], 3]*U[i, 3]";
put "    U[i, 1] ~ dnorm(0, 1)T(0, ) #NUISANCE PARAMETER";
put "    U[i, 2] ~ dnorm(0, 1)T(0, ) #NUISANCE PARAMETER";
put "    U[i, 3] ~ dnorm(0, 1)T(0, ) #NUISANCE PARAMETER";
put "    SMU[i, 1:3] ~ dmnorm(NMMU[i, 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3]) #MIXTURE";
put "    SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "    SGAMMA[i] ~ dnorm(MGAMMA[OKVTRTN[1 + &NTP.*(i - 1)]], GAMINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(0.1, 2)";
put "    SEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "  }";
put "  for (i in 1:&NTRT.) {";
put "    DM[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "    V[i] ~ dunif(2, 100)";
put "    MALPHA[i] <- MMU[i, 1]";
put "    MBETA1[i] <- MMU[i, 2]";
put "    MBETA2[i] <- MMU[i, 3]";
put "    MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "    MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "    DALPHA[i] <- DM[i, 1]";
put "    DBETA1[i] <- DM[i, 2]";
put "    DBETA2[i] <- DM[i, 3]";
put "    MMU[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "    MKAPPA[i] ~ dunif(2, 11)";
put "    MGAMMA[i] ~ dunif(0.1, 2)";
put "    INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "    SIGSQ[i] <- 1/INVSIGSQ[i]";
put "    KAPSIGSQ[i] ~ dunif(0.01, 30)";
```

```
put "      KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "      GAMSIGSQ[i] ~ dunif(0.01, 5)";
put "      GAMINVSQ[i] <- 1/GAMSIGSQ[i]";
put "      MEBA002[i] <- <SEE MODEL 1.1>";
put "      ...";
put "      for (j in 0:14) {";
put "          MPLOT[i, j + 1] <- <SEE MODEL 1.1>";
put "      }";
put "   }";
put "   for (i in 1:&NTRT.) {";
put "      MEBAD002[i] <- <SEE MODEL 1.1>";
put "      ...";
put "   }";
put "   for (i in 1:&NTRT.) { #DIFFERENCE VERSUS CONTROL";
put "      for (j in 0:14) {";
put "          MPLOTD[i, j + 1] <- MPLOT[i, j + 1] - MPLOT[&NTRT., j + 1]";
put "      }";
put "   }";
put "   D[1] <- 0";
put "   D[2] <- 0";
put "   D[3] <- 0";
put "   IDENX[1, 1] <- 0.0001";
put "   IDENX[1, 2] <- 0";
put "   IDENX[1, 3] <- 0";
put "   IDENX[2, 1] <- IDENX[1, 2]";
put "   IDENX[2, 2] <- 0.0001";
put "   IDENX[2, 3] <- 0";
put "   IDENX[3, 1] <- IDENX[1, 3]";
put "   IDENX[3, 2] <- IDENX[2, 3]";
put "   IDENX[3, 3] <- 0.0001";
```

```
    put "   for (i in 1:&NTRT.) {";
    put "      MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
    put "      MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
    put "      ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "      BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "      BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
    put "      ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "      ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
    put "      BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "   }";
    %do i = 1 %to &NTRT.;
        put "<SEE MODEL 1.1>";
    %end;
    put "}";
  run;

%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.5, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do; LIKER = ... ; end; else if CENSOR = 1 then do; LIKER = ... ; end;
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = trim(left(TOTALLIKER)) || "*2^3*(det((matrix(c(" || trim(left(put(ALPSIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3)) + (diag(c(" ||
                 trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(DBETA1, BEST.))) || ", " ||
                 trim(left(put(DBETA2, BEST.))) || ")))%*%(diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " ||
                 trim(left(put(DBETA1, BEST.))) || ", " || trim(left(put(DBETA2, BEST.))) ||
                 "))))^(-1/2))*dmnorm(t(eigen(solve((matrix(c(" || trim(left(put(ALPSIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
                 trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3)) + (diag(c(" ||
                 trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(DBETA1, BEST.))) || ", " ||
                 trim(left(put(DBETA2, BEST.))) || ")))%*%(diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " ||
                 trim(left(put(DBETA1, BEST.))) || ", " || trim(left(put(DBETA2, BEST.))) ||
                 "))))$vectors%*%diag(sqrt(eigen(solve((matrix(c(" || trim(left(put(ALPSIGSQ, BEST.))) || ", " ||
```

```
trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1SIGSQ, BEST.))) || ", " ||
trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3)) + (diag(c(" ||
trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(DBETA1, BEST.))) || ", " ||
trim(left(put(DBETA2, BEST.))) || "))))%*%(diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " ||
trim(left(put(DBETA1, BEST.))) || ", " || trim(left(put(DBETA2, BEST.))) ||
"))))$values))%*%solve(eigen(solve((matrix(c(" || trim(left(put(ALPSIGSQ, BEST.))) || ", " ||
trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1SIGSQ, BEST.))) || ", " ||
trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(BT2SIGSQ, BEST.))) ||
"), 3, 3)) + (diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(DBETA1, BEST.))) ||
"," || trim(left(put(DBETA2, BEST.))) || "))))%*%(diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " ||
trim(left(put(DBETA1, BEST.))) || ", " || trim(left(put(DBETA2, BEST.))) ||
"))))$vectors)%*%(c(x[1], x[2], x[3]) - c(" || trim(left(put(MALPHA, BEST.))) || ", " ||
trim(left(put(MBETA1, BEST.))) || ", " || trim(left(put(MBETA2, BEST.))) ||
"))), c(0, 0, 0), diag(3))*pmnorm(c(0, 0, 0), t((diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " ||
trim(left(put(DBETA1, BEST.))) || ", " || trim(left(put(DBETA2, BEST.))) || "))))%*%(solve((matrix(c(" ||
trim(left(put(ALPSIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " ||
trim(left(put(BT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3)) + (diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " ||
trim(left(put(DBETA1, BEST.))) || ", " || trim(left(put(DBETA2, BEST.))) || "))))%*%(diag(c(" ||
trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " ||
trim(left(put(DBETA2, BEST.))) || "))))%*%c(x[1], x[2], x[3]) - c(" || trim(left(put(MALPHA, BEST.))) ||
"," || trim(left(put(MBETA1, BEST.))) || ", " || trim(left(put(MBETA2, BEST.))) || "))), diag(3) - (diag(c(" ||
trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(DBETA1, BEST.))) || ", " ||
trim(left(put(DBETA2, BEST.))) || "))))%*%(solve((matrix(c(" || trim(left(put(ALPSIGSQ, BEST.))) || ", " ||
trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
trim(left(put(ALPBT1SIGSQ, BEST.))) || ", " || trim(left(put(BT1SIGSQ, BEST.))) || ", " ||
trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(ALPBT2SIGSQ, BEST.))) || ", " ||
```

```
        trim(left(put(BT1BT2SIGSQ, BEST.))) || ", " || trim(left(put(BT2SIGSQ, BEST.))) || "), 3, 3)) + (diag(c(" ||
        trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(DBETA1, BEST.))) || ", " ||
        trim(left(put(DBETA2, BEST.))) || ")))%*%(diag(c(" || trim(left(put(DALPHA, BEST.))) || ", " ||
        trim(left(put(DBETA1, BEST.))) || ", " || trim(left(put(DBETA2, BEST.))) || ")))))%*%(diag(c(" ||
        trim(left(put(DALPHA, BEST.))) || ", " || trim(left(put(DBETA1, BEST.))) || ", " ||
        trim(left(put(DBETA2, BEST.))) || "))))*dtruncnorm(x[4], a = 2, b = 11, mean = " ||
        trim(left(put(MKAPPA, BEST.))) || ", sd = " || trim(left(put(sqrt(KAPSIGSQ), BEST.))) ||
        ")*dtruncnorm(x[5], a = 0.1, b = 2, mean = " || trim(left(put(MGAMMA, BEST.))) || ", sd = " ||
        trim(left(put(sqrt(GAMSIGSQ), BEST.))) || ")";
    call symput("TOTALLIKER" || trim(left(put(NSUBJID, BEST.))), trim(left(TOTALLIKER)));
run;
...
```

Model 1.9: Residuals: Skew Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS (FILE);

    data _NULL_;
        file "&FILE." linesize = 600;
        put "model { #THE MODEL";
        put "    PI <- 3.14159265358979";
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dnorm(NMEAN[i], NINVSGSQ[i]) #DATA";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFU[i] ~ dnorm(NMEAN[i], NINVSGSQ[i])C(, C[i]) #CENSORED DATA";
        put "    }";
        put "    for (i in 1:&N.) { #MIXTURE";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] - SMU[NSUBJID[i], 3]*SGAMMA[NSUBJID[i]]*";
        put "                   log((exp((TIME[i] - SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(TIME[i] - SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]]))/(exp((SKAPPA[NSUBJID[i]])/SGAMMA[NSUBJID[i]]) + exp(-(SKAPPA[NSUBJID[i]])/";
        put "                   SGAMMA[NSUBJID[i]])))";
        put "        NMEAN[i] <- MEAN[i] - ADJMEAN[KVTRTN[i]]*D[KVTRTN[i]] + D[KVTRTN[i]]*U[i]";
        put "        NINVSGSQ[i] <- W[i]/SIGSQ[KVTRTN[i]]";
        put "        U[i] ~ dnorm(0, W[i])T(0, ) #NUISANCE PARAMETER";
        put "        W[i] ~ dgamma(GV[KVTRTN[i]], GV[KVTRTN[i]]) #NUISANCE PARAMETER";
        put "    }";
        put "    for (i in 1:&NSUBJ.) { #RANDOM EFFECTS";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
```

```
put "    SBETA2[i] <- SMU[i, 3]";
put "    SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
put "    SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "    SMU[i, 1:3] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3])";
put "    SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "    SGAMMA[i] ~ dnorm(MGAMMA[OKVTRTN[1 + &NTP.*(i - 1)]], GAMINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(0.1, 2)";
put "    SEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
put "  }";
put "  for (i in 1:&NTRT.) { #PRIORS";
put "    V[i] ~ dunif(2, 100)";
put "    GV[i] <- V[i]/2";
put "    D[i] ~ dnorm(0, 0.0001)";
put "    ADJMEAN[i] <- exp(loggam(0.5*(V[i] - 1)) - loggam(0.5*V[i]))*sqrt(V[i]/PI)";
put "    MALPHA[i] <- MMU[i, 1]";
put "    MBETA1[i] <- MMU[i, 2]";
put "    MBETA2[i] <- MMU[i, 3]";
put "    MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "    MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "    MMU[i, 1:3] ~ dmnorm(I[1:3], IDENX[1:3, 1:3])";
put "    MKAPPA[i] ~ dunif(2, 11)";
put "    MGAMMA[i] ~ dunif(0.1, 2)";
put "    INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "    SIGSQ[i] <- 1/INVSIGSQ[i]";
put "    KAPSIGSQ[i] ~ dunif(0.01, 30)";
put "    KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "    GAMSIGSQ[i] ~ dunif(0.01, 5)";
put "    GAMINVSQ[i] <- 1/GAMSIGSQ[i]";
put "    MEBAOO2[i] <- <SEE MODEL 1.1>";
put "    ...";
```

```
put "      for (j in 0:14) {";
put "         MPLOT[i, j + 1] <- <SEE MODEL 1.1>";
put "      }";
put "   }";
put "   for (i in 1:&NTRT.) {";
put "      MEBAD002[i] <- <SEE MODEL 1.1>";
put "      ...";
put "   }";
put "   for (i in 1:&NTRT.) { #DIFFERENCE VERSUS CONTROL";
put "      for (j in 0:14) {";
put "         MPLOTD[i, j + 1] <- MPLOT[i, j + 1] - MPLOT[&NTRT., j + 1]";
put "      }";
put "   }"; ";
put "   }";
put "   I[1] <- 0";
put "   I[2] <- 0";
put "   I[3] <- 0";
put "   IDENX[1, 1] <- 0.0001";
put "   IDENX[1, 2] <- 0";
put "   IDENX[1, 3] <- 0";
put "   IDENX[2, 1] <- IDENX[1, 2]";
put "   IDENX[2, 2] <- 0.0001";
put "   IDENX[2, 3] <- 0";
put "   IDENX[3, 1] <- IDENX[1, 3]";
put "   IDENX[3, 2] <- IDENX[2, 3]";
put "   IDENX[3, 3] <- 0.0001";
```

```
    put "    for (i in 1:&NTRT.) {";
    put "        MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
    put "        MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
    put "        ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "        BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "        BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
    put "        ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "        ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
    put "        BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "    }";
    %do i = 1 %to &NTRT.;
        put "<SEE MODEL 1.1>";
    %end;
    put "}";
run;

%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.1, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $32767.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do;
        LIKER = "(2*(" || trim(left(put(SIGSQ, BEST.))) || " + " || trim(left(put(D**2, BEST.))) || ")^(-0.5)*gamma((" ||
                trim(left(put(V, BEST.))) || " + 1)/2)/(gamma(" || trim(left(put(V, BEST.))) || "/2)*(" ||
                trim(left(put(V, BEST.))) || "*3.141592654)^(0.5))*(1 + (" || trim(left(put(LOGCFU, BEST.))) ||
                " - (x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" ||
                trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))) - ((" || trim(left(put(V, BEST.))) ||
                "/3.141592654)^(0.5))*(gamma((" || trim(left(put(V, BEST.))) || " - 1)/2)/gamma(" ||
                trim(left(put(V, BEST.))) || "/2))*" || trim(left(put(D, BEST.))) || ")))^2/(" ||
                trim(left(put(V, BEST.))) || "*(" || trim(left(put(SIGSQ, BEST.))) || " + " ||
                trim(left(put(D**2, BEST.))) || ")))^(-(" || trim(left(put(V, BEST.))) || " + 1)/2))*pst((((" ||
                trim(left(put(V, BEST.))) || " + ((" || trim(left(put(LOGCFU, BEST.))) || " - (x[1] - x[2]*" ||
                trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
                " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))) - ((" || trim(left(put(V, BEST.))) ||
                "/3.141592654)^(0.5))*(gamma((" || trim(left(put(V, BEST.))) || " - 1)/2)/gamma(" ||
                trim(left(put(V, BEST.))) || "/2))*" || trim(left(put(D, BEST.))) || ")))^2)*(" ||
                trim(left(put(SIGSQ, BEST.))) || " + " || trim(left(put(D**2, BEST.))) || ")^(-1))/((" ||
                trim(left(put(V, BEST.))) || " + 1)))^(-0.5))*(" || trim(left(put(D, BEST.))) || "/sqrt(" ||
                trim(left(put(SIGSQ, BEST.))) || "))*((" || trim(left(put(LOGCFU, BEST.))) || " - (x[1] - x[2]*" ||
                trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) ||
```

```
        " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
        " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))) - (((" || trim(left(put(V, BEST.))) ||
        "/3.141592654)^(0.5))*(gamma((" || trim(left(put(V, BEST.))) || " - 1)/2)/gamma(" ||
        trim(left(put(V, BEST.))) || "/2))*" || trim(left(put(D, BEST.))) || "))))/sqrt(" ||
        trim(left(put(SIGSQ, BEST.))) || " + " || trim(left(put(D**2, BEST.))) || ")), 0, 1, 0, " ||
        trim(left(put(V, BEST.))) || " + 1)";
    end; else
    if CENSOR = 1 then do;
        LIKER = "integrate(function(y) { " ||
            "(2*(" || trim(left(put(SIGSQ, BEST.))) || " + " || trim(left(put(D**2, BEST.))) || ")^(-0.5)*gamma((" ||
            trim(left(put(V, BEST.))) || " + 1)/2)/(gamma(" || trim(left(put(V, BEST.))) || "/2)*(" ||
            trim(left(put(V, BEST.))) || "*3.1415926654)^(0.5))*(1 + (y - (x[1] - x[2]*" || trim(left(put(TIME, BEST.))) ||
            " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" ||
            trim(left(put(TIME, BEST.))) || " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))) - (((" ||
            trim(left(put(V, BEST.))) || "/3.1415926654)^(0.5))*(gamma((" || trim(left(put(V, BEST.))) ||
            " - 1)/2)/gamma(" || trim(left(put(V, BEST.))) || "/2))*" || trim(left(put(D, BEST.))) || "))^2/(" ||
            trim(left(put(V, BEST.))) || "*(" || trim(left(put(SIGSQ, BEST.))) || " + " || trim(left(put(D**2, BEST.))) ||
            "))^(-(" || trim(left(put(V, BEST.))) || " + 1)/2))*pst((((" || trim(left(put(V, BEST.))) ||
            " + ((y - (x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " - x[3]*x[5]*log((exp((" ||
            trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" || trim(left(put(TIME, BEST.))) ||
            " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))) - (((" || trim(left(put(V, BEST.))) ||
            "/3.141592654)^(0.5))*(gamma((" || trim(left(put(V, BEST.))) || " - 1)/2)/gamma(" ||
            trim(left(put(V, BEST.))) || "/2))*" || trim(left(put(D, BEST.))) || "))^2)*(" ||
            trim(left(put(V, BEST.))) || " + " || trim(left(put(D**2, BEST.))) || ")^(-1))/((" ||
            trim(left(put(V, BEST.))) || " + 1))^(-0.5))*(" || trim(left(put(D, BEST.))) || "/sqrt(" ||
            trim(left(put(SIGSQ, BEST.))) || "))*((y - (x[1] - x[2]*" || trim(left(put(TIME, BEST.))) ||
            " - x[3]*x[5]*log((exp((" || trim(left(put(TIME, BEST.))) || " - x[4])/x[5]) + exp(-(" ||
            trim(left(put(TIME, BEST.))) || " - x[4])/x[5]))/(exp(x[4]/x[5]) + exp(-x[4]/x[5]))) - (((" ||
            trim(left(put(V, BEST.))) || "/3.1415926654)^(0.5))*(gamma((" || trim(left(put(V, BEST.))) ||
            " - 1)/2)/gamma(" || trim(left(put(V, BEST.))) || "/2))*" || trim(left(put(D, BEST.))) || "))))/sqrt(" ||
            trim(left(put(SIGSQ, BEST.))) || " + " || trim(left(put(D**2, BEST.))) || ")), 0, 1, 0, " ||
            trim(left(put(V, BEST.))) || " + 1)}, " || "lower = -Inf, upper = " ||  trim(left(put(C, BEST.))) || ")$value";
    end; ... ; run;
```

B.3.2 Other Regression Models

B.3.2.1 Linear Regression Model

Model 2.1: Residuals: Normal
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS ();

    data _NULL_;
        file "&OPENBUGS./NC001 &TYPE1. Model.txt";
        put "model {";
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]])";
        put "        X[i] <- density(LOGCFU[i], DATA[i])";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]])C(, C[i])";
        put "        X[i] <- cumulative(LOGCFU[i], C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i]";
        put "        PPO[i] <- X[i]";
        put "    }";
```

```
put "   for (i in 1:&NSUBJ.) {";
put "      SALPHA[i] <- SMU[i, 1]";
put "      SLAMBDA[i] <- SMU[i, 2]";
put "      SMU[i, 1:2] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:2], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:2, 1:2])";
put "      SEBA002[i] <- SLAMBDA[i]";
put "      SEBA007[i] <- SLAMBDA[i]";
put "      SEBA014[i] <- SLAMBDA[i]";
put "      SEBA214[i] <- SLAMBDA[i]";
put "      SEBA714[i] <- SLAMBDA[i]";
put "   }";
put "   for (i in 1:&NTRT.) {";
put "      MALPHA[i] <- MMU[i, 1]";
put "      MLAMBDA[i] <- MMU[i, 2]";
put "      MMU[i, 1:2] ~ dmnorm(D[1:2], IDENX[1:2, 1:2])";
put "      INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "      SIGSQ[i] <- 1/INVSIGSQ[i]";
put "      SMUTILDA[i, 1:2] ~ dmnorm(MMU[i, 1:2], MOMGINV[i, 1:2, 1:2])";
put "      SALPHATILDA[i] <- SMUTILDA[i, 1]";
put "      SLAMBDATILDA[i] <- SMUTILDA[i, 2]";
put "      MEBA002[i] <- MLAMBDA[i]";
put "      MEBA007[i] <- MLAMBDA[i]";
put "      MEBA014[i] <- MLAMBDA[i]";
put "      MEBA214[i] <- MLAMBDA[i]";
put "      MEBA714[i] <- MLAMBDA[i]";
put "      for (j in 0:14) {";
put "         MPLOT[i, j + 1] <- MMU[i, 1] - MMU[i, 2]*j";
put "      }";
put "   }";
```

```
    put "   for (i in 1:&NTRT.) {";
    put "       MEBAD002[i] <-  MEBA002[i] -  MEBA002[&NTRT.]";
    put "       MEBAD007[i] <-  MEBA007[i] -  MEBA007[&NTRT.]";
    put "       MEBAD014[i] <-  MEBA014[i] -  MEBA014[&NTRT.]";
    put "       MEBAD214[i] <-  MEBA214[i] -  MEBA214[&NTRT.]";
    put "       MEBAD714[i] <-  MEBA714[i] -  MEBA714[&NTRT.]";
    put "   }";
    put "   D[1] <- 0";
    put "   D[2] <- 0";
    put "   IDENX[1, 1] <- 0.0001";
    put "   IDENX[1, 2] <- 0";
    put "   IDENX[2, 1] <- IDENX[1, 2]";
    put "   IDENX[2, 2] <- 0.0001";
    put "   for (i in 1:&NTRT.) {";
    put "       MOMGINV[i, 1:2, 1:2] ~ dwish(IDEN[i, 1:2, 1:2], &WDF.)";
    put "       MOMEGA[i, 1:2, 1:2] <- inverse(MOMGINV[i, 1:2, 1:2])";
    put "       ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "       LMSIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "       ALPLMSIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "   }";
    %do i = 1 %to &NTRT.;
        put "    IDEN[&i., 1, 1] <- &&WAT&i..";
        put "    IDEN[&i., 1, 2] <- &&WALT&i..";
        put "    IDEN[&i., 2, 1] <- IDEN[&i., 1, 2]";
        put "    IDEN[&i., 2, 2] <- &&WLT&i..";
    %end;
    put "}";
run;
%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.1, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do;
        LIKER = "dnorm(" || trim(left(put(LOGCFU, BEST.))) || ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) ||
                ", " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end; else
    if CENSOR = 1 then do;
        LIKER = "pnorm(" || trim(left(put(C, BEST.))) || ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) ||
                ", " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end;
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = trim(left(TOTALLIKER)) || "*dmnorm(cbind(x[1], x[2]), c(" || trim(left(put(MALPHA, BEST.))) || ", "  ||
                 trim(left(put(MLAMBDA, BEST.))) || "), SIGMA <- matrix(c(" || trim(left(put(ALPSIGSQ, BEST.))) || ", " ||
                 trim(left(put(ALPLMSIGSQ, BEST.))) || ", " || trim(left(put(ALPLMSIGSQ, BEST.))) || ", " ||
                 trim(left(put(LMSIGSQ, BEST.))) || "), 2, 2))";
    call symput("TOTALLIKER" || trim(left(put(NSUBJID, BEST.))), trim(left(TOTALLIKER)));
run;

...
```

Model 2.2: Residuals: Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS ();

    data _NULL_;
        file "&OPENBUGS./NC001 &TYPE1. Model.txt";
        put "model {"
                                        ;
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])";
        put "        LOGCFUC[i] ~ dunif(0, 1)";
        put "        X[i] <- density(LOGCFU[i], DATA[i])";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFUC[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])C(, C[i])";
        put "        X[i] <- cumulative(LOGCFUC[i], C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i]";
        put "        PPO[i] <- X[i]";
        put "    }";
        put "    for (i in 1:&NSUBJ.) {";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SLAMBDA[i] <- SMU[i, 2]";
        put "        SMU[i, 1:2] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:2], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:2, 1:2])";
        put "        SEBA002[i] <- SLAMBDA[i]";
        put "        SEBA007[i] <- SLAMBDA[i]";
```

```
put "      SEBA014[i] <- SLAMBDA[i]";
put "      SEBA214[i] <- SLAMBDA[i]";
put "      SEBA714[i] <- SLAMBDA[i]";
put "   }";
put "   for (i in 1:&NTRT.) {";
put "      V[i] ~ dunif(2, 100)";
put "      MALPHA[i] <- MMU[i, 1]";
put "      MLAMBDA[i] <- MMU[i, 2]";
put "      MMU[i, 1:2] ~ dmnorm(D[1:2], IDENX[1:2, 1:2])";
put "      INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "      SIGSQ[i] <- 1/INVSIGSQ[i]";
put "      SMUTILDA[i, 1:2] ~ dmnorm(MMU[i, 1:2], MOMGINV[i, 1:2, 1:2])";
put "      SALPHATILDA[i] <- SMUTILDA[i, 1]";
put "      SLAMBDATILDA[i] <- SMUTILDA[i, 2]";
put "      MEBA002[i] <- MLAMBDA[i]";
put "      MEBA007[i] <- MLAMBDA[i]";
put "      MEBA014[i] <- MLAMBDA[i]";
put "      MEBA214[i] <- MLAMBDA[i]";
put "      MEBA714[i] <- MLAMBDA[i]";
put "      for (j in 0:14) {";
put "         MPLOT[i, j + 1] <- MMU[i, 1] - MMU[i, 2]*j";
put "      }";
put "   }";
put "   for (i in 1:&NTRT.) {";
put "      MEBAD002[i] <-  MEBA002[i] -  MEBA002[&NTRT.]";
put "      MEBAD007[i] <-  MEBA007[i] -  MEBA007[&NTRT.]";
put "      MEBAD014[i] <-  MEBA014[i] -  MEBA014[&NTRT.]";
put "      MEBAD214[i] <-  MEBA214[i] -  MEBA214[&NTRT.]";
put "      MEBAD714[i] <-  MEBA714[i] -  MEBA714[&NTRT.]";
put "   }";
put "   D[1] <- 0";
put "   D[2] <- 0";
put "   IDENX[1, 1] <- 0.0001";
```

```
    put "   IDENX[1, 2] <- 0";
    put "   IDENX[2, 1] <- IDENX[1, 2]";
    put "   IDENX[2, 2] <- 0.0001";
    put "   for (i in 1:&NTRT.) {";
    put "      MOMGINV[i, 1:2, 1:2] ~ dwish(IDEN[i, 1:2, 1:2], &WDF.)";
    put "      MOMEGA[i, 1:2, 1:2] <- inverse(MOMGINV[i, 1:2, 1:2])";
    put "      ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "      LMSIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "      ALPLMSIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "   }";
    %do i = 1 %to &NTRT.;
        put "   IDEN[&i., 1, 1] <- &&WAT&i..";
        put "   IDEN[&i., 1, 2] <- &&WALT&i..";
        put "   IDEN[&i., 2, 1] <- IDEN[&i., 1, 2]";
        put "   IDEN[&i., 2, 2] <- &&WLT&i..";
    %end;
    put "}";
  run;

%mend;
```

B.3.2.2 Conventional Bilinear Regression Model

Model 3.1: Residuals: Normal
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS ();

    data _NULL_;
       file "&OPENBUGS./NC001 &TYPE1. Model.txt";
        put "model {";
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]])";
        put "        X[i] <- density(LOGCFU[i], DATA[i])";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFU[i] ~ dnorm(MEAN[i], INVSIGSQ[KVTRTN[i]])C(, C[i])";
        put "        X[i] <- cumulative(LOGCFU[i], C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] + pow(-1, J[i] + 1)*SMU[NSUBJID[i], 3]*TIME[i] + ";
        put "                   (J[i] - 1)*2*SMU[NSUBJID[i], 3]*SKAPPA[NSUBJID[i]]";
        put "        J[i] <- 1 + step(TIME[i] - SKAPPA[NSUBJID[i]])";
        put "        PPO[i] <- X[i]";
        put "    }";
        put "    for (i in 1:&NSUBJ.) {";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
```

```
put "   SBETA2[i] <- SMU[i, 3]";
put "   SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
put "   SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "   SMU[i, 1:3] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3])";
put "   SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "   SEBA002[i] <- -((SALPHA[i] - SBETA1[i] + 1)*SBETA2[i]*2 + (JS11[i] - 1)*2*";
put "                 SBETA2[i]*SKAPPA[i]) - (SALPHA[i] - SBETA1[i]*0 + pow(-1, JS12[i] + 1)*SBETA2[i]*0 + ";
put "                 (JS12[i] - 1)*2*SBETA2[i]*SKAPPA[i]))/(2 - 0)";
put "   SEBA007[i] <- -((SALPHA[i] - SBETA1[i]*7 + pow(-1, JS21[i] + 1)*SBETA2[i]*7 + (JS21[i] - 1)*2*";
put "                 SBETA2[i]*SKAPPA[i]) - (SALPHA[i] - SBETA1[i]*0 + pow(-1, JS22[i] + 1)*SBETA2[i]*0 + ";
put "                 (JS22[i] - 1)*2*SBETA2[i]*SKAPPA[i]))/(7 - 0)";
put "   SEBA014[i] <- -((SALPHA[i] - SBETA1[i]*14 + pow(-1, JS31[i] + 1)*SBETA2[i]*14 + (JS31[i] - 1)*2*";
put "                 SBETA2[i]*SKAPPA[i]) - (SALPHA[i] - SBETA1[i]*0 + pow(-1, JS32[i] + 1)*SBETA2[i]*0 + ";
put "                 (JS32[i] - 1)*2*SBETA2[i]*SKAPPA[i]))/(14 - 0)";
put "   SEBA214[i] <- -((SALPHA[i] - SBETA1[i]*14 + pow(-1, JS41[i] + 1)*SBETA2[i]*14 + (JS41[i] - 1)*2*";
put "                 SBETA2[i]*SKAPPA[i]) - (SALPHA[i] - SBETA1[i]*2 + pow(-1, JS42[i] + 1)*SBETA2[i]*2 + ";
put "                 (JS42[i] - 1)*2*SBETA2[i]*SKAPPA[i]))/(14 - 2)";
put "   SEBA714[i] <- -((SALPHA[i] - SBETA1[i]*14 + pow(-1, JS51[i] + 1)*SBETA2[i]*14 + (JS51[i] - 1)*2*";
put "                 SBETA2[i]*SKAPPA[i]) - (SALPHA[i] - SBETA1[i]*7 + pow(-1, JS52[i] + 1)*SBETA2[i]*7 + ";
put "                 (JS52[i] - 1)*2*SBETA2[i]*SKAPPA[i]))/(14 - 7)";
put "   JS11[i] <- 1 + step(2 - SKAPPA[i])";
put "   JS12[i] <- 1 + step(0 - SKAPPA[i])";
put "   JS21[i] <- 1 + step(7 - SKAPPA[i])";
put "   JS22[i] <- 1 + step(0 - SKAPPA[i])";
put "   JS31[i] <- 1 + step(14 - SKAPPA[i])";
put "   JS32[i] <- 1 + step(0 - SKAPPA[i])";
put "   JS41[i] <- 1 + step(14 - SKAPPA[i])";
put "   JS42[i] <- 1 + step(2 - SKAPPA[i])";
put "   JS51[i] <- 1 + step(14 - SKAPPA[i])";
put "   JS52[i] <- 1 + step(7 - SKAPPA[i])";
put "}";
```

```
put "   for (i in 1:&NTRT.) {";
put "      MALPHA[i] <- MMU[i, 1]";
put "      MBETA1[i] <- MMU[i, 2]";
put "      MBETA2[i] <- MMU[i, 3]";
put "      MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "      MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "      MMU[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "      MKAPPA[i] ~ dunif(2, 11)";
put "      INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "      SIGSQ[i] <- 1/INVSIGSQ[i]";
put "      KAPSIGSQ[i] ~ dunif(0.01, 30)";
put "      KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "      MEBA002[i] <- -((MALPHA[i] - MBETA1[i]*2 + pow(-1, JM11[i] + 1)*MBETA2[i]*2 + (JM11[i] - 1)*2*MBETA2[i]*MKAPPA[i]) - ";
put "                     (MALPHA[i] - MBETA1[i]*0 + pow(-1, JM12[i] + 1)*MBETA2[i]*0 + (JM12[i] - 1)*2*MBETA2[i]*MKAPPA[i]))/(2 - 0)";
put "      MEBA007[i] <- -((MALPHA[i] - MBETA1[i]*7 + pow(-1, JM21[i] + 1)*MBETA2[i]*7 + (JM21[i] - 1)*2*MBETA2[i]*MKAPPA[i]) - ";
put "                     (MALPHA[i] - MBETA1[i]*0 + pow(-1, JM22[i] + 1)*MBETA2[i]*0 + (JM22[i] - 1)*2*MBETA2[i]*MKAPPA[i]))/(7 - 0)";
put "      MEBA014[i] <- -((MALPHA[i] - MBETA1[i]*14 + pow(-1, JM31[i] + 1)*MBETA2[i]*14 + (JM31[i] - 1)*2*MBETA2[i]*MKAPPA[i]) - ";
put "                     (MALPHA[i] - MBETA1[i]*0 + pow(-1, JM32[i] + 1)*MBETA2[i]*0 + (JM32[i] - 1)*2*MBETA2[i]*MKAPPA[i]))/(14 - 0)";
put "      MEBA214[i] <- -((MALPHA[i] - MBETA1[i]*14 + pow(-1, JM41[i] + 1)*MBETA2[i]*14 + (JM41[i] - 1)*2*MBETA2[i]*MKAPPA[i]) - ";
put "                     (MALPHA[i] - MBETA1[i]*2 + pow(-1, JM42[i] + 1)*MBETA2[i]*2 + (JM42[i] - 1)*2*MBETA2[i]*MKAPPA[i]))/(14 - 2)";
put "      MEBA714[i] <- -((MALPHA[i] - MBETA1[i]*14 + pow(-1, JM51[i] + 1)*MBETA2[i]*14 + (JM51[i] - 1)*2*MBETA2[i]*MKAPPA[i]) - ";
put "                     (MALPHA[i] - MBETA1[i]*7 + pow(-1, JM52[i] + 1)*MBETA2[i]*7 + (JM52[i] - 1)*2*MBETA2[i]*MKAPPA[i]))/(14 - 7)";
put "      JM11[i] <- 1 + step(2 - SKAPPA[i])";
put "      JM12[i] <- 1 + step(0 - SKAPPA[i])";
put "      JM21[i] <- 1 + step(7 - SKAPPA[i])";
put "      JM22[i] <- 1 + step(0 - SKAPPA[i])";
put "      JM31[i] <- 1 + step(14 - SKAPPA[i])";
put "      JM32[i] <- 1 + step(0 - SKAPPA[i])";
put "      JM41[i] <- 1 + step(14 - SKAPPA[i])";
put "      JM42[i] <- 1 + step(2 - SKAPPA[i])";
put "      JM51[i] <- 1 + step(14 - SKAPPA[i])";
put "      JM52[i] <- 1 + step(7 - SKAPPA[i])";
```

```
put "    for (j in 0:14) {";
put "        MPLOT[i, j + 1] <- MMU[i, 1] - MMU[i, 2]*j + pow(-1, JP[i, j + 1] + 1)*MMU[i, 3]*j + ";
put "                           (JP[i, j + 1] - 1)*2*MMU[i, 3]*MKAPPA[i]";
put "        JP[i, j + 1] <- 1 + step(j - MKAPPA[i])";
put "    }";
put "}";
put "for (i in 1:&NTRT.) {";
put "    MEBAD002[i] <-  MEBA002[i] -  MEBA002[&NTRT.]";
put "    MEBAD007[i] <-  MEBA007[i] -  MEBA007[&NTRT.]";
put "    MEBAD014[i] <-  MEBA014[i] -  MEBA014[&NTRT.]";
put "    MEBAD214[i] <-  MEBA214[i] -  MEBA214[&NTRT.]";
put "    MEBAD714[i] <-  MEBA714[i] -  MEBA714[&NTRT.]";
put "}";
put "D[1] <- 0";
put "D[2] <- 0";
put "D[3] <- 0";
put "IDENX[1, 1] <- 0.0001";
put "IDENX[1, 2] <- 0";
put "IDENX[1, 3] <- 0";
put "IDENX[2, 1] <- IDENX[1, 2]";
put "IDENX[2, 2] <- 0.0001";
put "IDENX[2, 3] <- 0";
put "IDENX[3, 1] <- IDENX[1, 3]";
put "IDENX[3, 2] <- IDENX[2, 3]";
put "IDENX[3, 3] <- 0.0001";
put "for (i in 1:&NTRT.) {";
put "    MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
put "    MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
put "    ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
put "    BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
put "    BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
put "    ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
put "    ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
```

```
    put "      BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "    }";
    %do i = 1 %to &NTRT.;
        put "    IDEN[&i., 1, 1] <- &&WAT&i..";
        put "    IDEN[&i., 1, 2] <- &&WAB1T&i..";
        put "    IDEN[&i., 1, 3] <- &&WAB2T&i..";
        put "    IDEN[&i., 2, 1] <- IDEN[&i., 1, 2]";
        put "    IDEN[&i., 2, 2] <- &&WB1T&i..";
        put "    IDEN[&i., 2, 3] <- &&WB1B2T&i..";
        put "    IDEN[&i., 3, 1] <- IDEN[&i., 1, 3]";
        put "    IDEN[&i., 3, 2] <- IDEN[&i., 2, 3]";
        put "    IDEN[&i., 3, 3] <- &&WB2T&i..";
    %end;
    put "}";
run;
%mend;
```

SAS® and R Example Code: Bayes Factors

```
/*CODE SIMILAR TO MODEL 1.1, SNIPPETS PRESENTED BELOW*/

...

data NC001CMP03; /*R CODE FOR PRODUCT OF LIKELIHOODS PER PATIENT*/
    length LIKER TOTALLIKER $9999.;
    set NC001CMP02 (where = (LOGCFU ne . or C ne .));
    by NSUBJID;
    if first.NSUBJID then NOBSV = 1; else NOBSV + 1;
    retain TOTALLIKER;
    if CENSOR = 0 then do;
        LIKER = "dnorm(" || trim(left(put(LOGCFU, BEST.))) ||
                ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " + (-1)^((" || trim(left(put(TIME, BEST.))) ||
                " <= x[4]) + 2)*x[3]*" || trim(left(put(TIME, BEST.))) || " + (" || trim(left(put(TIME, BEST.))) ||
                " <= x[4])*2*x[3]*x[4], " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end; else
    if CENSOR = 1 then do;
        LIKER = "pnorm(" || trim(left(put(C, BEST.))) ||
                ", x[1] - x[2]*" || trim(left(put(TIME, BEST.))) || " + (-1)^((" || trim(left(put(TIME, BEST.))) ||
                " <= x[4]) + 2)*x[3]*" || trim(left(put(TIME, BEST.))) || " + (" || trim(left(put(TIME, BEST.))) ||
                " <= x[4])*2*x[3]*x[4], " || trim(left(put(sqrt(SIGSQ), BEST.))) || ")";
    end;
    if first.NSUBJID then TOTALLIKER = trim(left(LIKER)); else
                          TOTALLIKER = trim(left(TOTALLIKER)) || "*" || trim(left(LIKER));
    if last.NSUBJID;
    TOTALLIKER = ... ;
run;

...
```

Model 3.2: Residuals: Student t
Random Coefficients: Normal
Prior for Covariance Matrix: "Default" Wishart

OpenBUGS Example Code: Model Building

```
%macro OPENBUGS ();

    data _NULL_;
       file "&OPENBUGS./NC001 &TYPE1. Model.txt";
        put "model {";
        put "    for (i in 1:&NCNSNOBS.) {";
        put "        LOGCFU[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])";
        put "        LOGCFUC[i] ~ dunif(0, 1)";
        put "        X[i] <- density(LOGCFU[i], DATA[i])";
        put "    }";
        put "    for (i in &CNSNOBS.:&N.) {";
        put "        LOGCFUC[i] ~ dt(MEAN[i], INVSIGSQ[KVTRTN[i]], V[KVTRTN[i]])C(, C[i])";
        put "        X[i] <- cumulative(LOGCFUC[i], C[i])";
        put "    }";
        put "    for (i in 1:&N.) {";
        put "        MEAN[i] <- SMU[NSUBJID[i], 1] - SMU[NSUBJID[i], 2]*TIME[i] + pow(-1, J[i] + 1)*SMU[NSUBJID[i], 3]*TIME[i] + ";
        put "                   (J[i] - 1)*2*SMU[NSUBJID[i], 3]*SKAPPA[NSUBJID[i]]";
        put "        J[i] <- 1 + step(TIME[i] - SKAPPA[NSUBJID[i]])";
        put "        PPO[i] <- X[i]";
        put "    }";
        put "    for (i in 1:&NSUBJ.) {";
        put "        SALPHA[i] <- SMU[i, 1]";
        put "        SBETA1[i] <- SMU[i, 2]";
        put "        SBETA2[i] <- SMU[i, 3]";
        put "        SLAMBDA1[i] <- SBETA1[i] - SBETA2[i]";
```

```
put "    SLAMBDA2[i] <- SBETA1[i] + SBETA2[i]";
put "    SMU[i, 1:3] ~ dmnorm(MMU[OKVTRTN[1 + &NTP.*(i - 1)], 1:3], MOMGINV[OKVTRTN[1 + &NTP.*(i - 1)], 1:3, 1:3])";
put "    SKAPPA[i] ~ dnorm(MKAPPA[OKVTRTN[1 + &NTP.*(i - 1)]], KAPINVSQ[OKVTRTN[1 + &NTP.*(i - 1)]])T(2, 11)";
put "    SEBAOO2[i] <- <SEE MODEL 3.1>";
put "    ...";
put "    JS11[i] <- <SEE MODEL 3.1>";
put "    ...";
put "  }";
put "  for (i in 1:&NTRT.) {";
put "    V[i] ~ dunif(2, 100)";
put "    MALPHA[i] <- MMU[i, 1]";
put "    MBETA1[i] <- MMU[i, 2]";
put "    MBETA2[i] <- MMU[i, 3]";
put "    MLAMBDA1[i] <- MBETA1[i] - MBETA2[i]";
put "    MLAMBDA2[i] <- MBETA1[i] + MBETA2[i]";
put "    MMU[i, 1:3] ~ dmnorm(D[1:3], IDENX[1:3, 1:3])";
put "    MKAPPA[i] ~ dunif(2, 11)";
put "    INVSIGSQ[i] ~ dgamma(0.0001, 0.0001)";
put "    SIGSQ[i] <- 1/INVSIGSQ[i]";
put "    KAPSIGSQ[i] ~ dunif(0.01, 30)";
put "    KAPINVSQ[i] <- 1/KAPSIGSQ[i]";
put "    MEBAOO2[i] <- <SEE MODEL 3.1>";
put "    ...";
put "    JM11[i] <- <SEE MODEL 3.1>";
put "    ...";
put "    for (j in 0:14) {";
put "      MPLOT[i, j + 1] <- <SEE MODEL 3.1>";
put "    }";
put "  }";
put "  for (i in 1:&NTRT.) {";
put "    MEBADOO2[i] <- <SEE MODEL 3.1>";
put "  }";
```

```
    put "   D[1] <- 0";
    put "   D[2] <- 0";
    put "   D[3] <- 0";
    put "   IDENX[1, 1] <- 0.0001";
    put "   IDENX[1, 2] <- 0";
    put "   IDENX[1, 3] <- 0";
    put "   IDENX[2, 1] <- IDENX[1, 2]";
    put "   IDENX[2, 2] <- 0.0001";
    put "   IDENX[2, 3] <- 0";
    put "   IDENX[3, 1] <- IDENX[1, 3]";
    put "   IDENX[3, 2] <- IDENX[2, 3]";
    put "   IDENX[3, 3] <- 0.0001";
    put "   for (i in 1:&NTRT.) {";
    put "      MOMGINV[i, 1:3, 1:3] ~ dwish(IDEN[i, 1:3, 1:3], &WDF.)";
    put "      MOMEGA[i, 1:3, 1:3] <- inverse(MOMGINV[i, 1:3, 1:3])";
    put "      ALPSIGSQ[i] <- MOMEGA[i, 1, 1]";
    put "      BT1SIGSQ[i] <- MOMEGA[i, 2, 2]";
    put "      BT2SIGSQ[i] <- MOMEGA[i, 3, 3]";
    put "      ALPBT1SIGSQ[i] <- MOMEGA[i, 1, 2]";
    put "      ALPBT2SIGSQ[i] <- MOMEGA[i, 1, 3]";
    put "      BT1BT2SIGSQ[i] <- MOMEGA[i, 2, 3]";
    put "   }";
    %do i = 1 %to &NTRT.;
       put "<SEE MODEL 3.1>";
    %end;
    put "}";
run;
%mend;
```

Appendix C

Empirical Study

C.1 Colony Forming Unit Count

Figure C.1: Observed and Fitted log(CFU) Count, Trial **CL001**, Treatment Group **TMC207 100 mg**

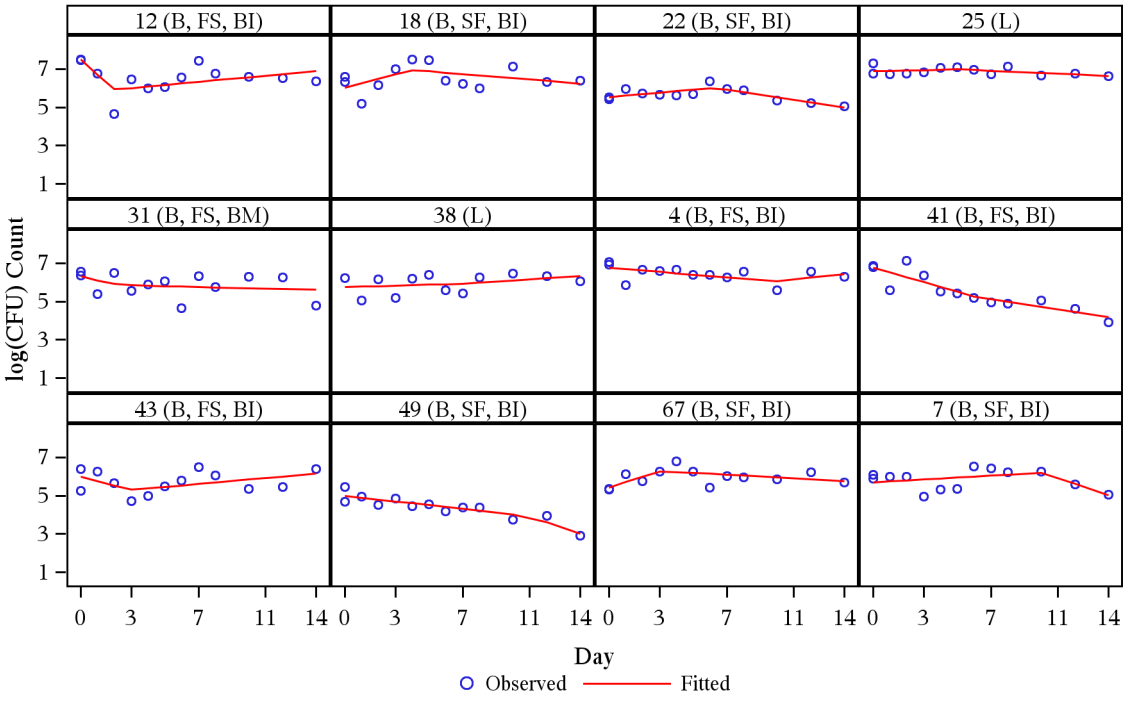


Figure C.2: Observed and Fitted log(CFU) Count, Trial **CL001**, Treatment Group **TMC207 200 mg**

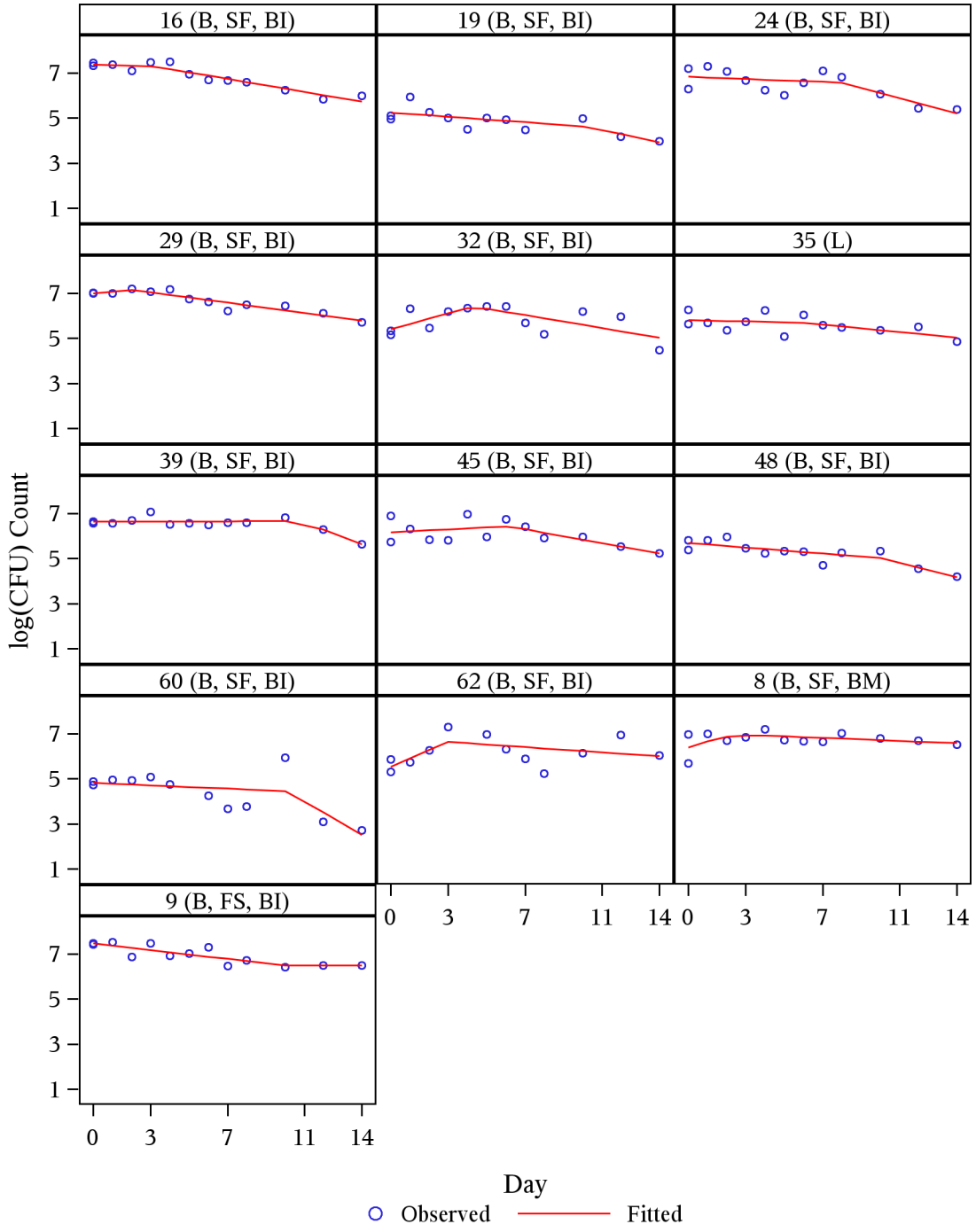


Figure C.3: Observed and Fitted log(CFU) Count, Trial **CL001**, Treatment Group **TMC207 300 mg**

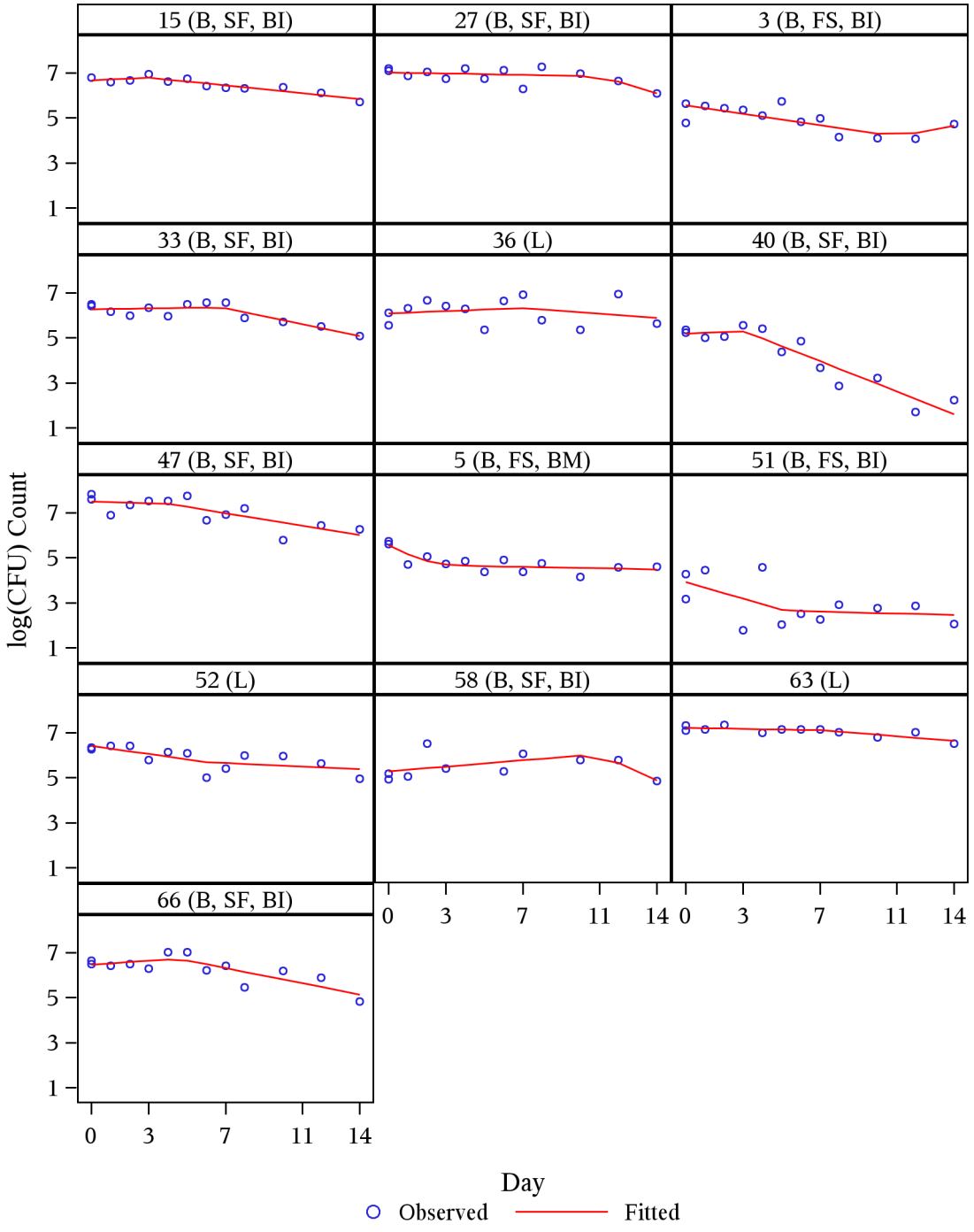


Figure C.4: Observed and Fitted log(CFU) Count, Trial **CL001**, Treatment Group **TMC207 400 mg**

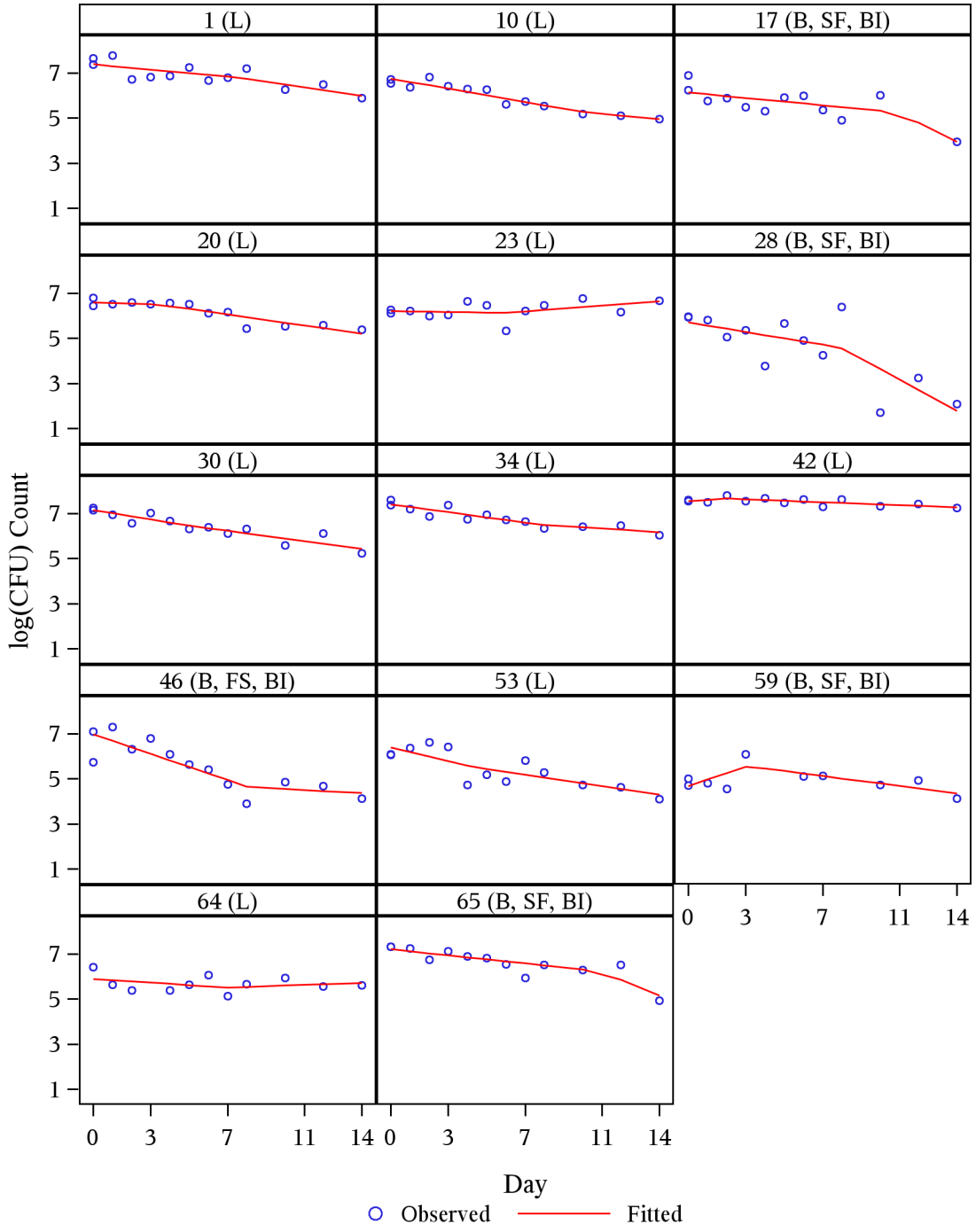


Figure C.5: Observed and Fitted log(CFU) Count, Trial **CL001**, Treatment Group **Rifafour**

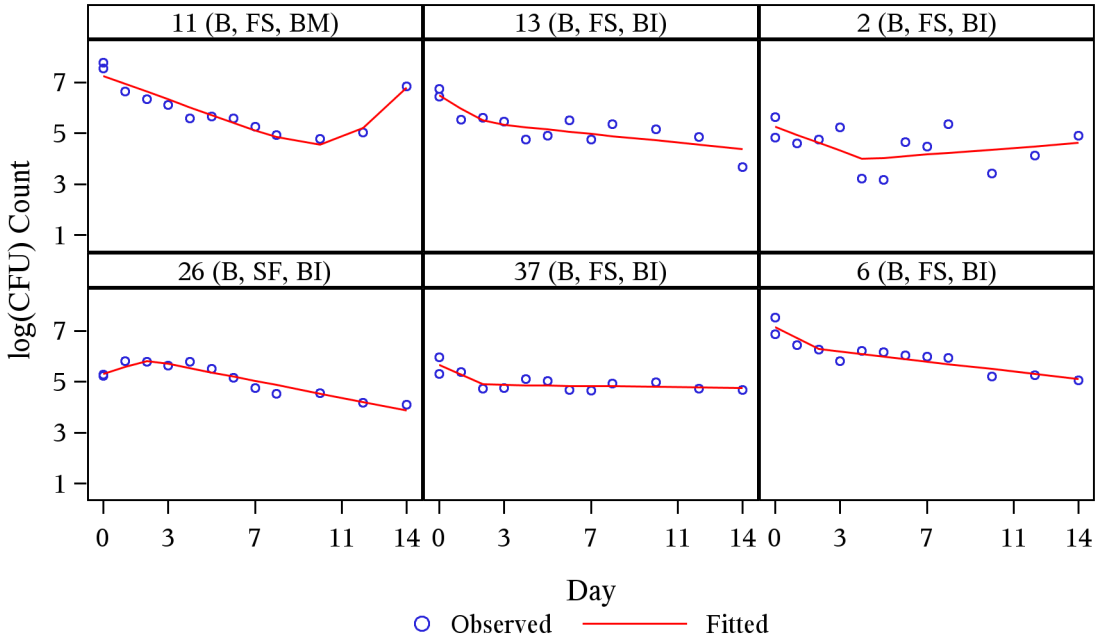


Figure C.6: Observed and Fitted log(CFU) Count, Trial **CL007**, Treatment Group **PA-824 200 mg**

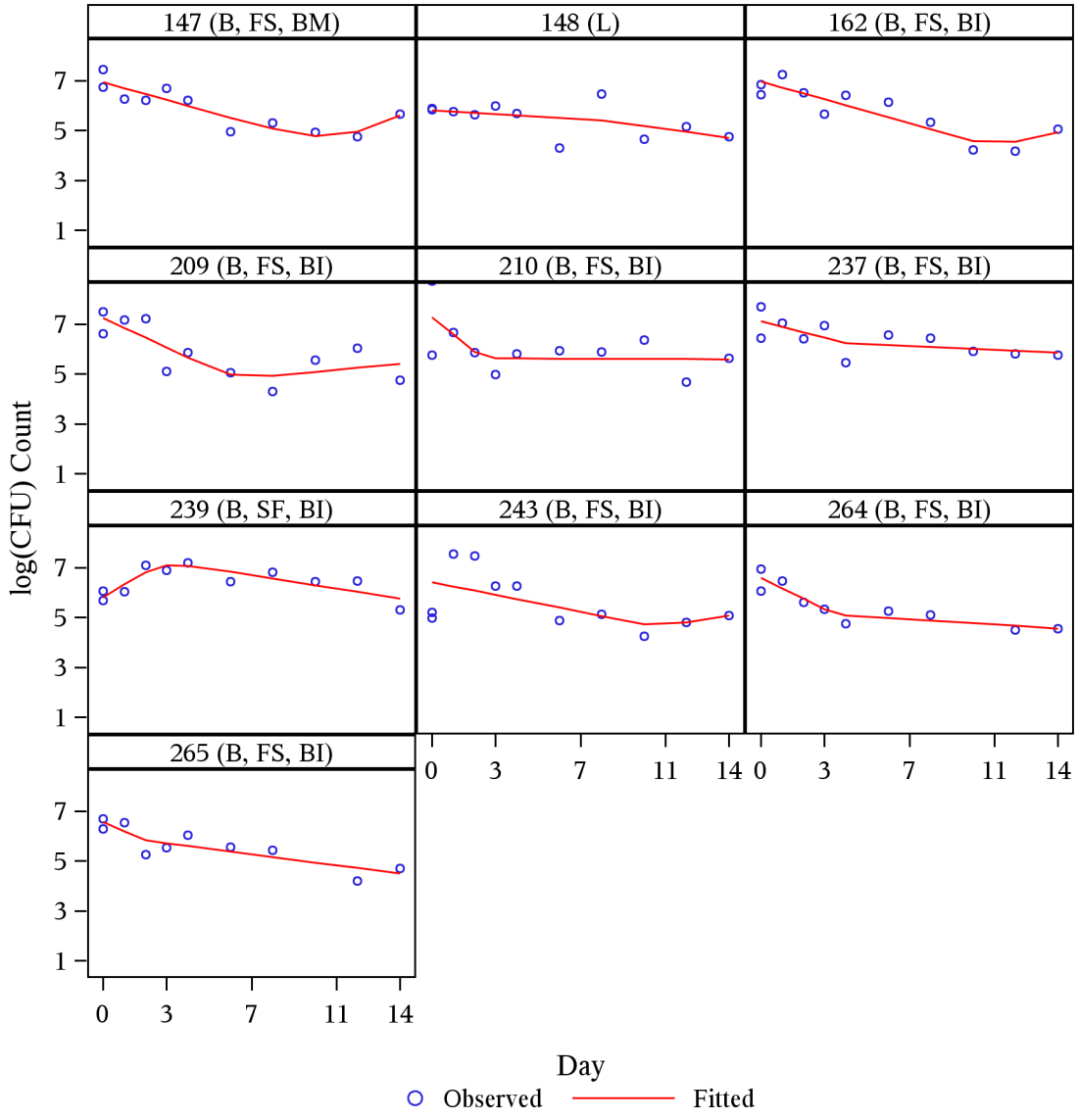


Figure C.7: Observed and Fitted log(CFU) Count, Trial **CL007**, Treatment Group **PA-824 600 mg**

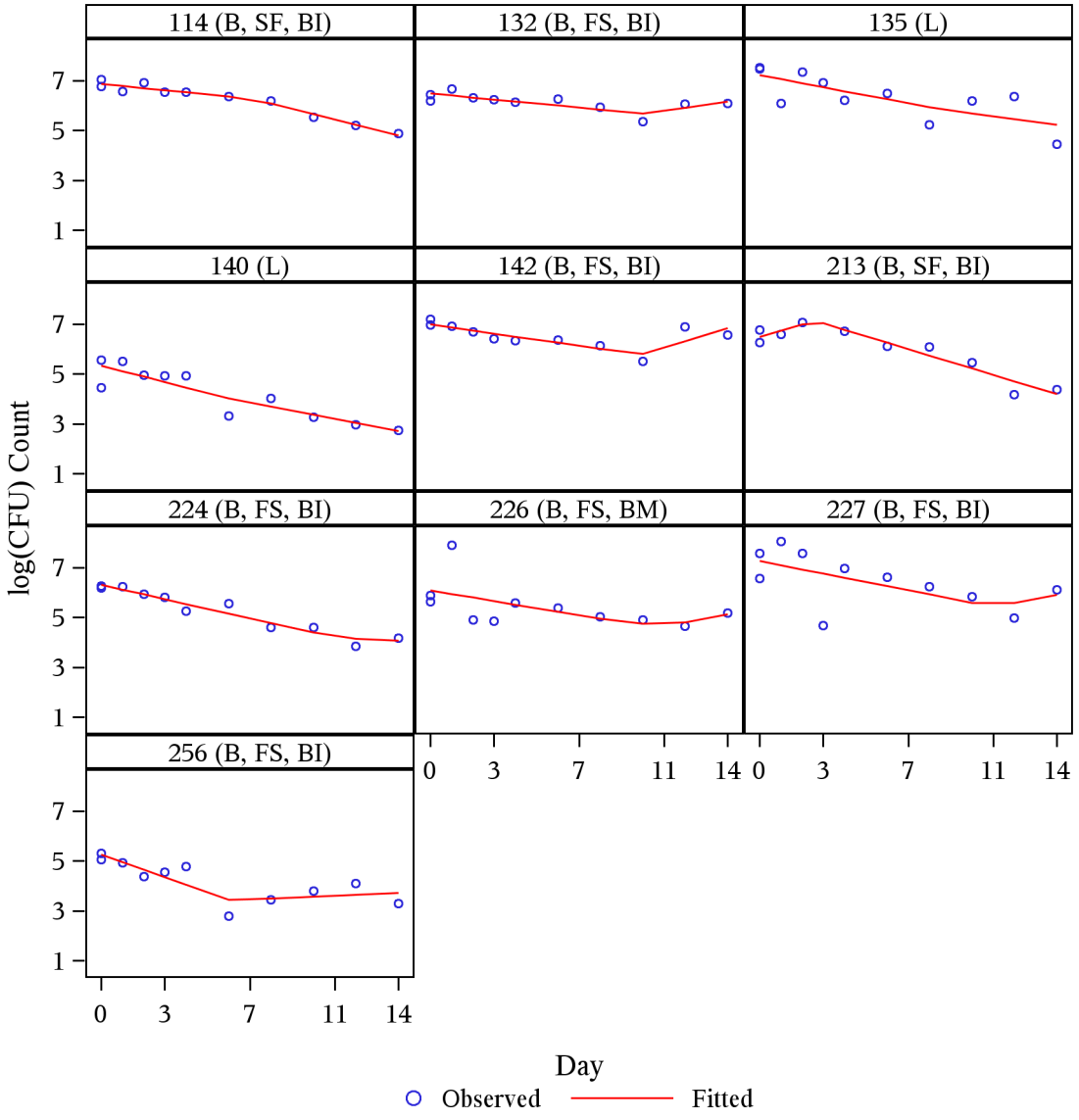


Figure C.8: Observed and Fitted log(CFU) Count, Trial **CL007**, Treatment Group **PA-824 1000 mg**

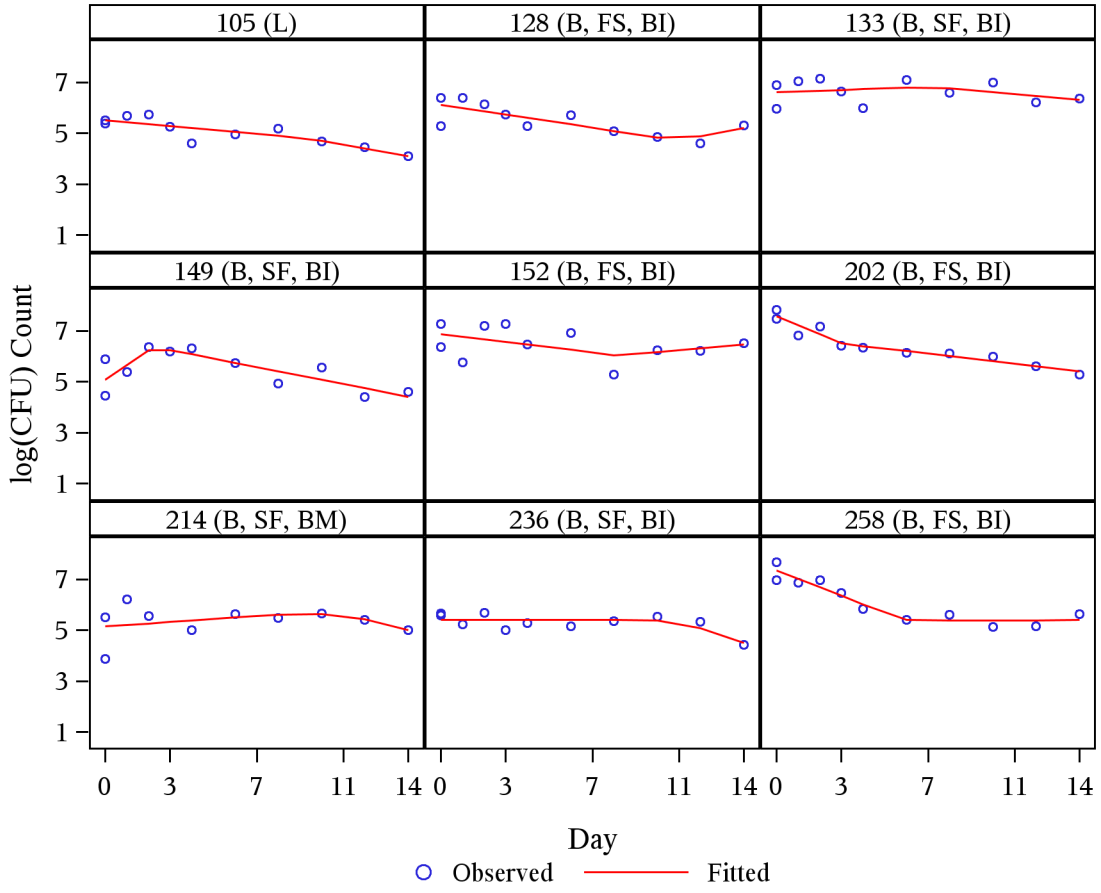


Figure C.9: Observed and Fitted log(CFU) Count, Trial **CL007**, Treatment Group **PA-824 1200 mg**

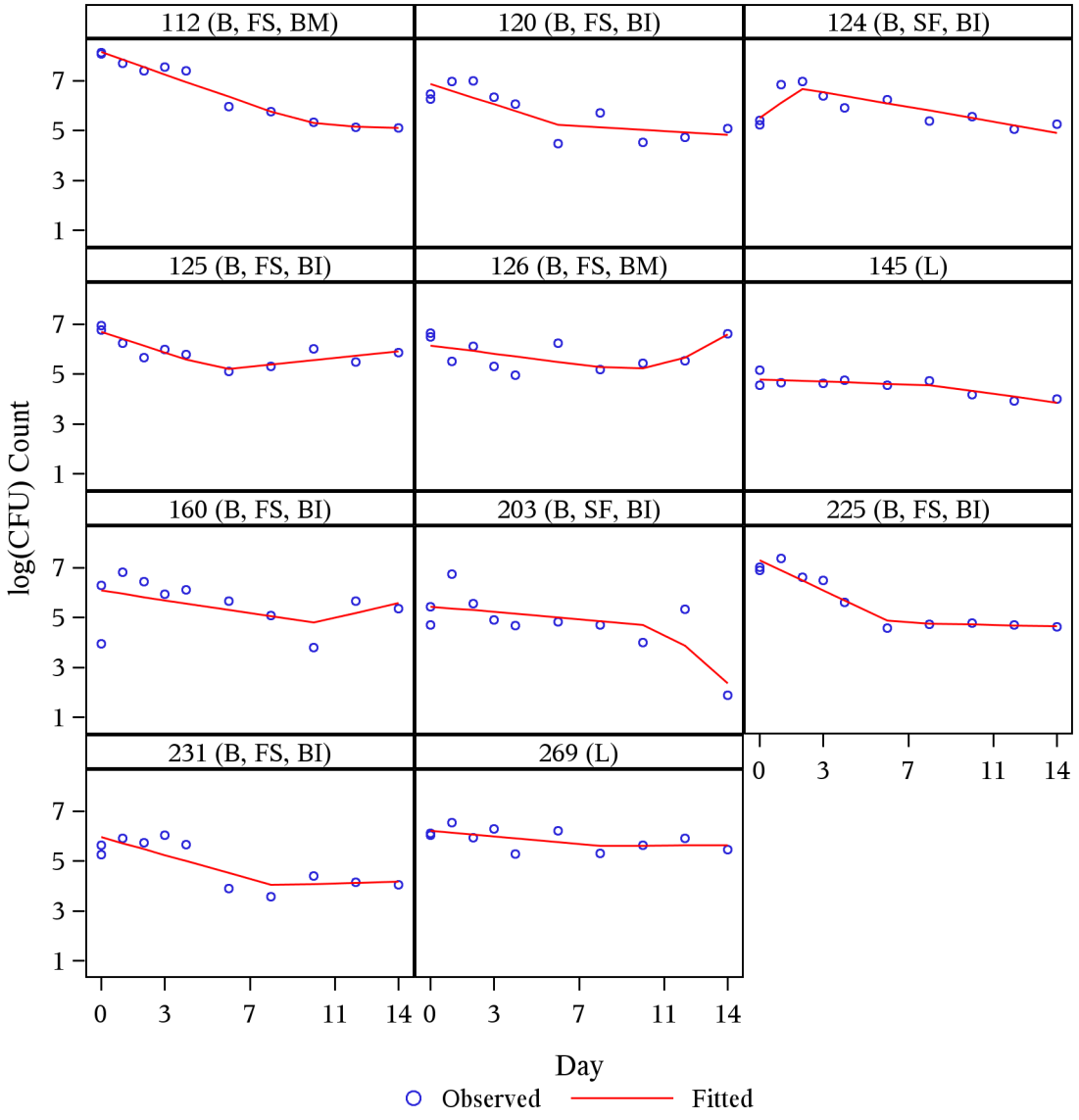


Figure C.10: Observed and Fitted log(CFU) Count, Trial **CL007**, Treatment Group **Rifafour**

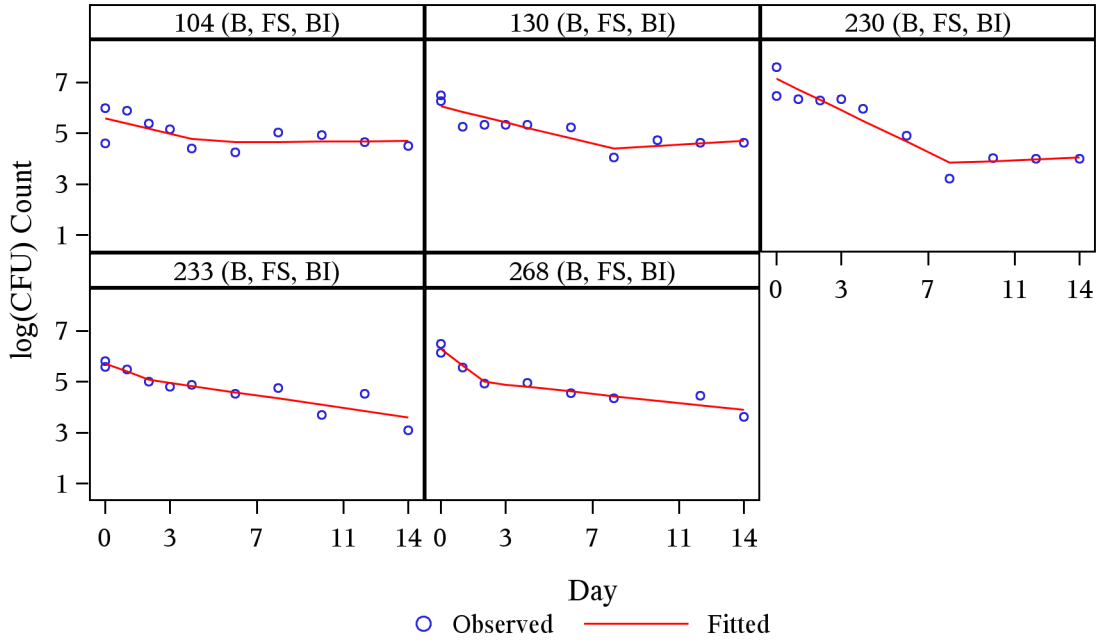


Figure C.11: Observed and Fitted log(CFU) Count, Trial **CL010**, Treatment Group **PA-824 50 mg**

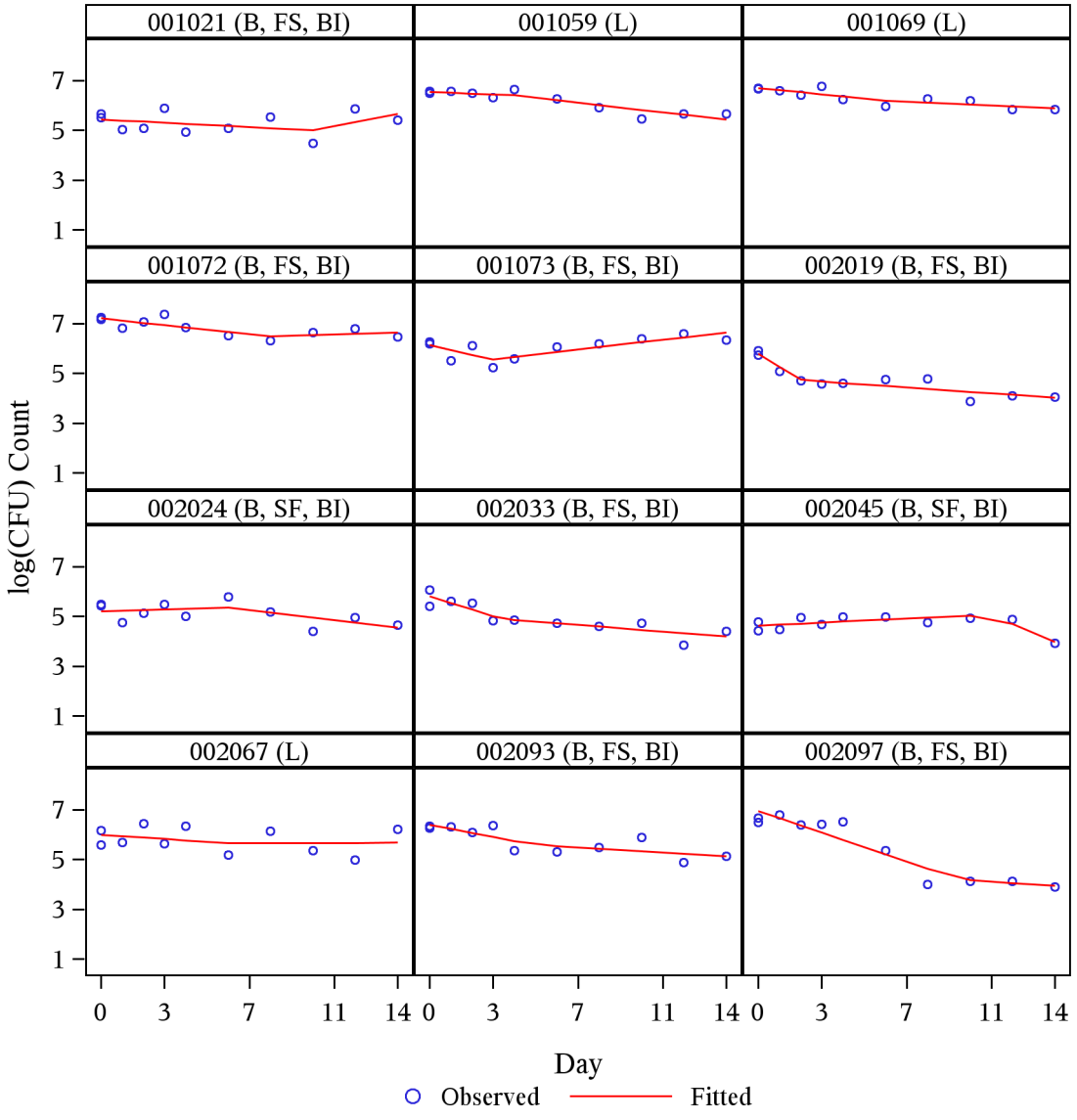


Figure C.12: Observed and Fitted log(CFU) Count, Trial **CL010**, Treatment Group **PA-824 100 mg**

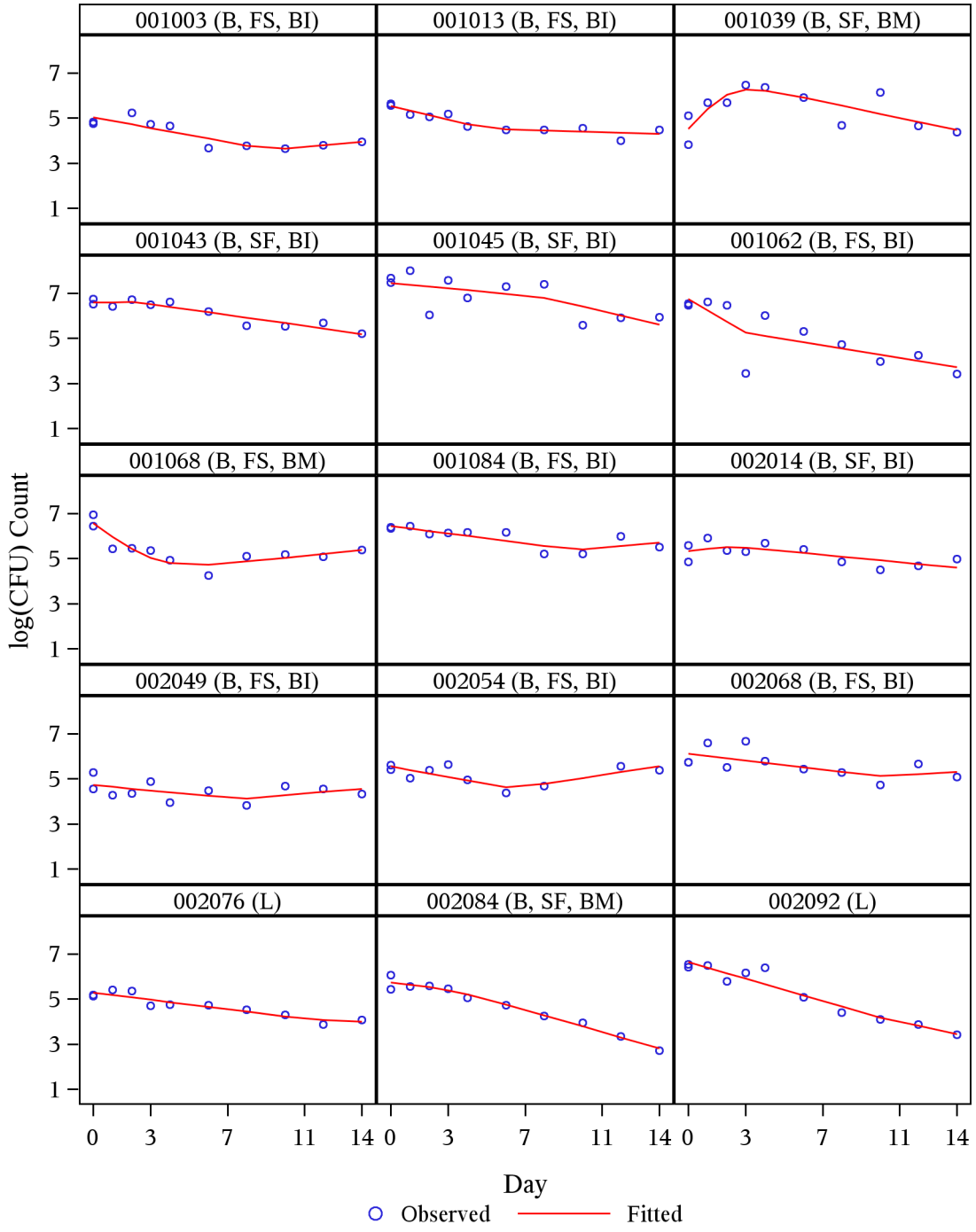


Figure C.13: Observed and Fitted log(CFU) Count, Trial **CL010**, Treatment Group **PA-824 150 mg**

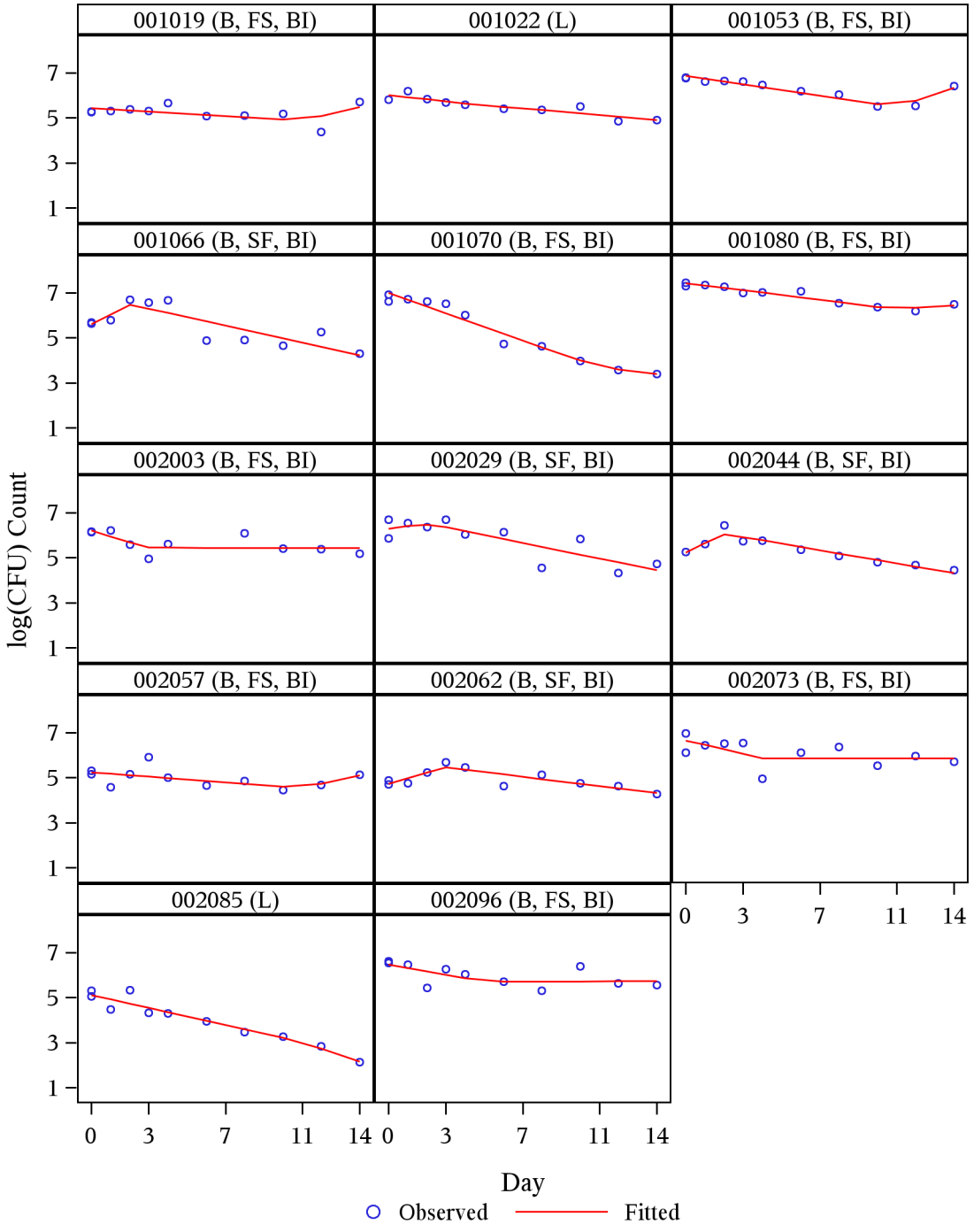


Figure C.14: Observed and Fitted log(CFU) Count, Trial **CL010**, Treatment Group **PA-824 200 mg**

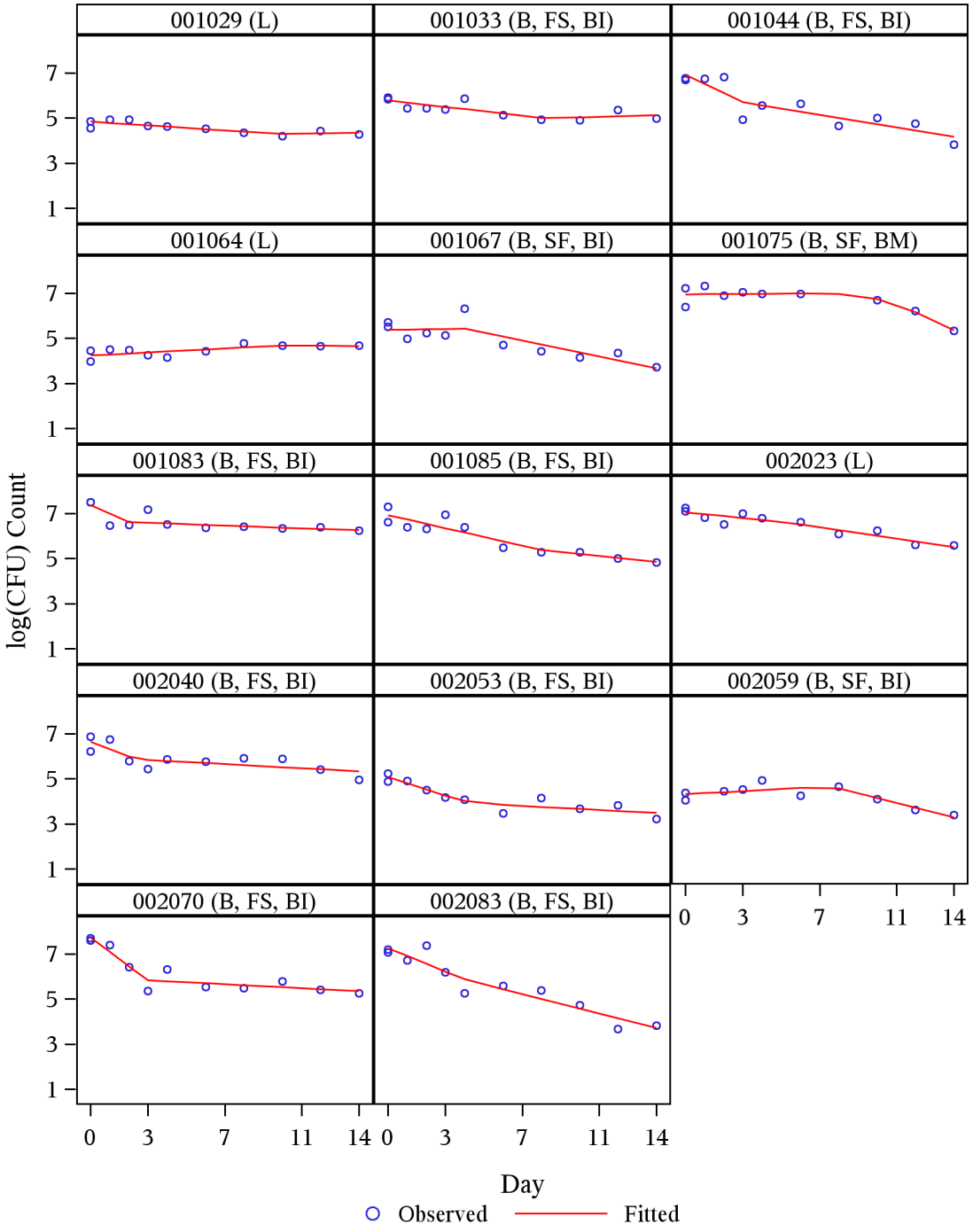


Figure C.15: Observed and Fitted log(CFU) Count, Trial **CL010**, Treatment Group **Rifafour**

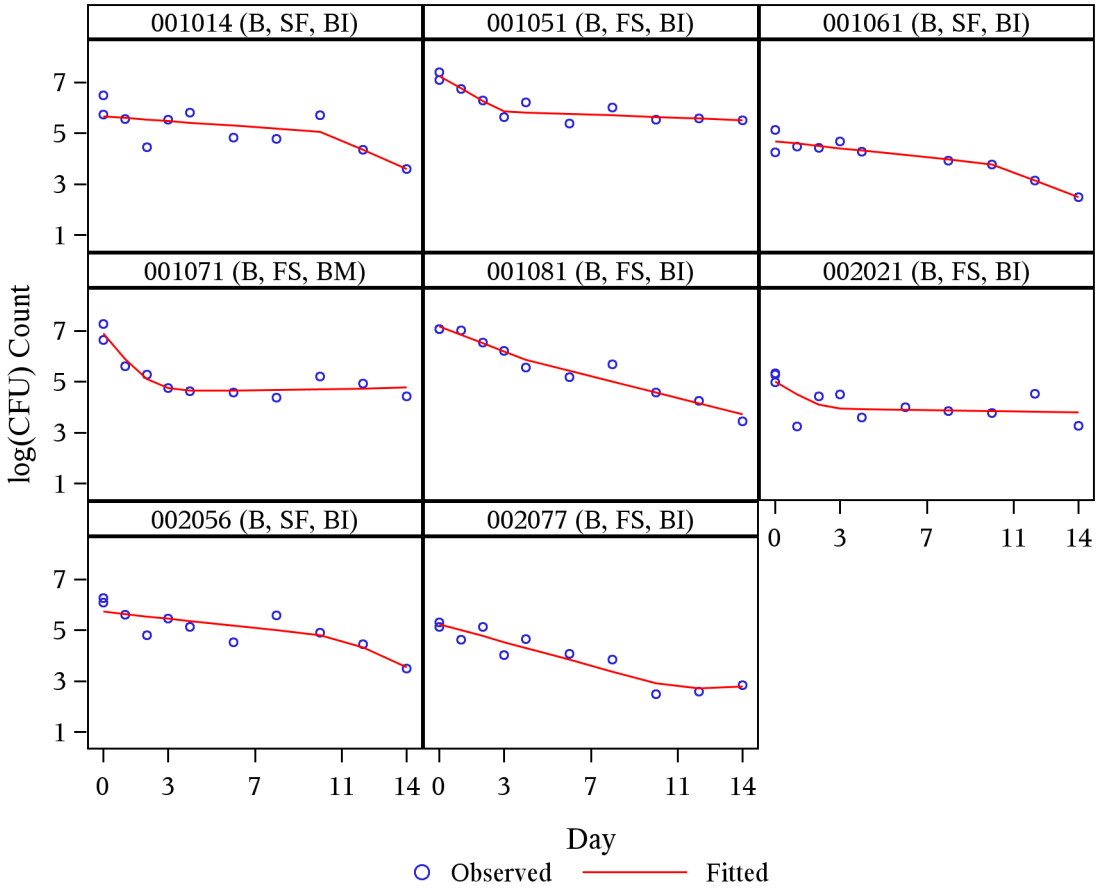


Figure C.16: Observed and Fitted log(CFU) Count, Trial **NC001**, Treatment Group **J**

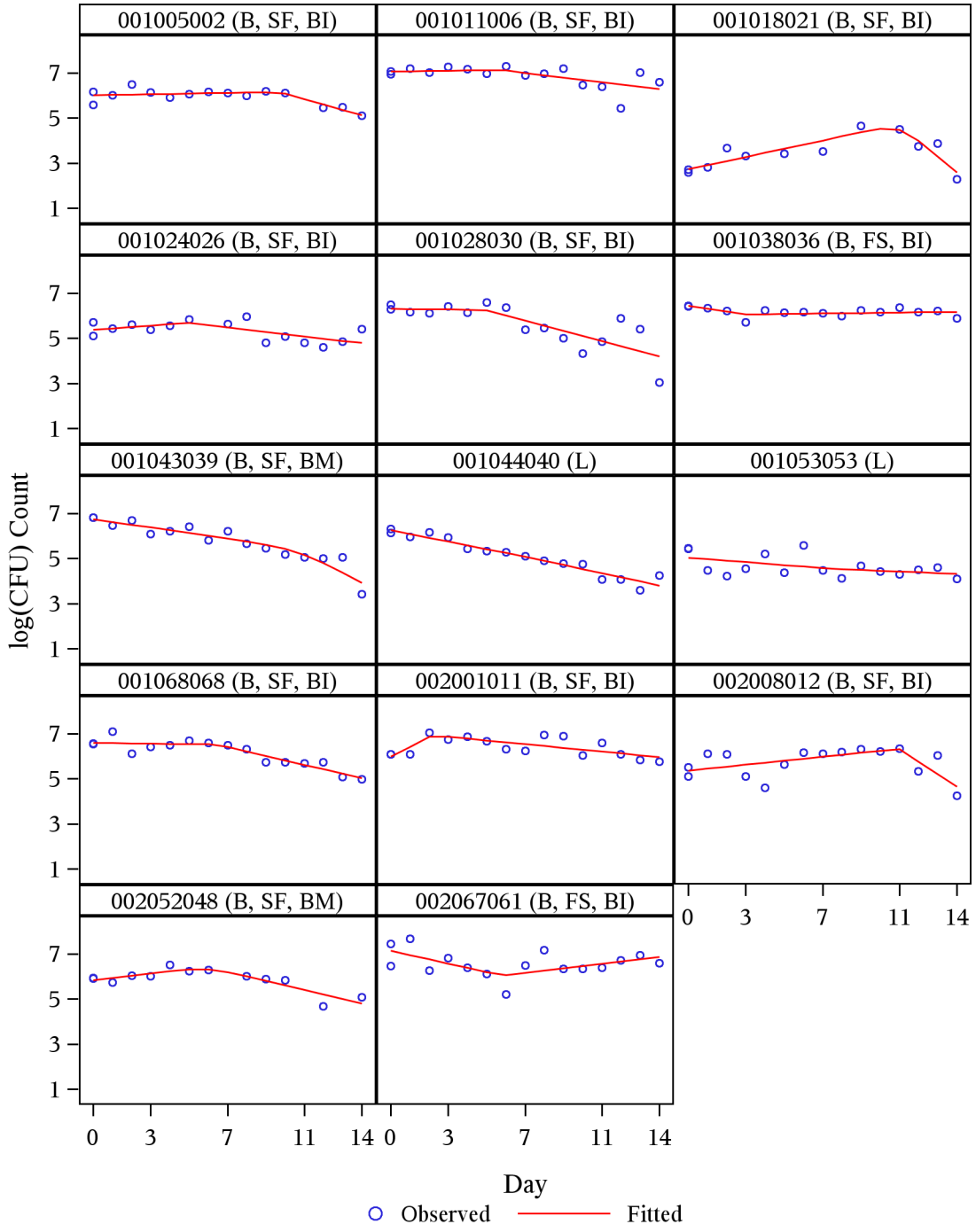


Figure C.17: Observed and Fitted log(CFU) Count, Trial **NC001**, Treatment Group **J-Z**

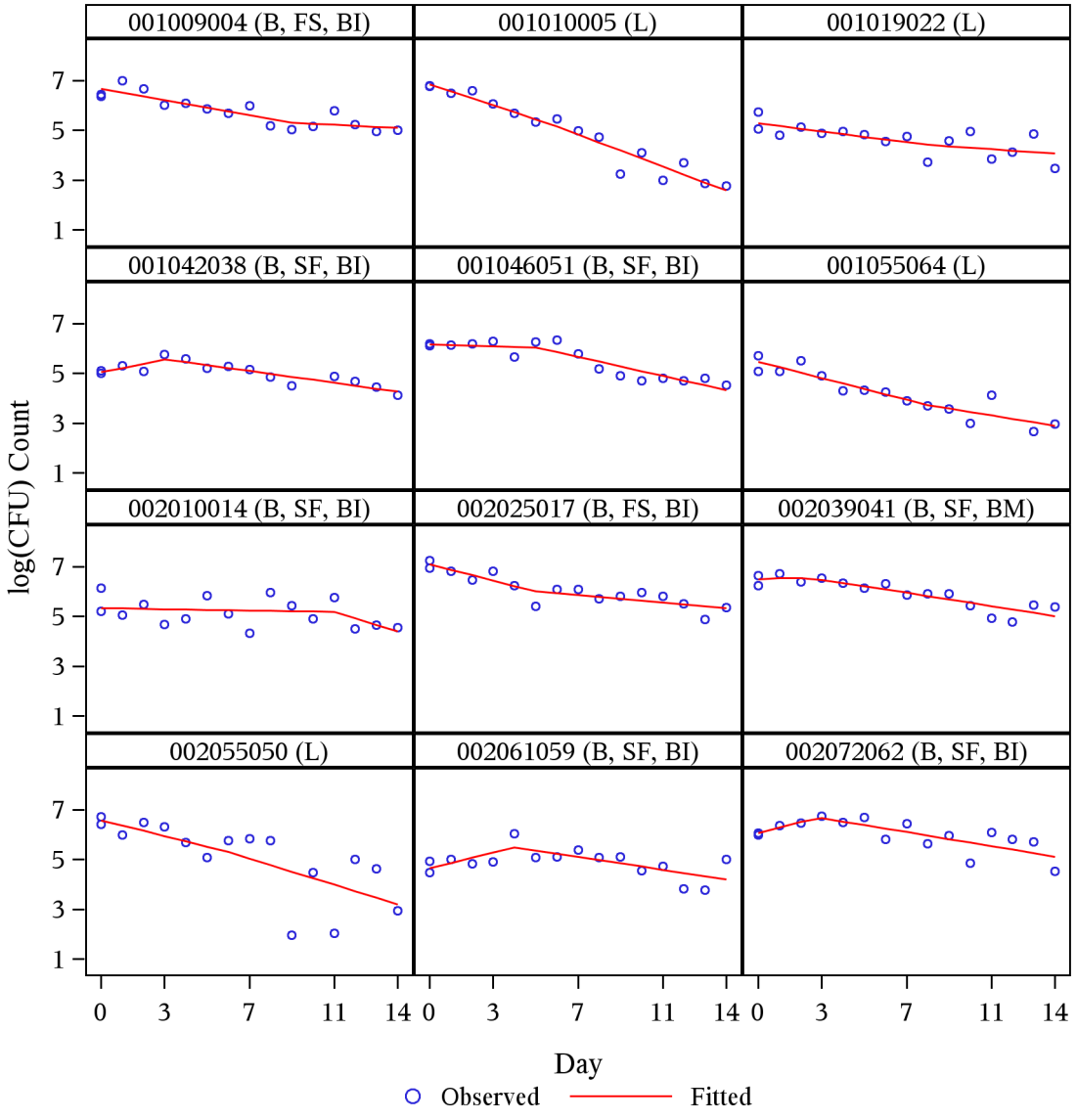


Figure C.18: Observed and Fitted log(CFU) Count, Trial **NC001**, Treatment Group **J-Pa**

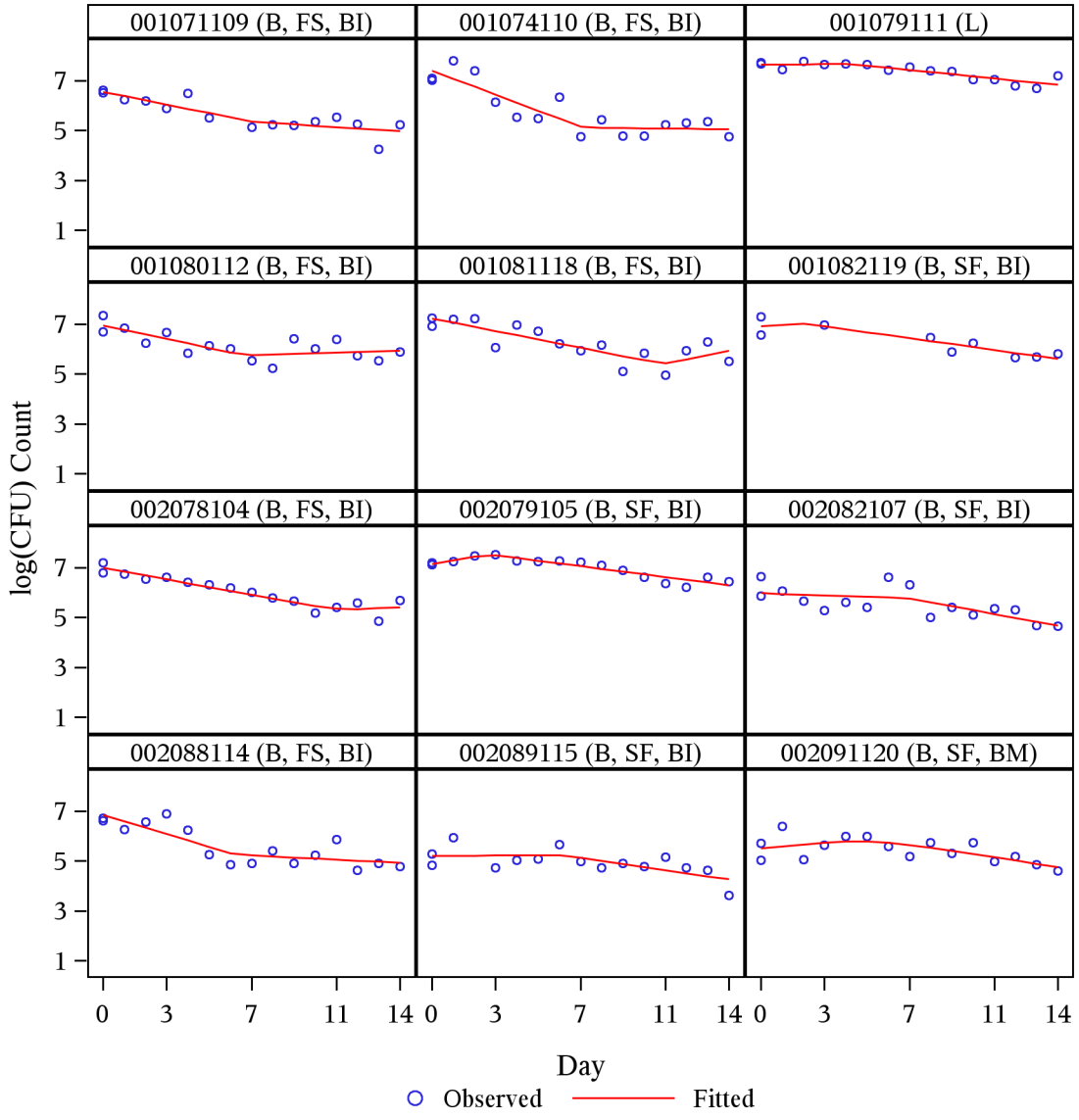


Figure C.19: Observed and Fitted log(CFU) Count, Trial **NC001**, Treatment Group **Pa-Z**

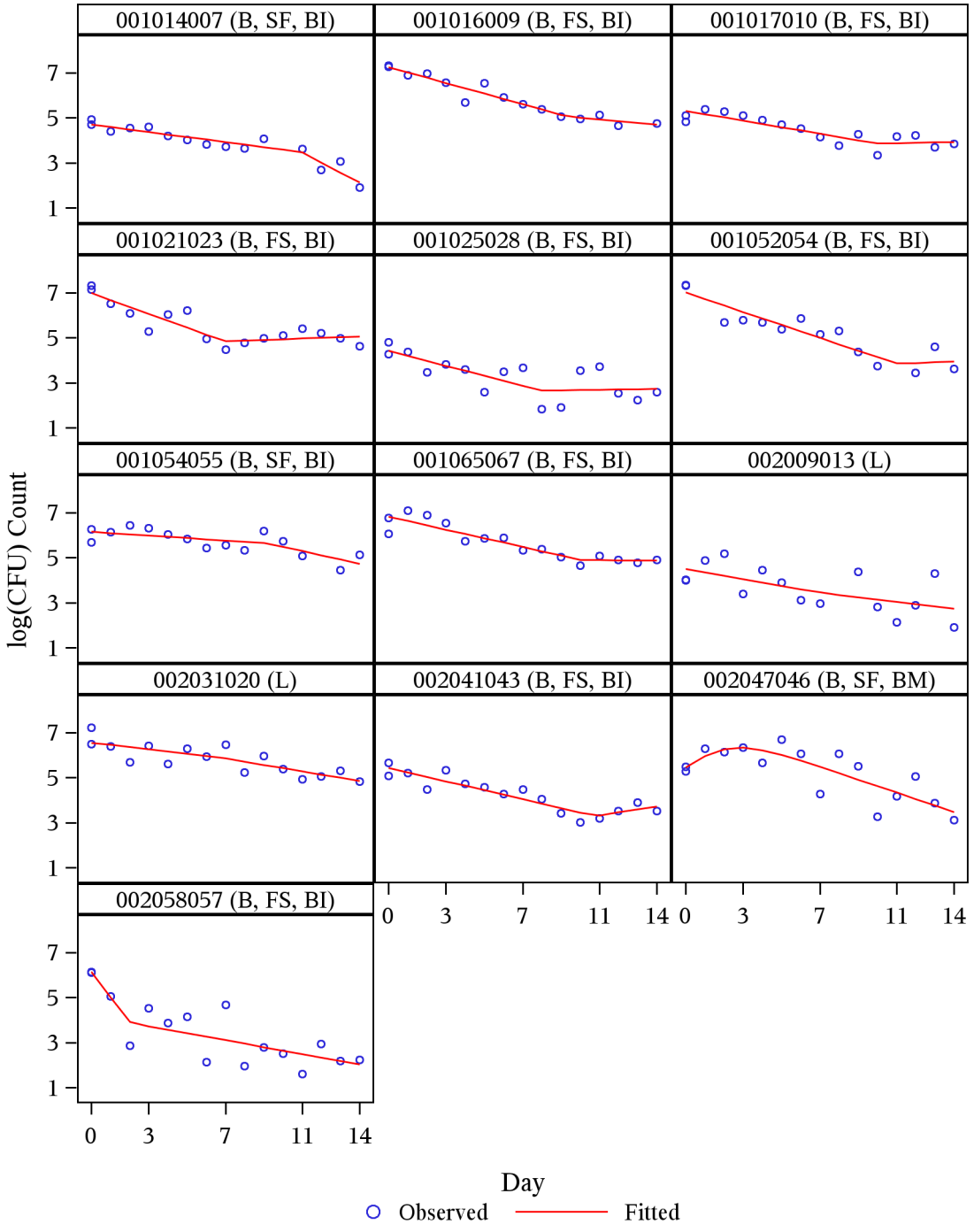


Figure C.20: Observed and Fitted log(CFU) Count, Trial **NC001**, Treatment Group **Pa-Z-M**

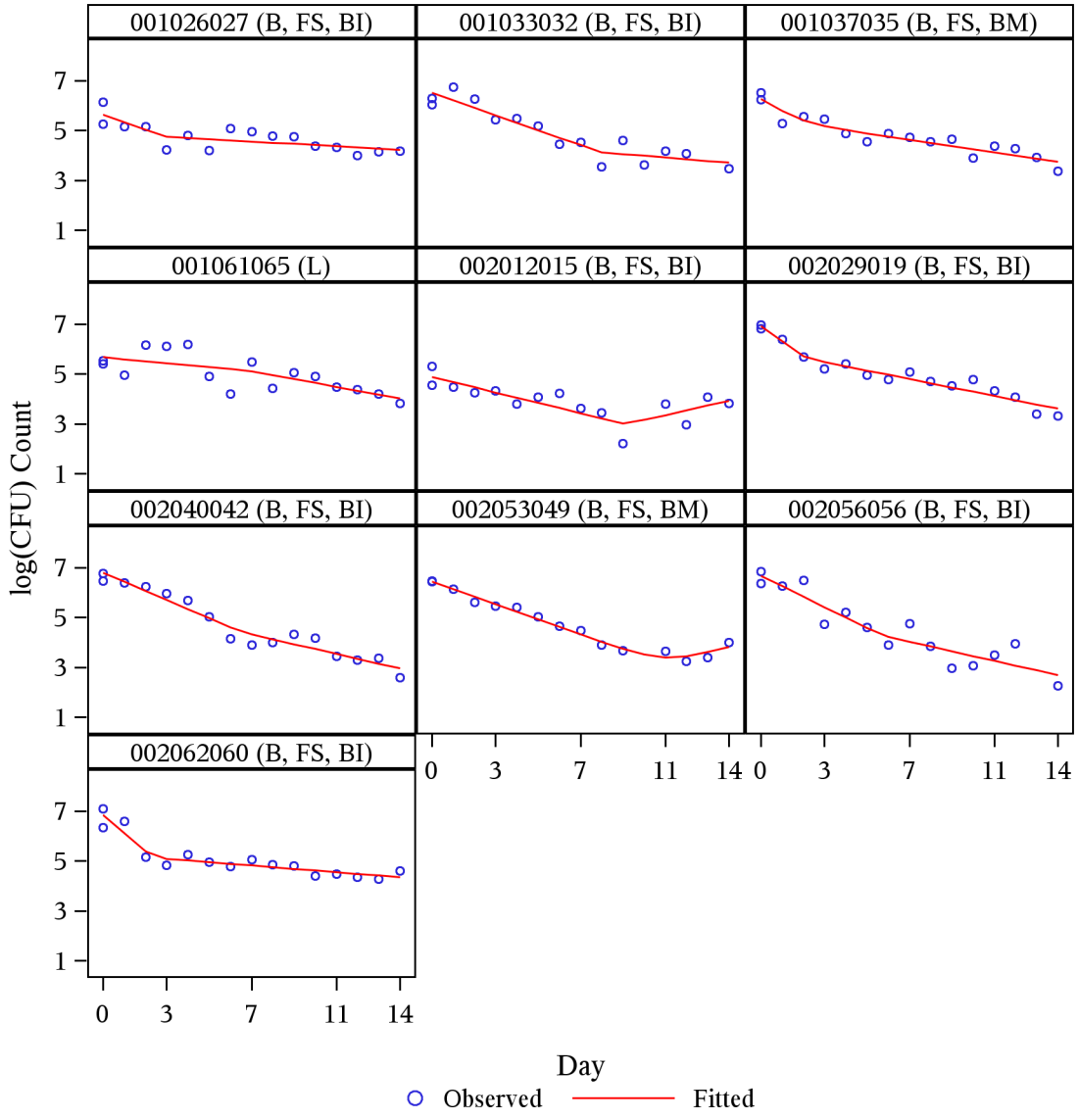


Figure C.21: Observed and Fitted log(CFU) Count, Trial **NC001**, Treatment Group **Rifafour**

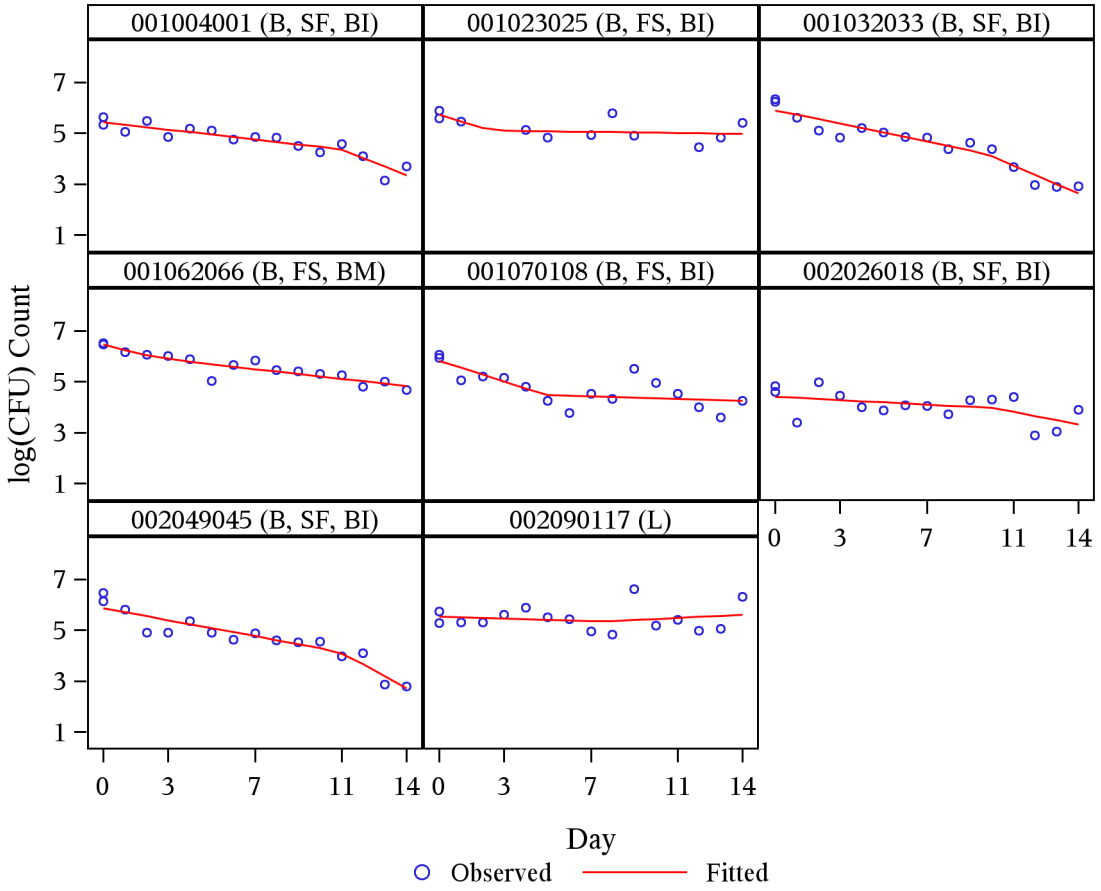


Figure C.22: Observed and Fitted log(CFU) Count, Trial **NC002 (EBA)**, Treatment Group **M-PA100-Z**

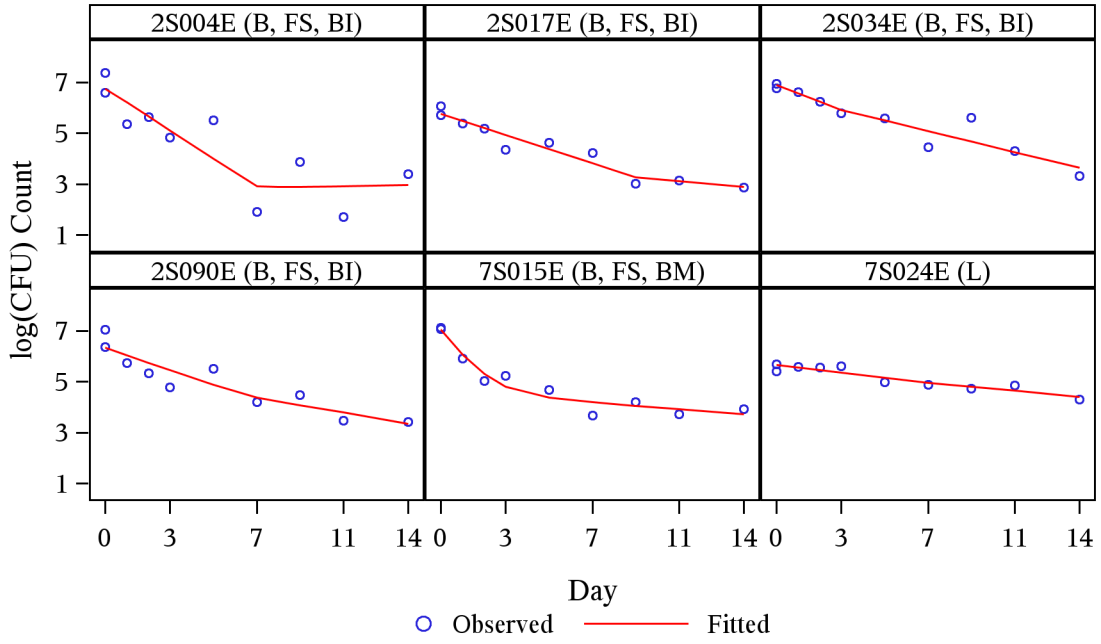


Figure C.23: Observed and Fitted log(CFU) Count, Trial **NC002 (EBA)**, Treatment Group **M-PA200-Z**

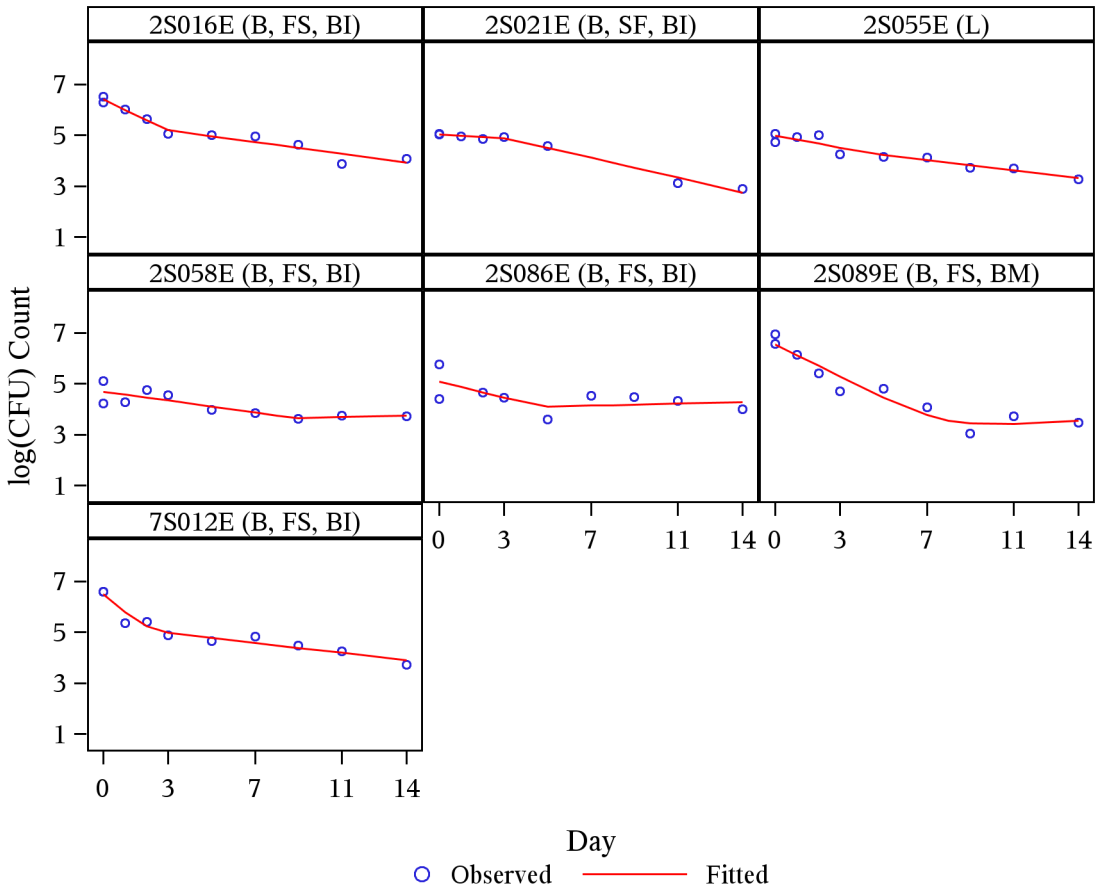


Figure C.24: Observed and Fitted log(CFU) Count, Trial **NC002 (EBA)**, Treatment Group **M-PA200-Z-MDR**

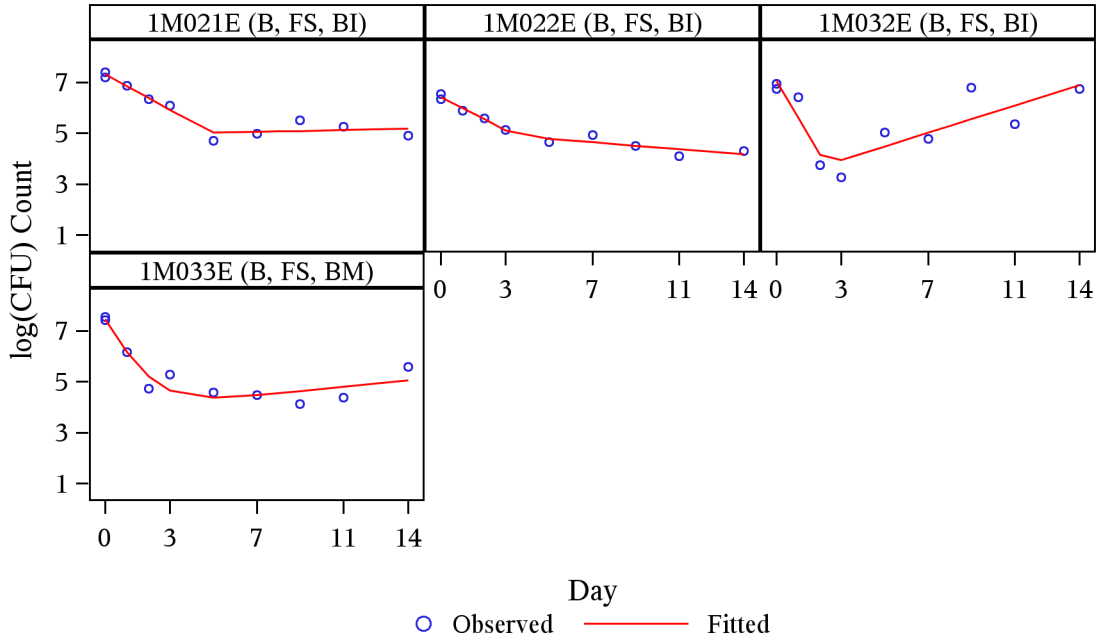


Figure C.25: Observed and Fitted log(CFU) Count, Trial **NC002 (EBA)**, Treatment Group **Rifafour**

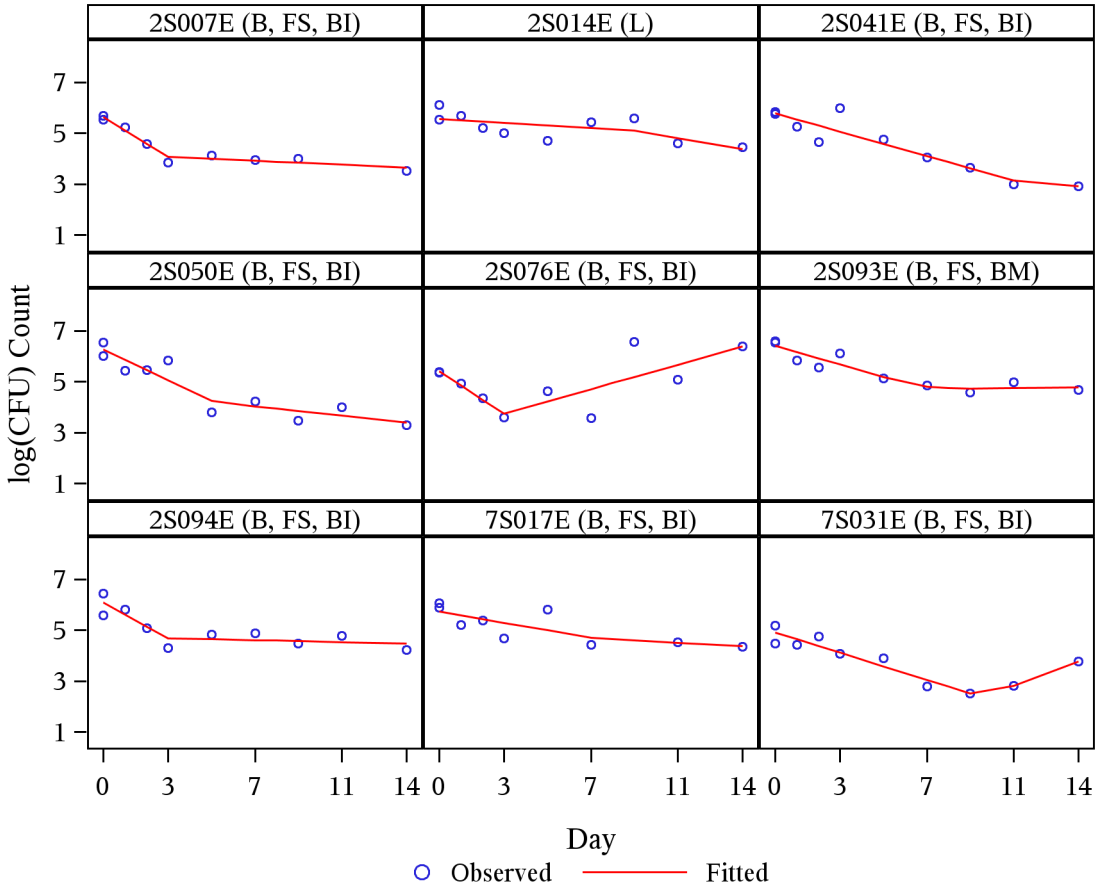


Figure C.26: Observed and Fitted log(CFU) Count, Trial **NC002 ("SSCC")**, Treatment Group **M-PA100-Z**

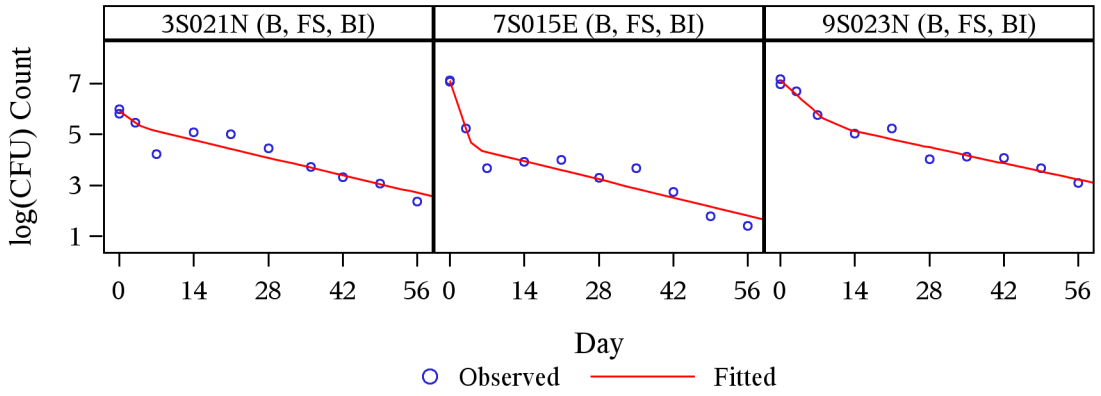


Figure C.27: Observed and Fitted log(CFU) Count, Trial **NC002 ("SSCC")**, Treatment Group **M-PA200-Z**

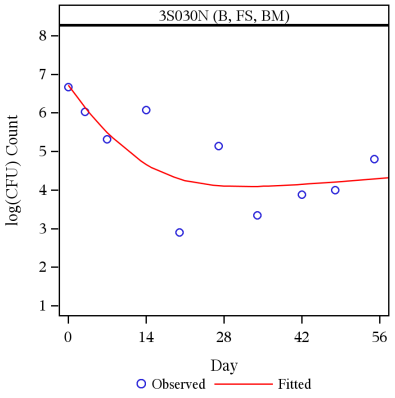


Figure C.28: Observed and Fitted log(CFU) Count, Trial **NC002 ("SSCC")**, Treatment Group **M-PA200-Z-MDR**

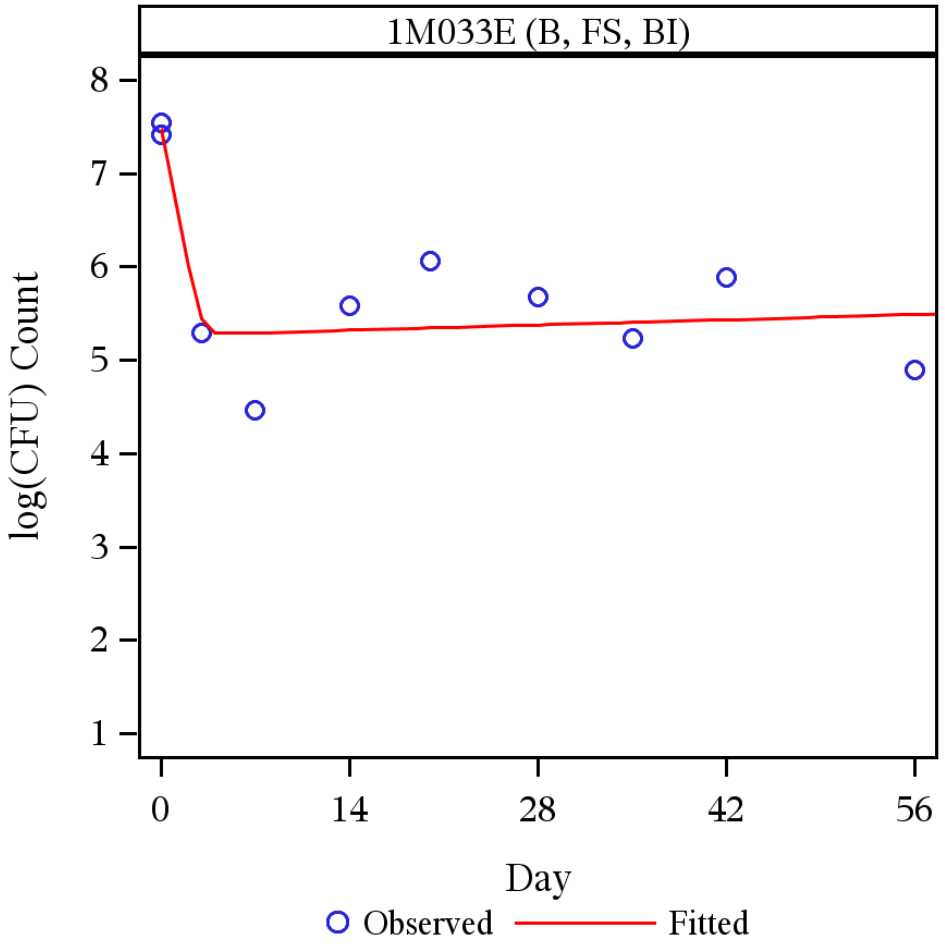


Figure C.29: Observed and Fitted log(CFU) Count, Trial **NC002 ("SSCC")**, Treatment Group **Rifafour**

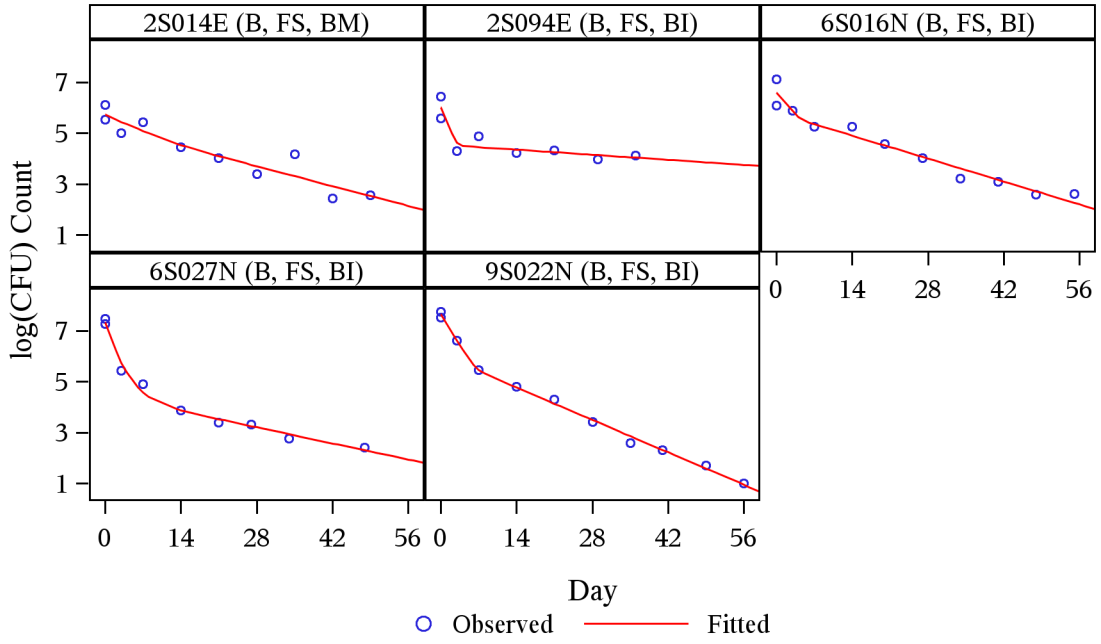


Figure C.30: Observed and Fitted log(CFU) Count, Trial **NC003**, Treatment Group **J-Pa-Z-C**

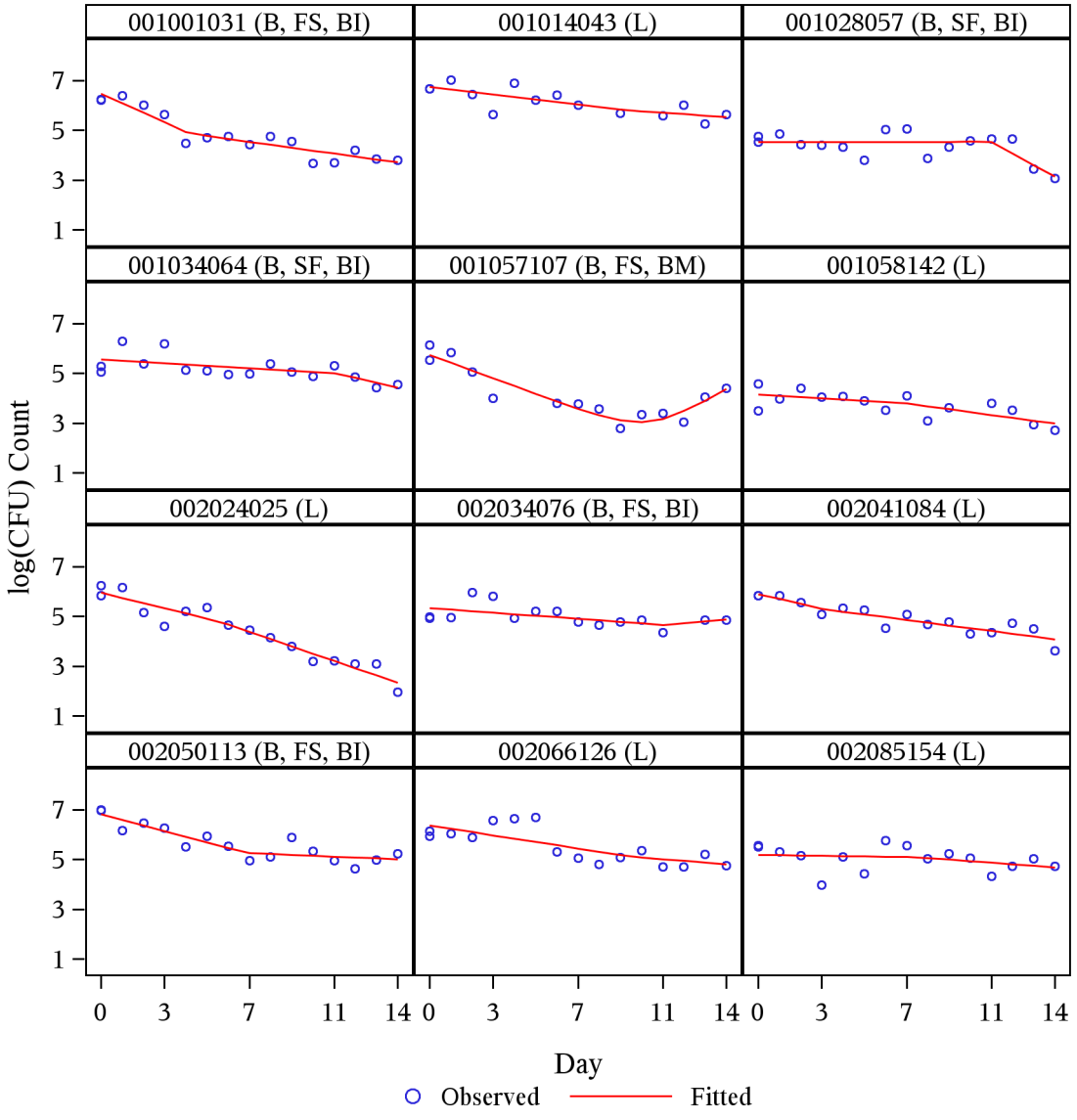


Figure C.31: Observed and Fitted log(CFU) Count, Trial **NC003**, Treatment Group **J-Pa-Z**

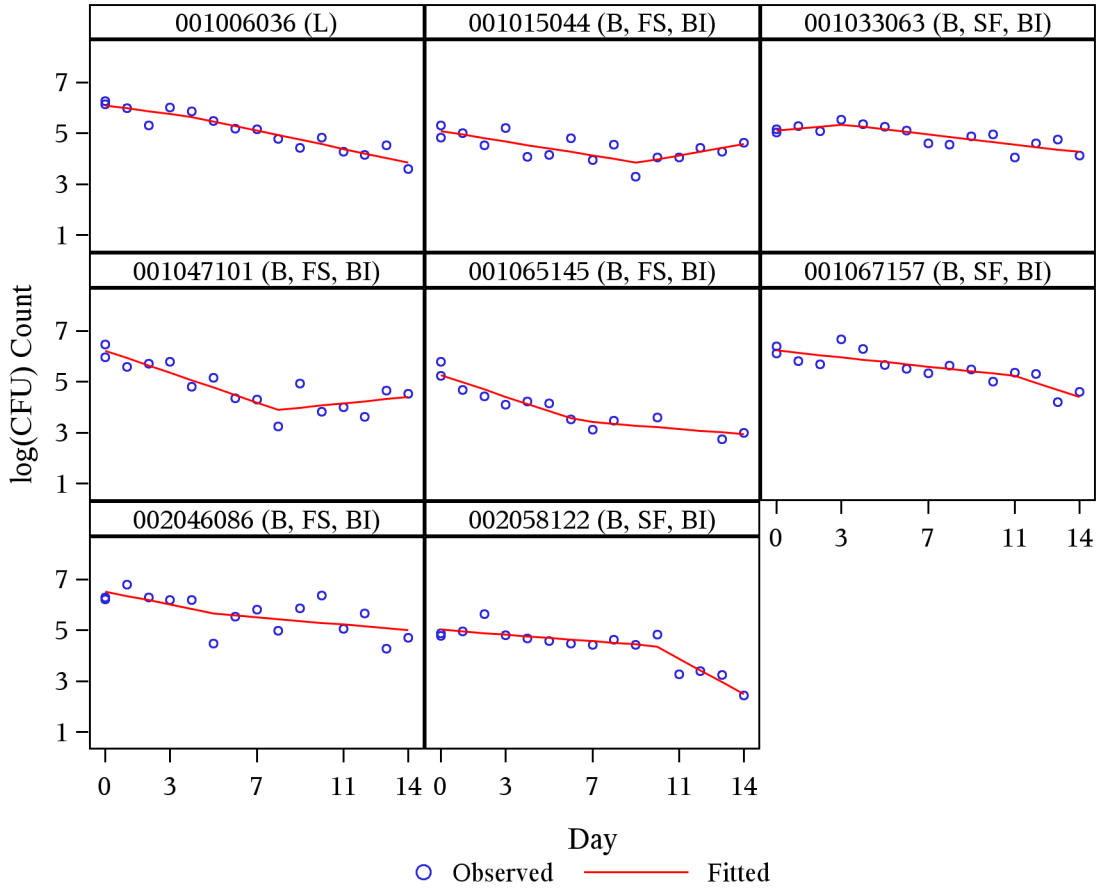


Figure C.32: Observed and Fitted log(CFU) Count, Trial **NC003**, Treatment Group **J-Pa-C**

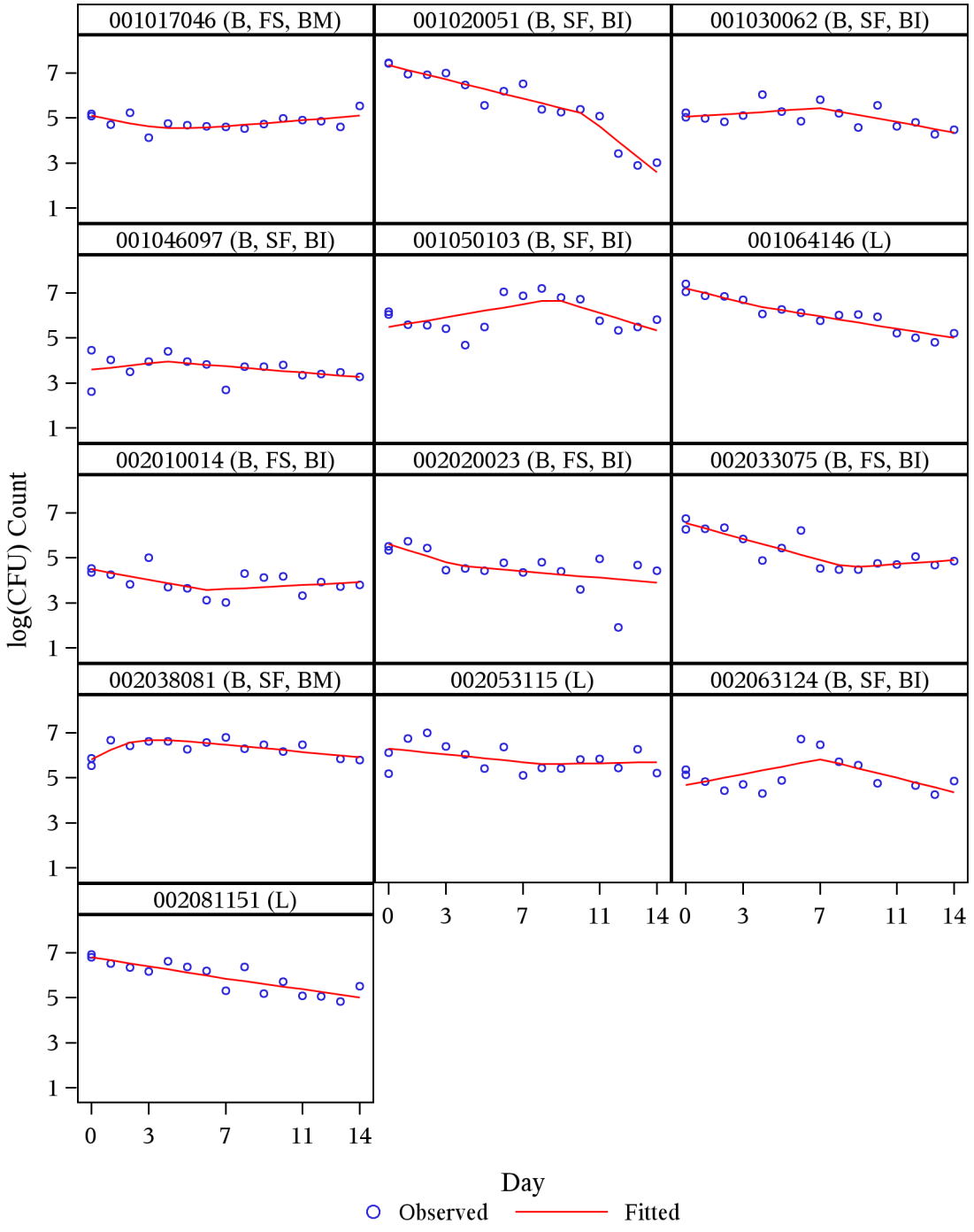


Figure C.33: Observed and Fitted log(CFU) Count, Trial **NC003**, Treatment Group **J-Z-C**

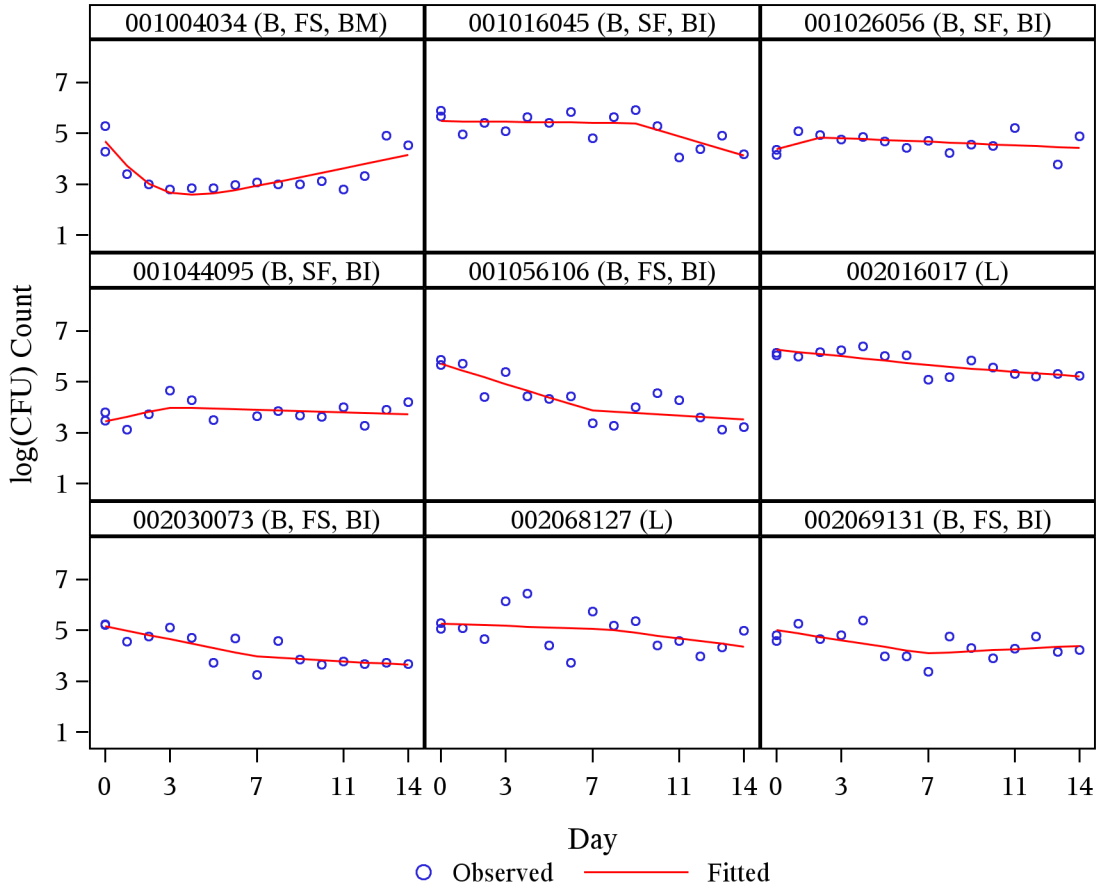


Figure C.34: Observed and Fitted log(CFU) Count, Trial **NC003**, Treatment Group **Z**

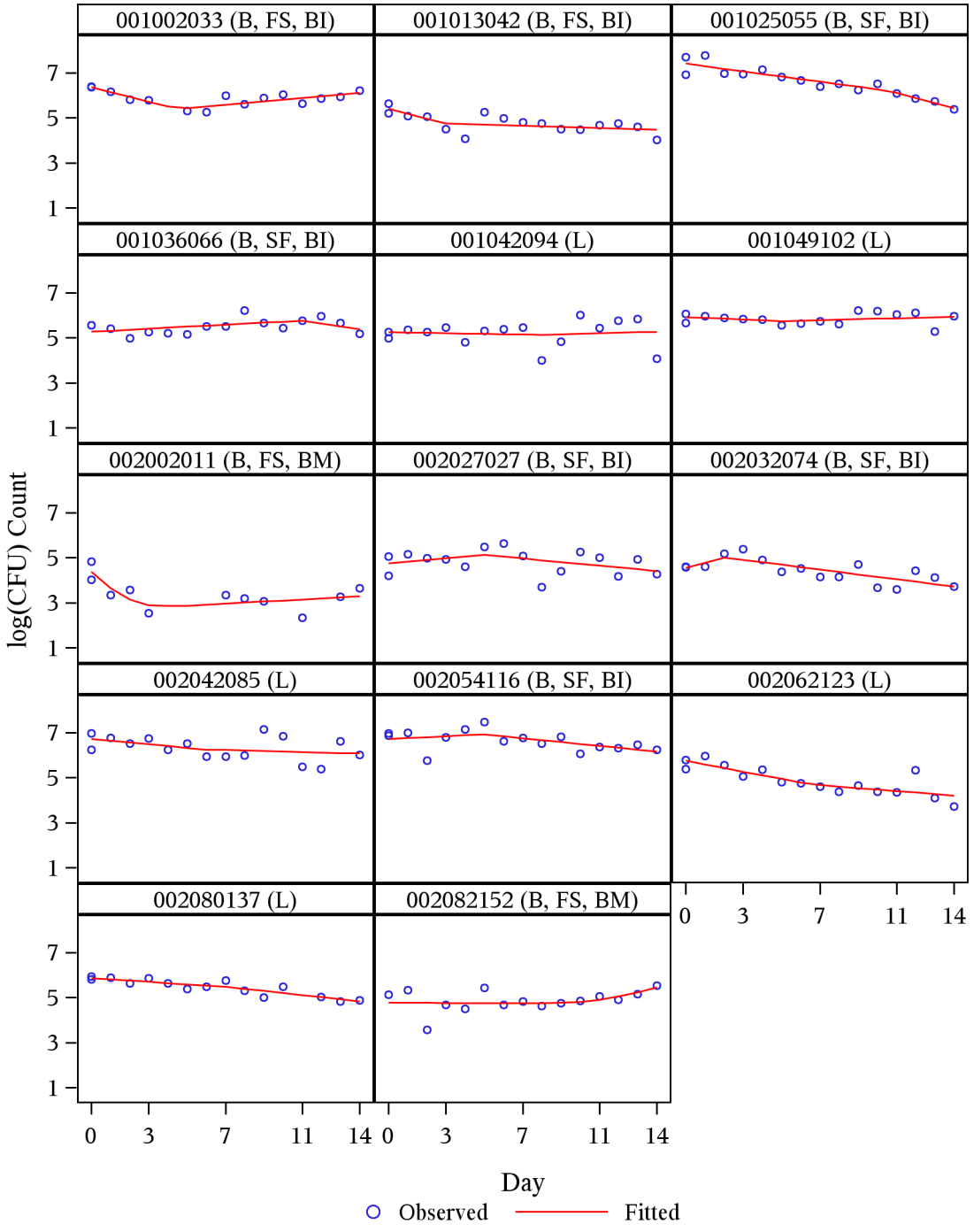


Figure C.35: Observed and Fitted log(CFU) Count, Trial **NC003**, Treatment Group **C**

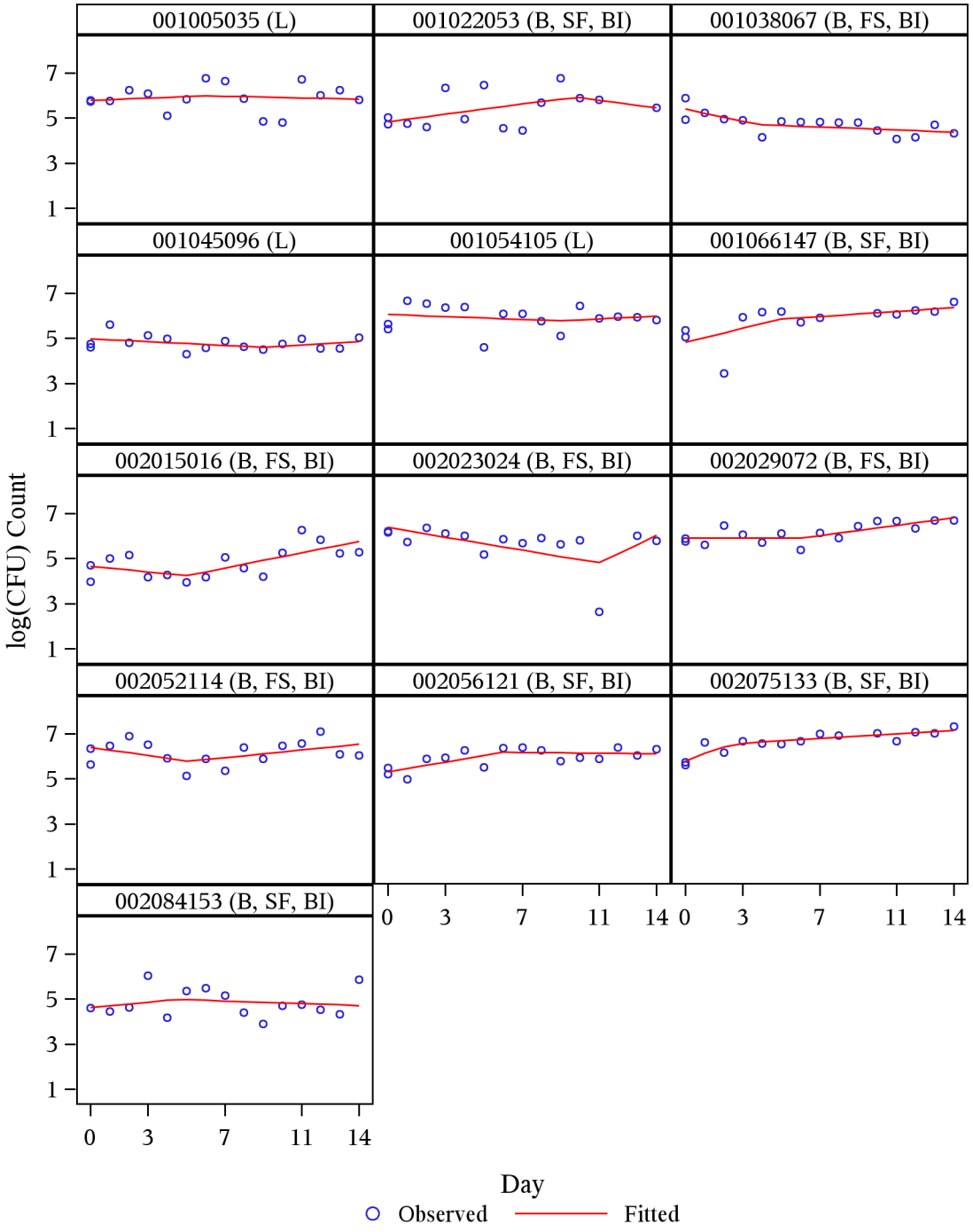
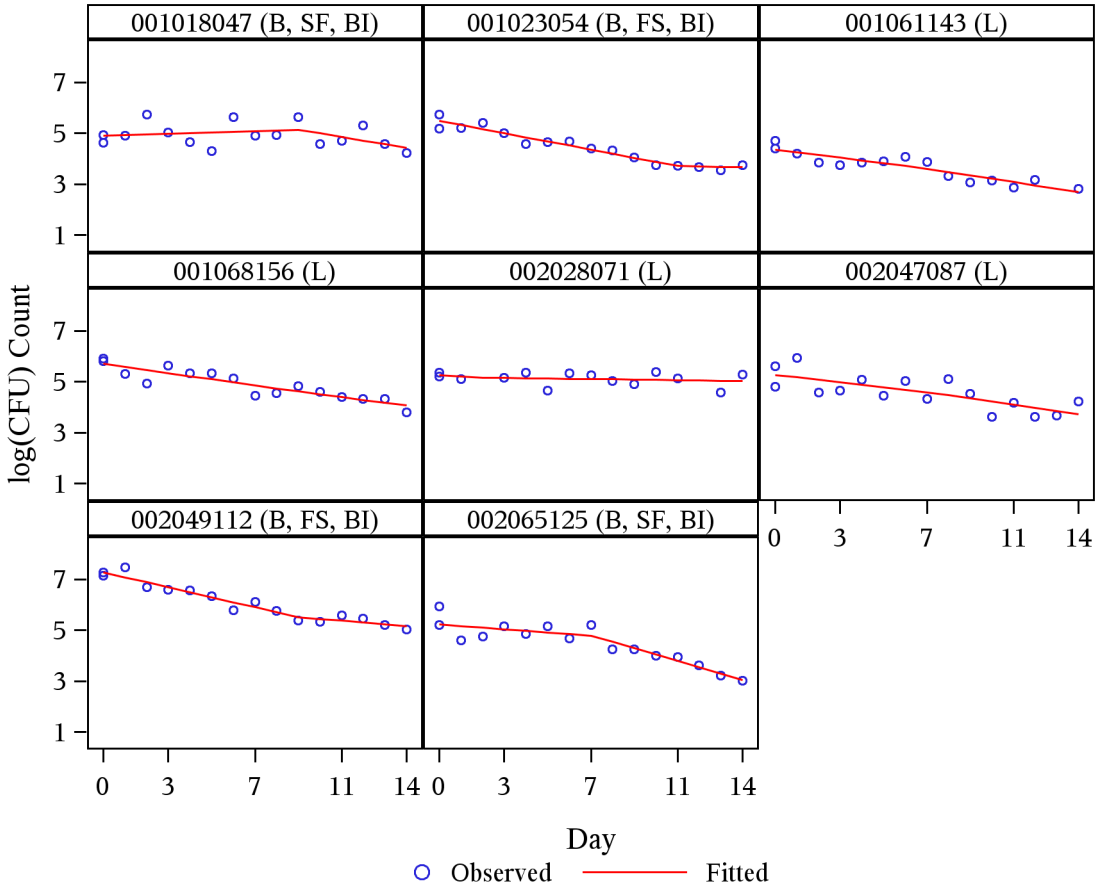


Figure C.36: Observed and Fitted log(CFU) Count, Trial **NC003**, Treatment Group **Rifafour**



C.2 Time to Positivity

Figure C.37: Observed and Fitted log(TTP), Trial **CL001**, Treatment Group **TMC207 100 mg**

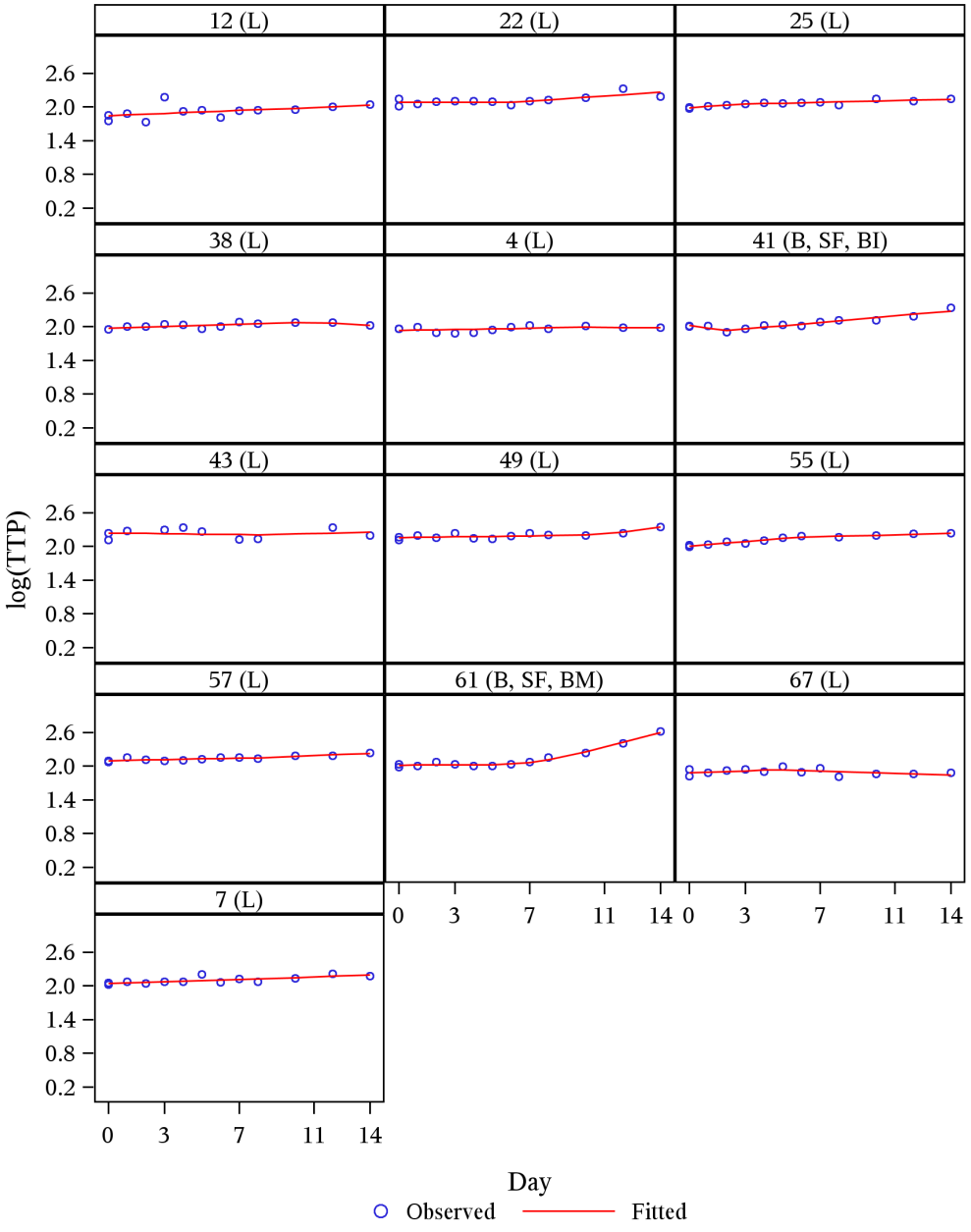


Figure C.38: Observed and Fitted log(TTP), Trial **CL001**, Treatment Group **TMC207 200 mg**

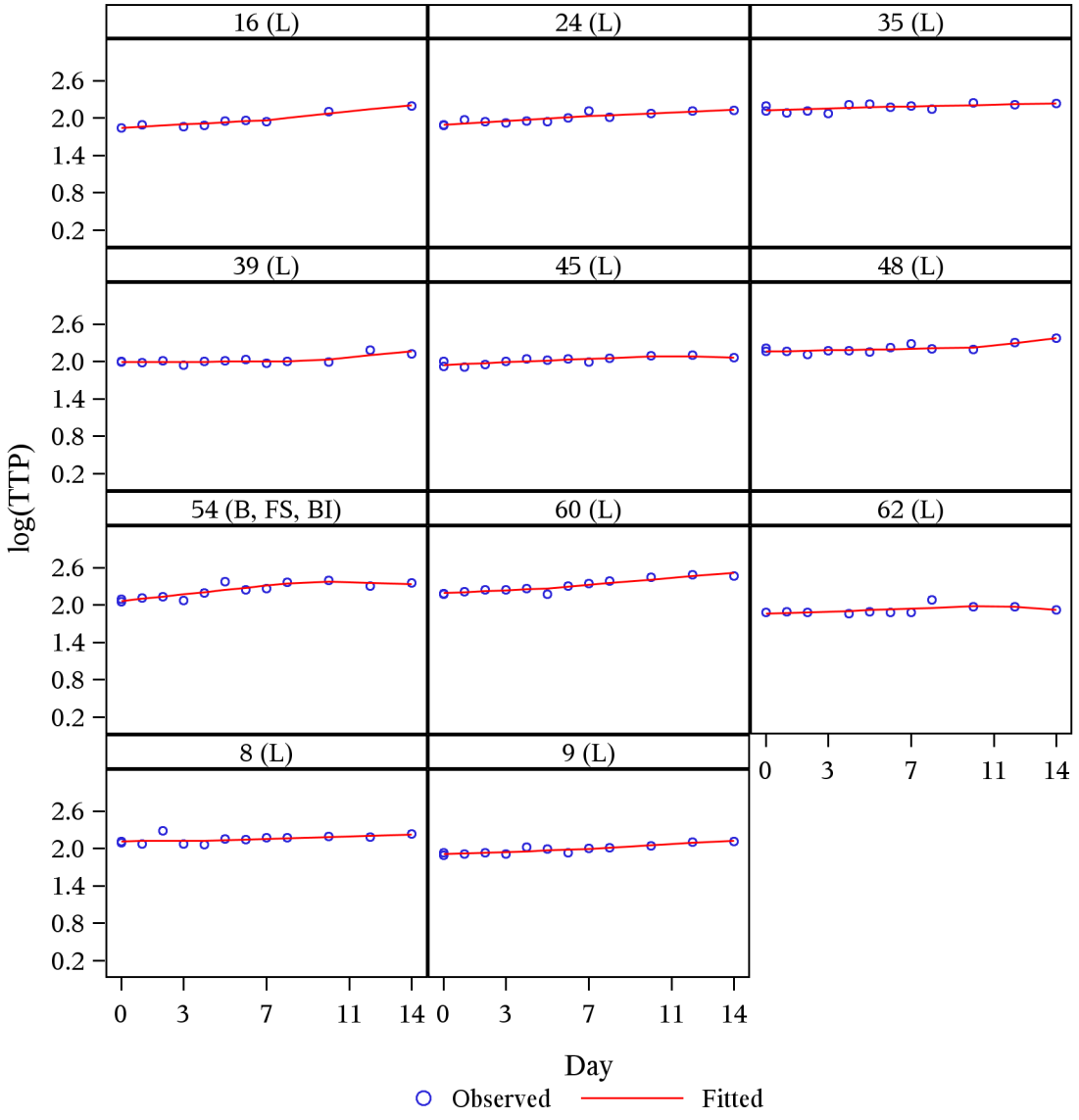


Figure C.39: Observed and Fitted log(TTP), Trial **CL001**, Treatment Group **TMC207 300 mg**

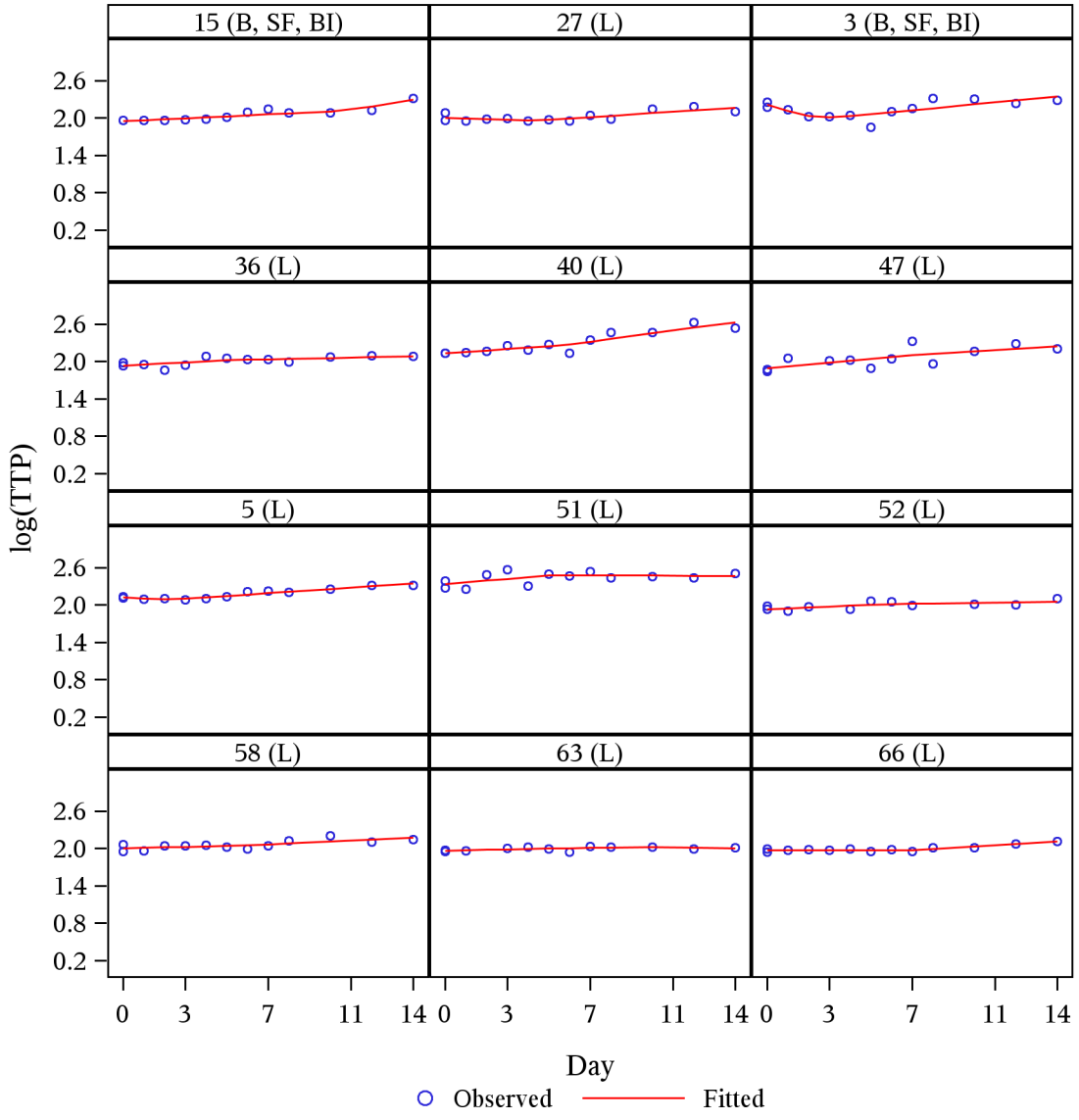


Figure C.40: Observed and Fitted log(TTP), Trial **CL001**, Treatment Group **TMC207 400 mg**

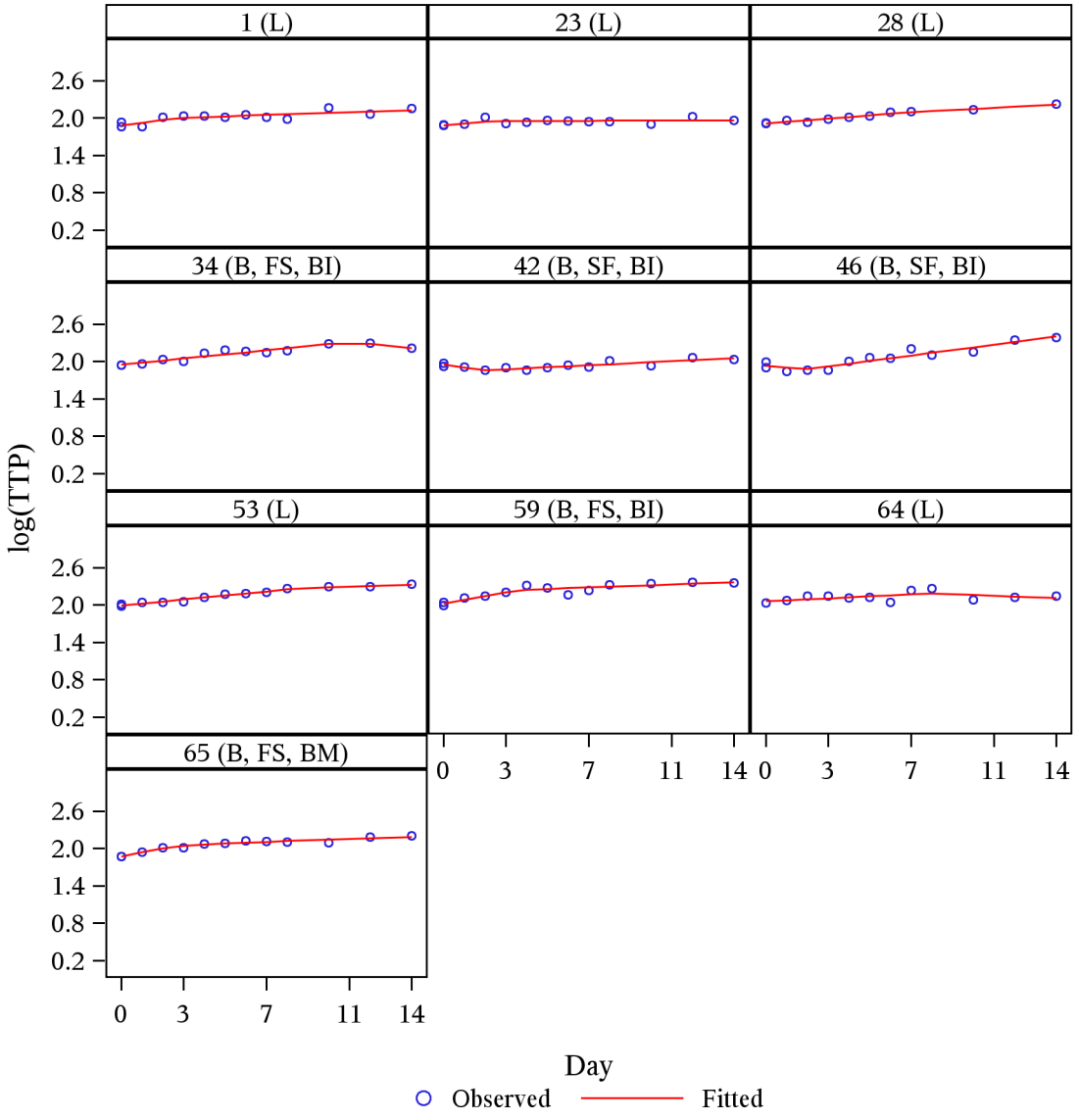


Figure C.41: Observed and Fitted log(TTP), Trial **CL001**, Treatment Group **Rifafour**

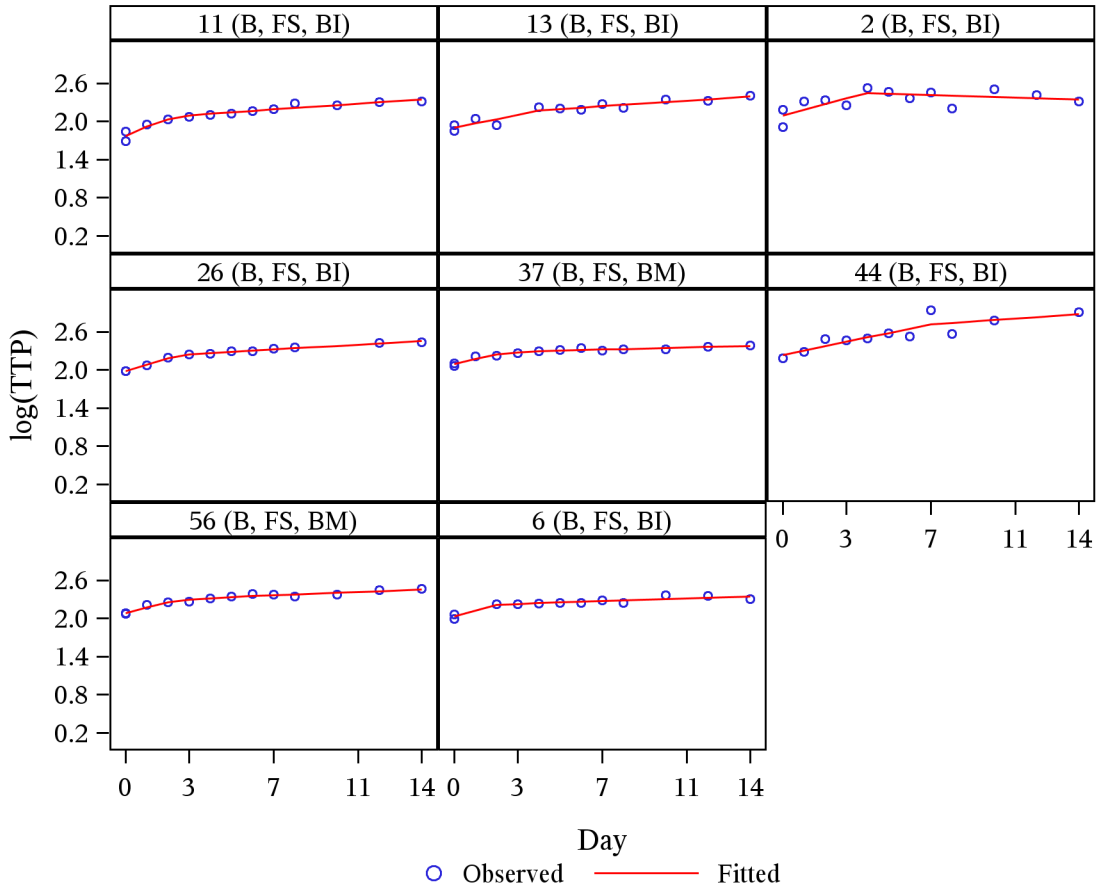


Figure C.42: Observed and Fitted log(TTP), Trial **CL007**, Treatment Group **PA-824 200 mg**

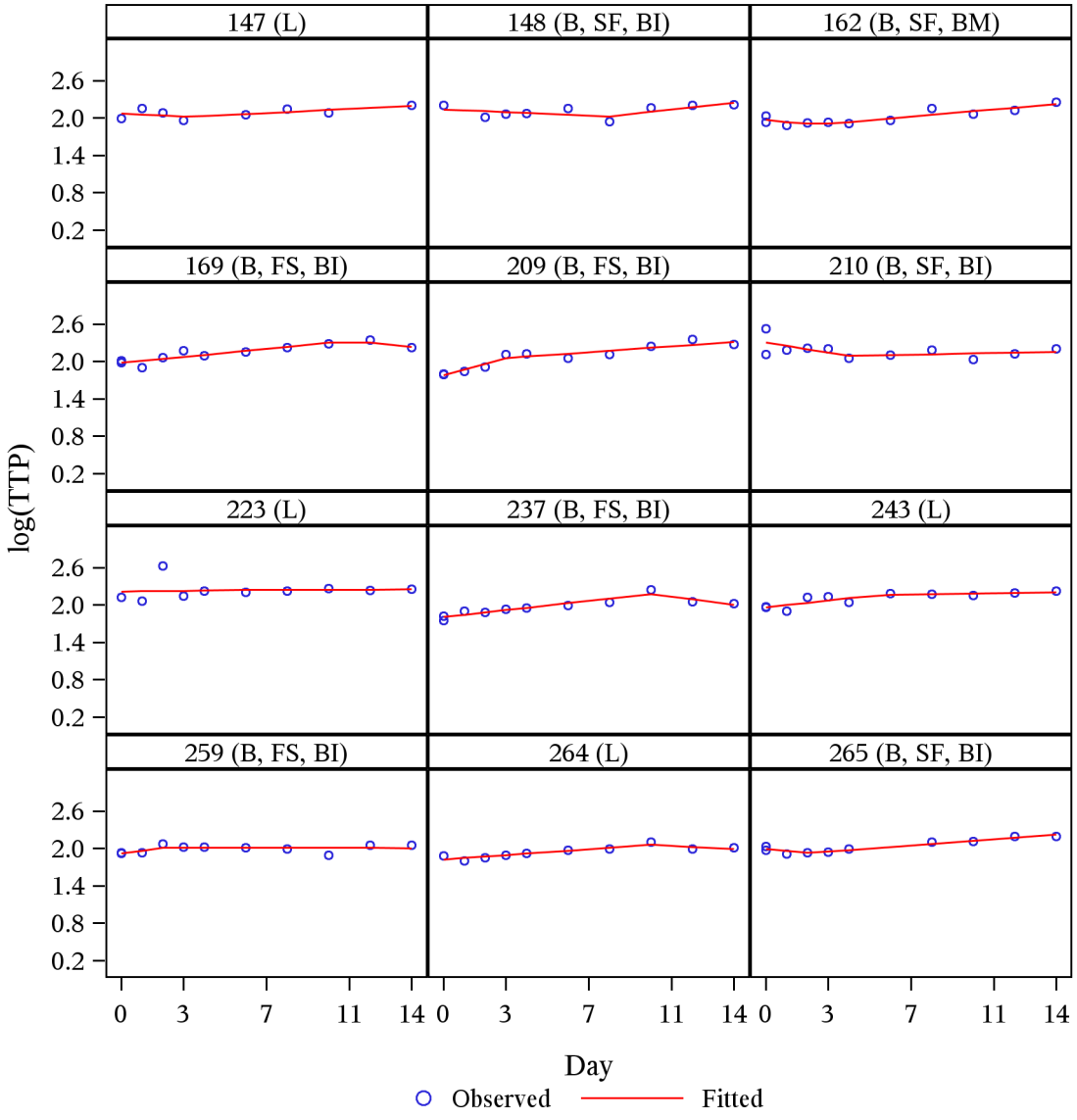


Figure C.43: Observed and Fitted log(TTP), Trial **CL007**, Treatment Group **PA-824 600 mg**

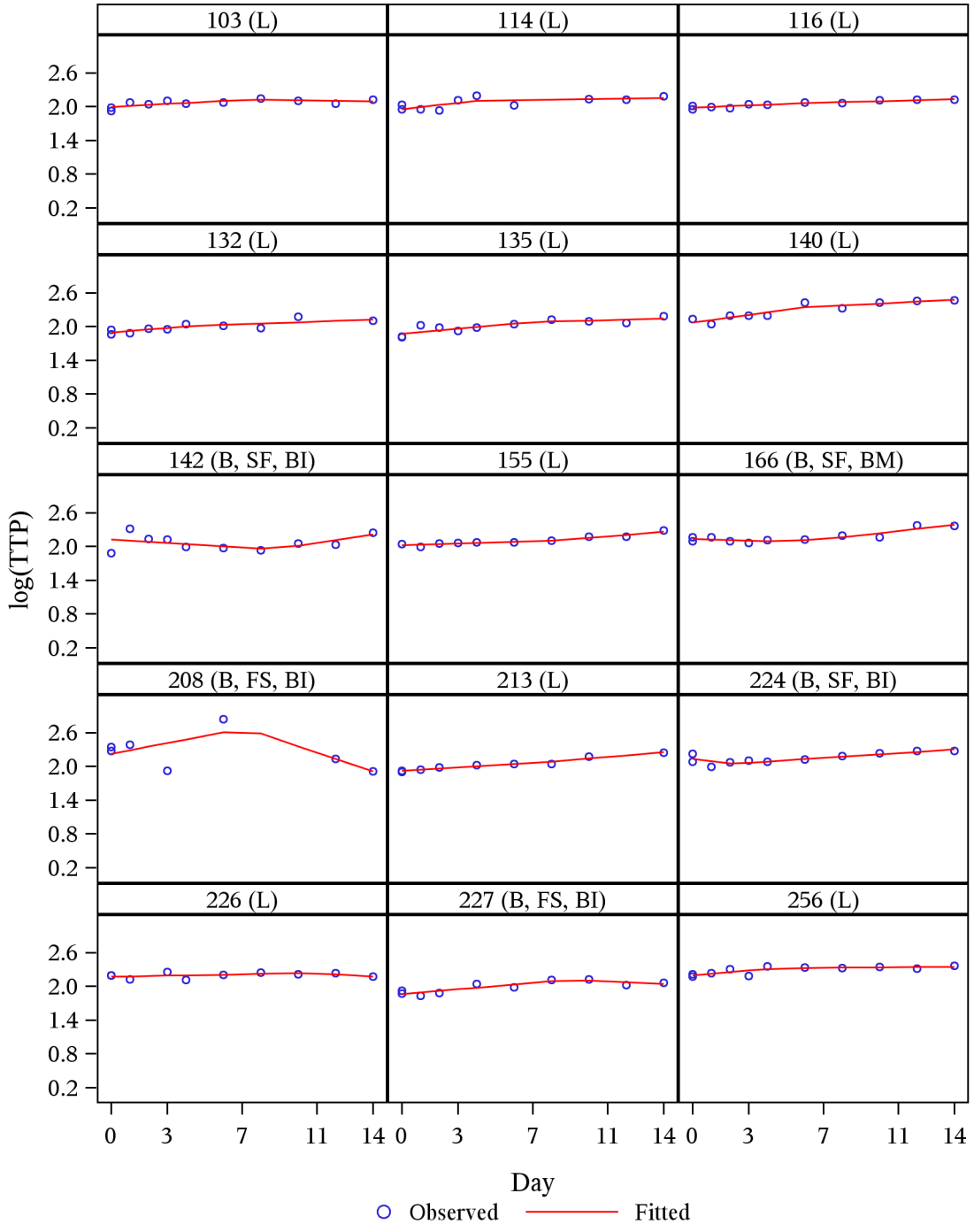


Figure C.44: Observed and Fitted log(TTP), Trial **CL007**, Treatment Group **PA-824 1000 mg**

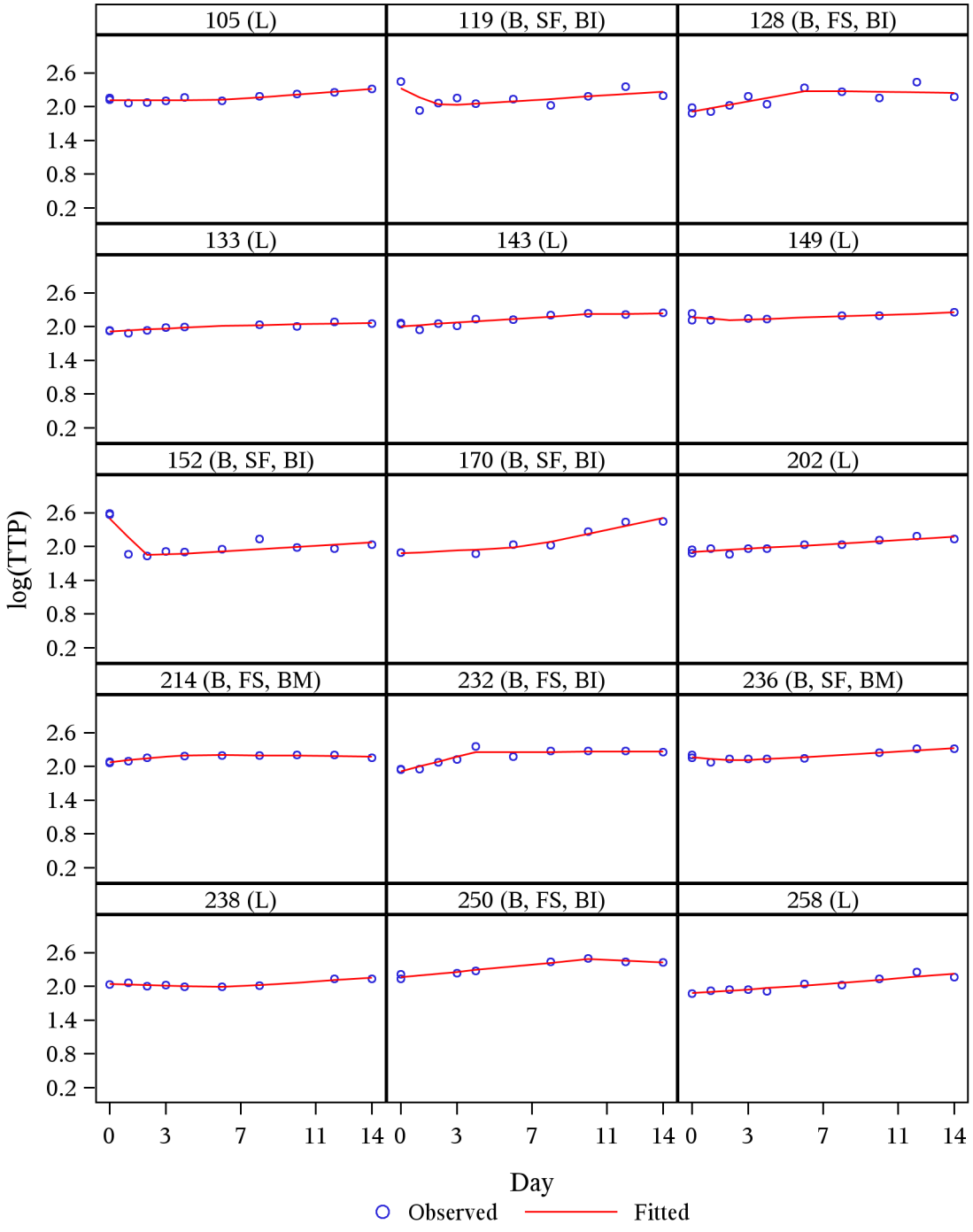


Figure C.45: Observed and Fitted log(TTP), Trial **CL007**, Treatment Group **PA-824 1200 mg**

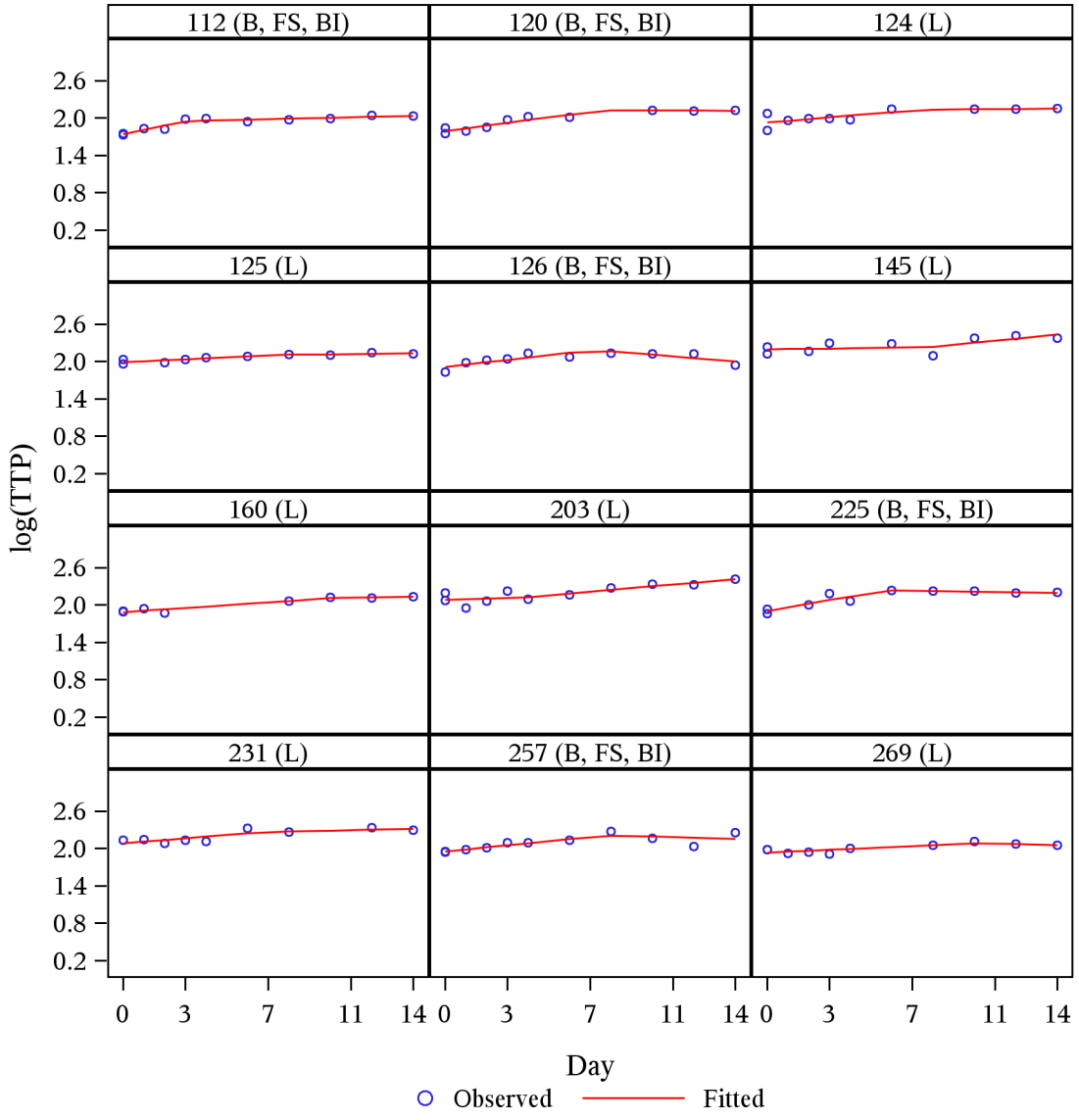


Figure C.46: Observed and Fitted log(TTP), Trial **CL007**, Treatment Group **Rifafour**

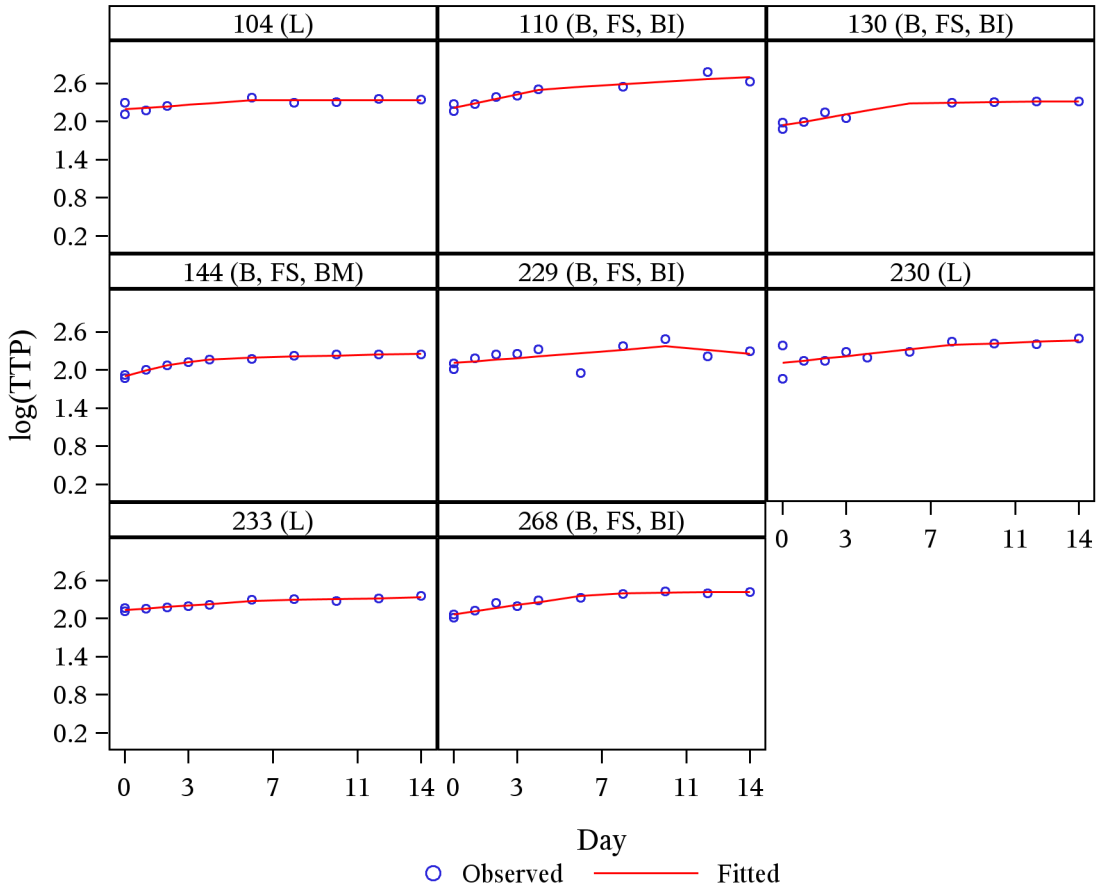


Figure C.47: Observed and Fitted log(TTP), Trial **CL010**, Treatment Group **PA-824 50 mg**

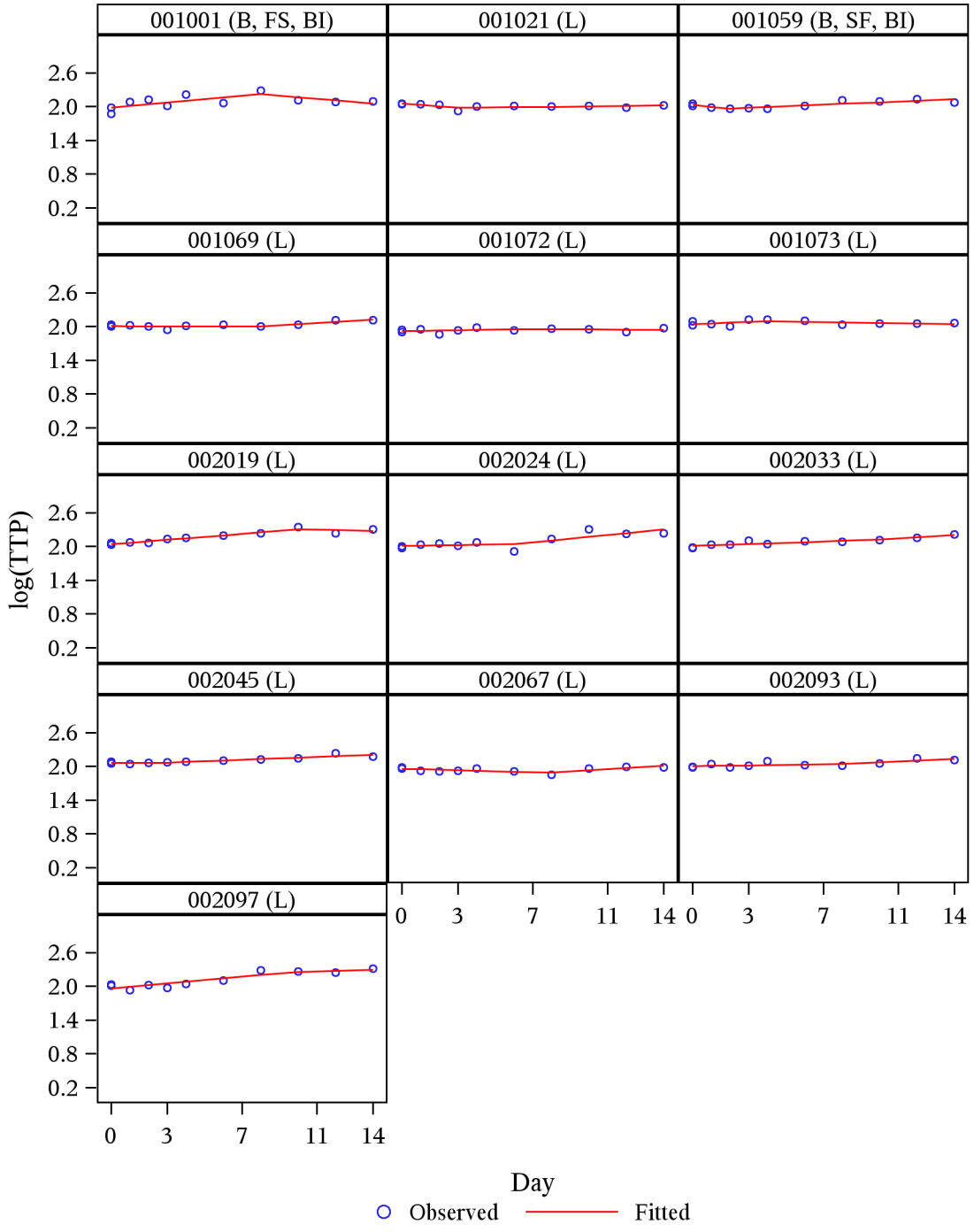


Figure C.48: Observed and Fitted log(TTP), Trial **CL010**, Treatment Group **PA-824 100 mg**

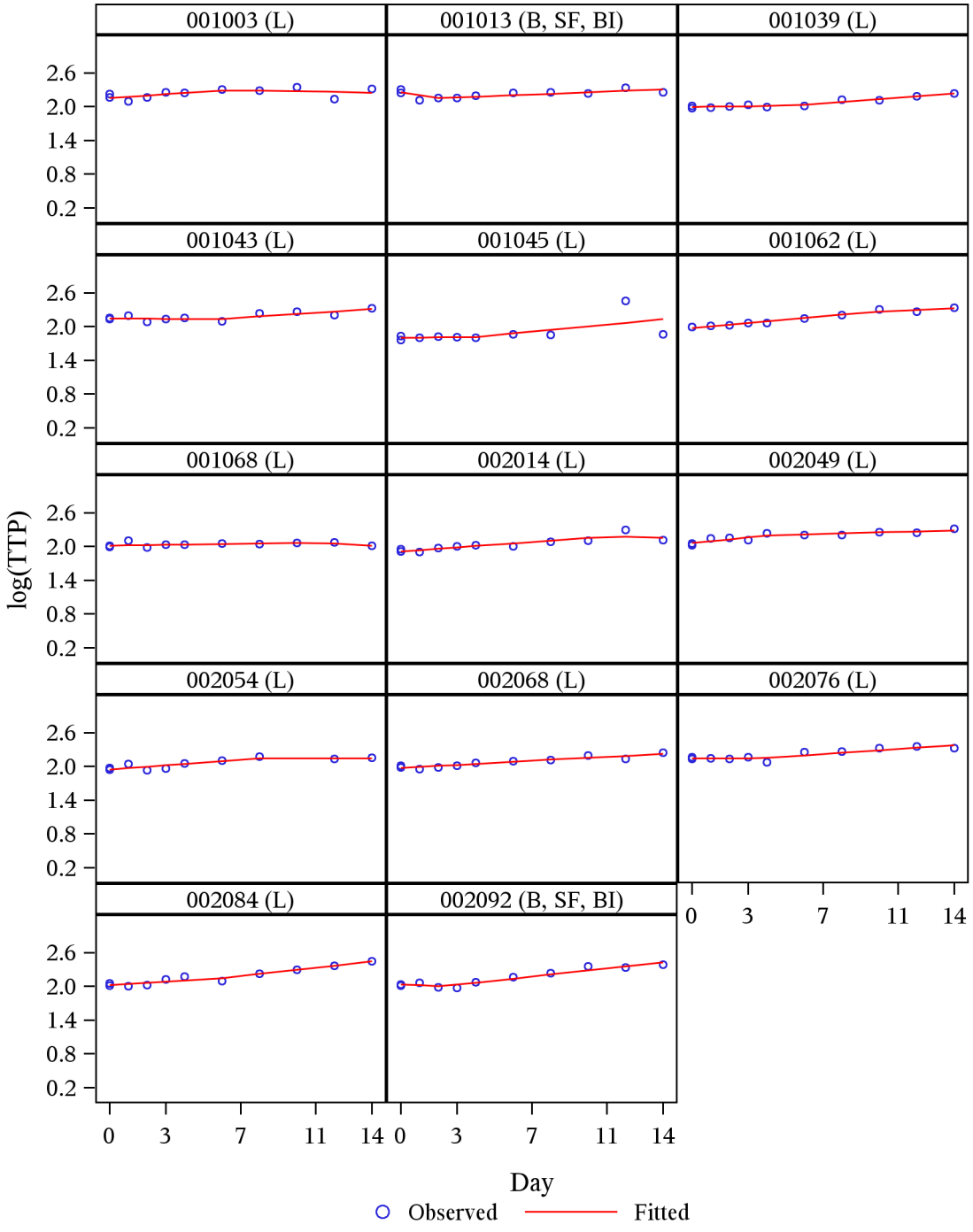


Figure C.49: Observed and Fitted log(TTP), Trial **CL010**, Treatment Group **PA-824 150 mg**

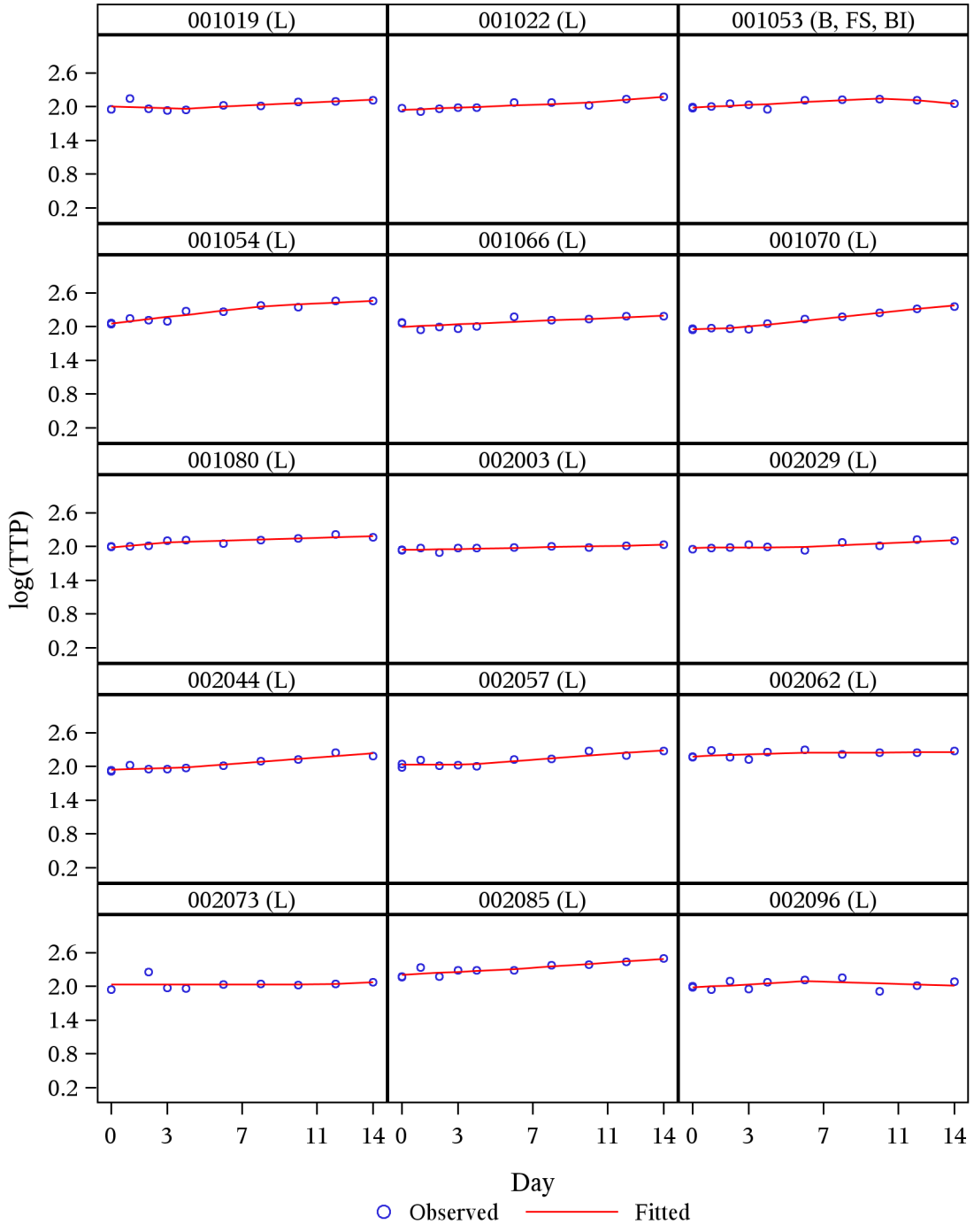


Figure C.50: Observed and Fitted log(TTP), Trial **CL010**, Treatment Group **PA-824 200 mg**

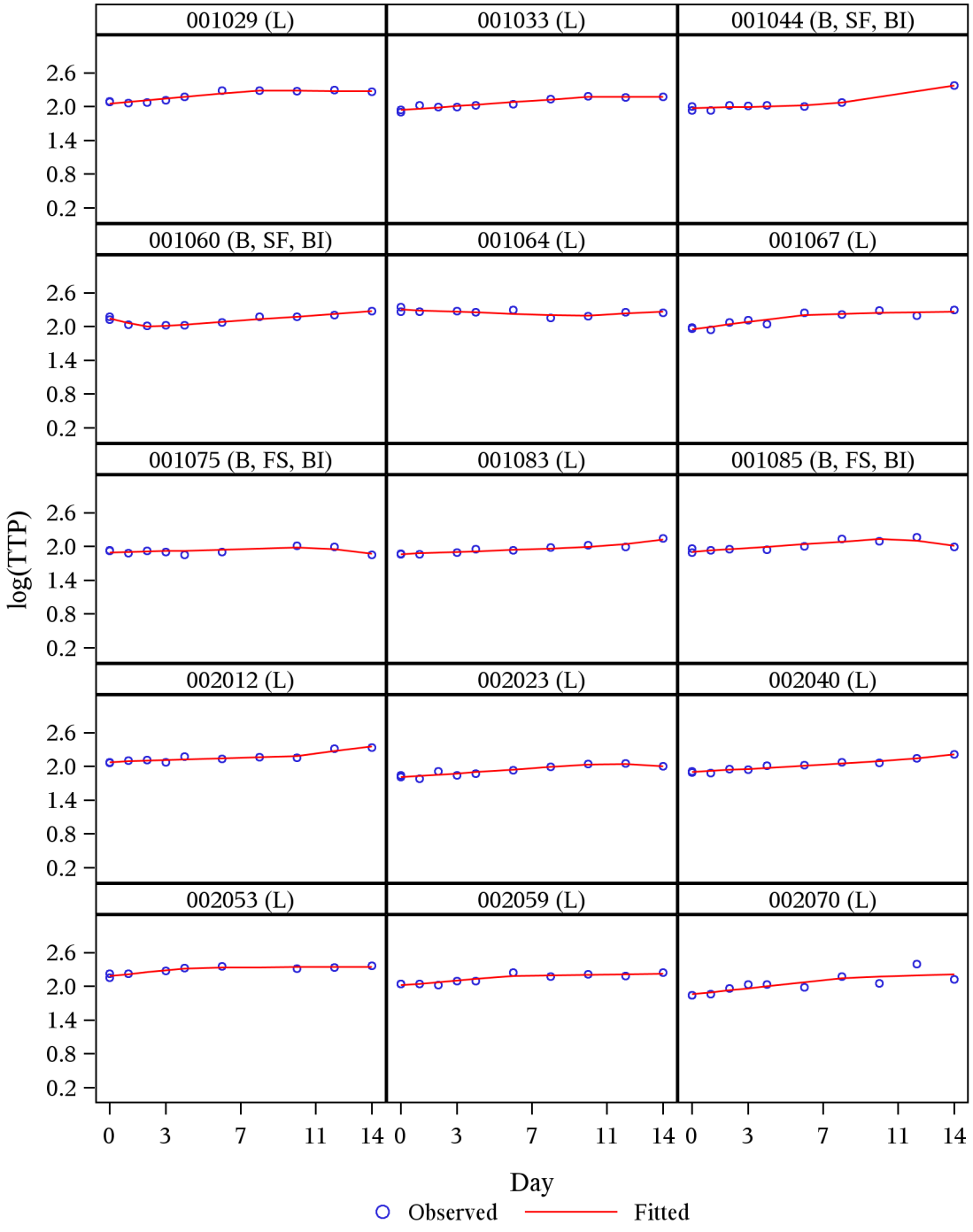


Figure C.51: Observed and Fitted log(TTP), Trial **CL010**, Treatment Group **PA-824 200 mg**

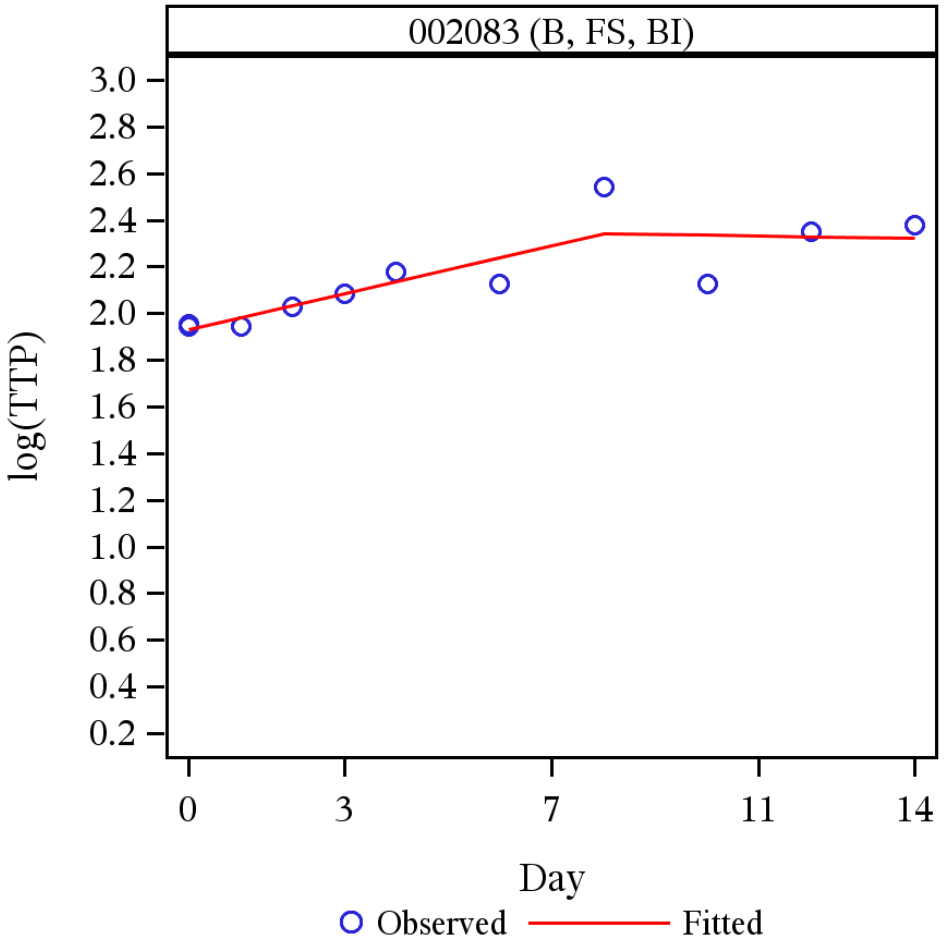


Figure C.52: Observed and Fitted log(TTP), Trial **CL010**, Treatment Group **Rifafour**

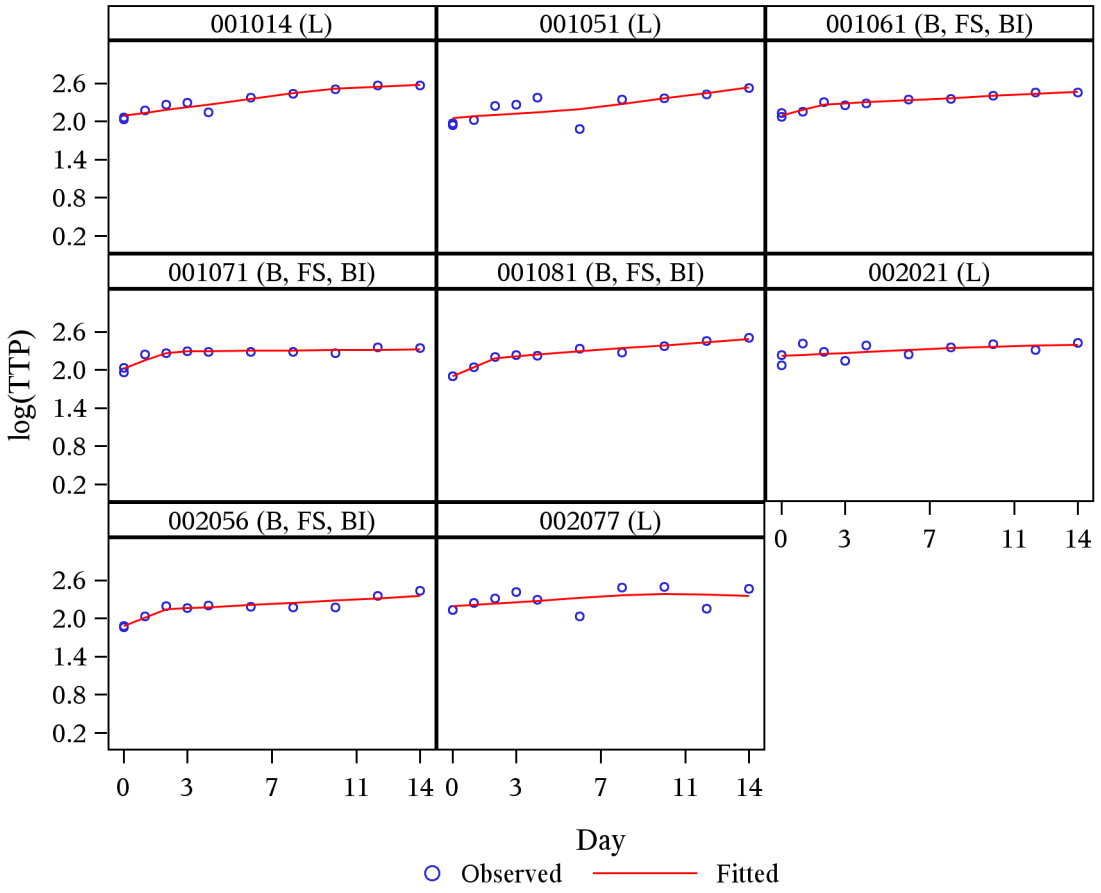


Figure C.53: Observed and Fitted log(TTP), Trial **NC001**, Treatment Group **J**

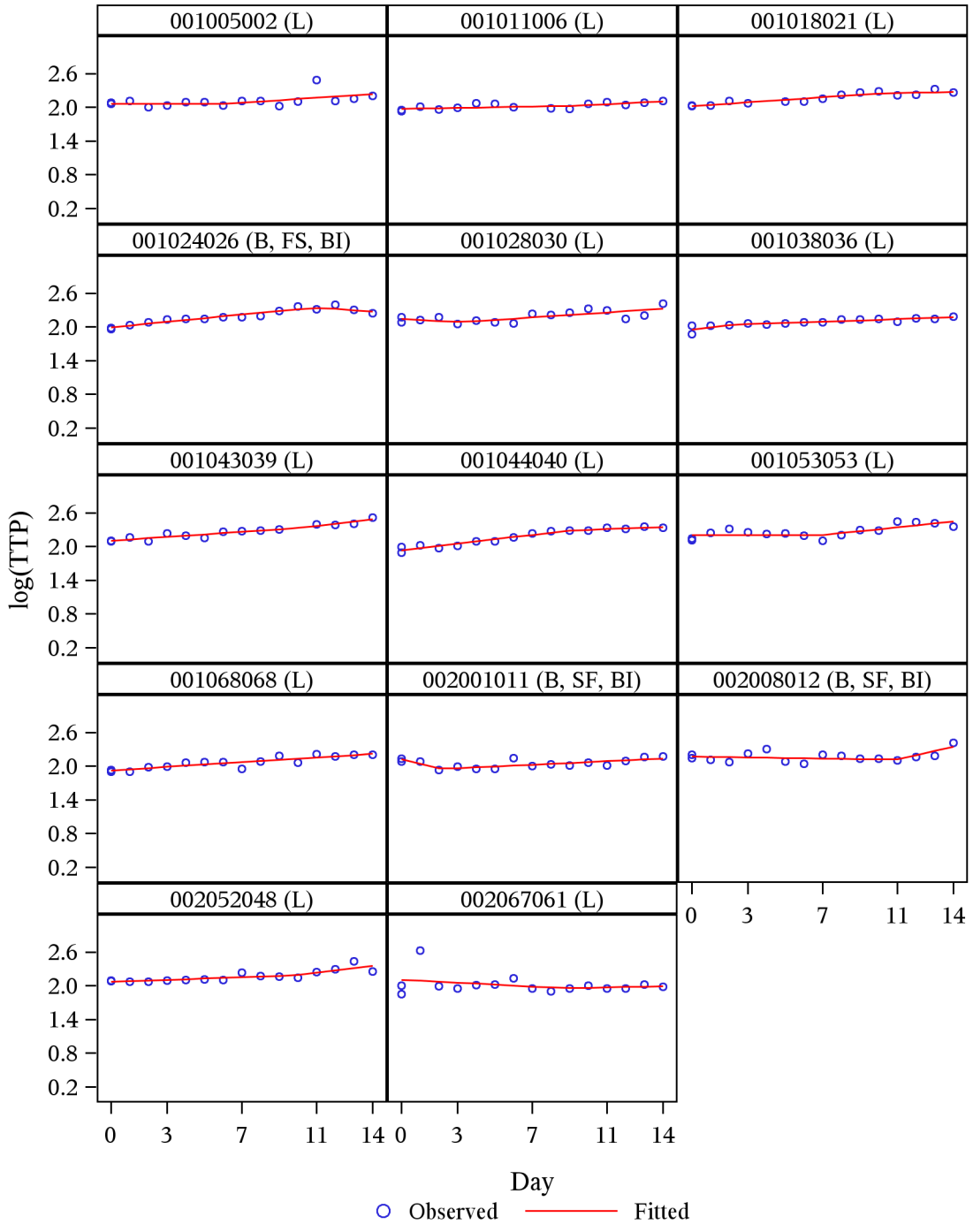


Figure C.54: Observed and Fitted log(TTP), Trial **NC001**, Treatment Group **J-Z**

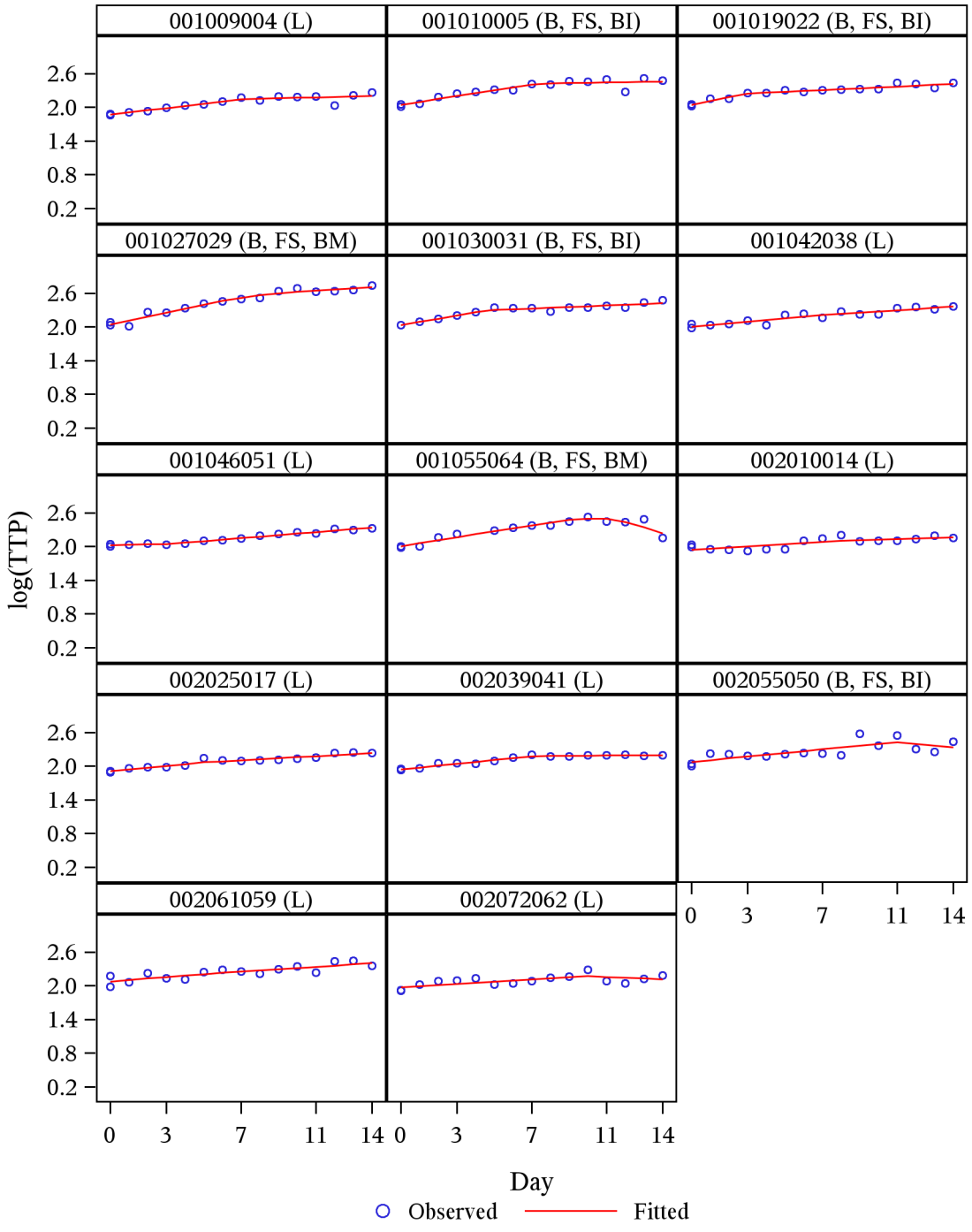


Figure C.55: Observed and Fitted log(TTP), Trial **NC001**, Treatment Group **J-Pa**

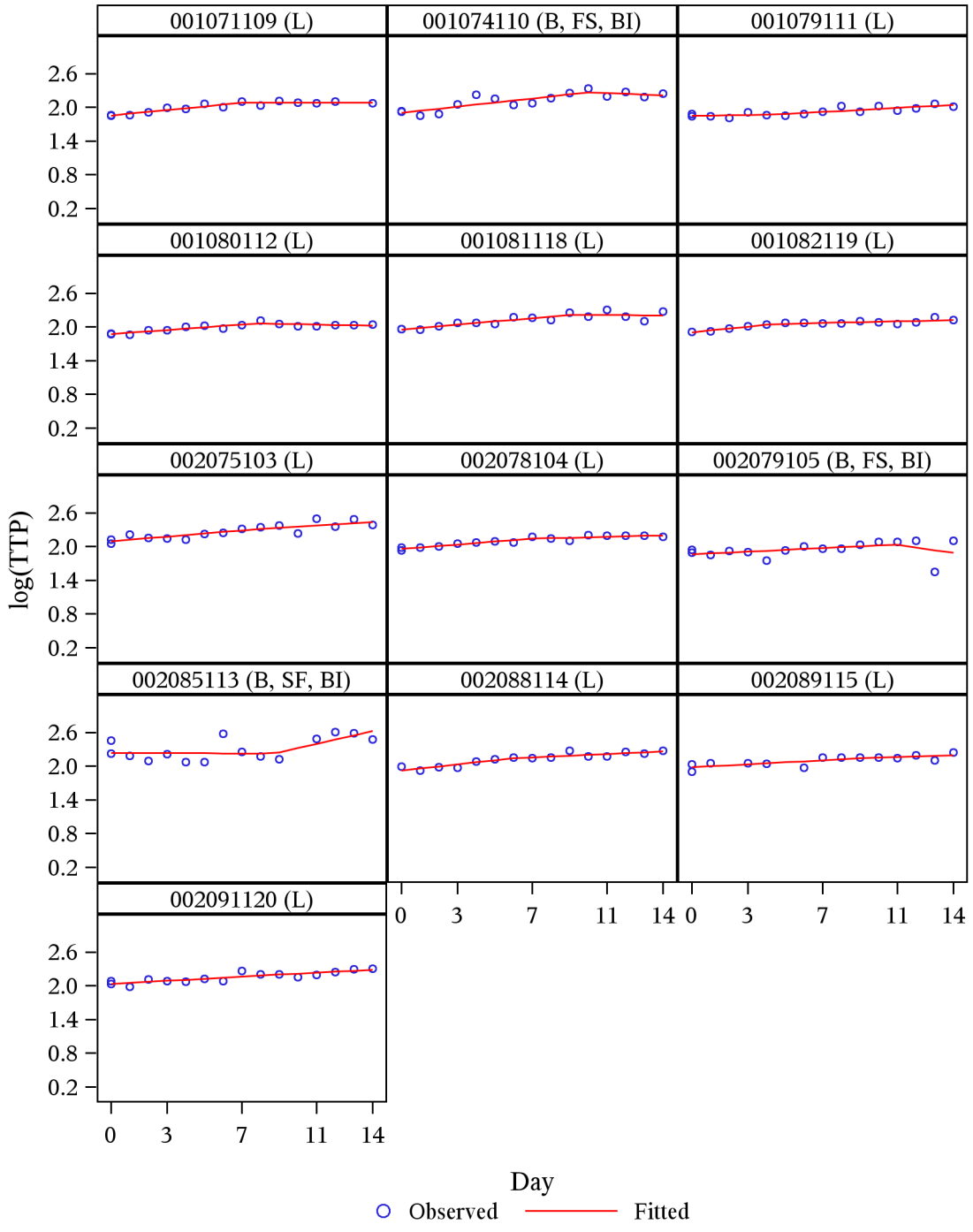


Figure C.56: Observed and Fitted log(TTP), Trial **NC001**, Treatment Group **Pa-Z**

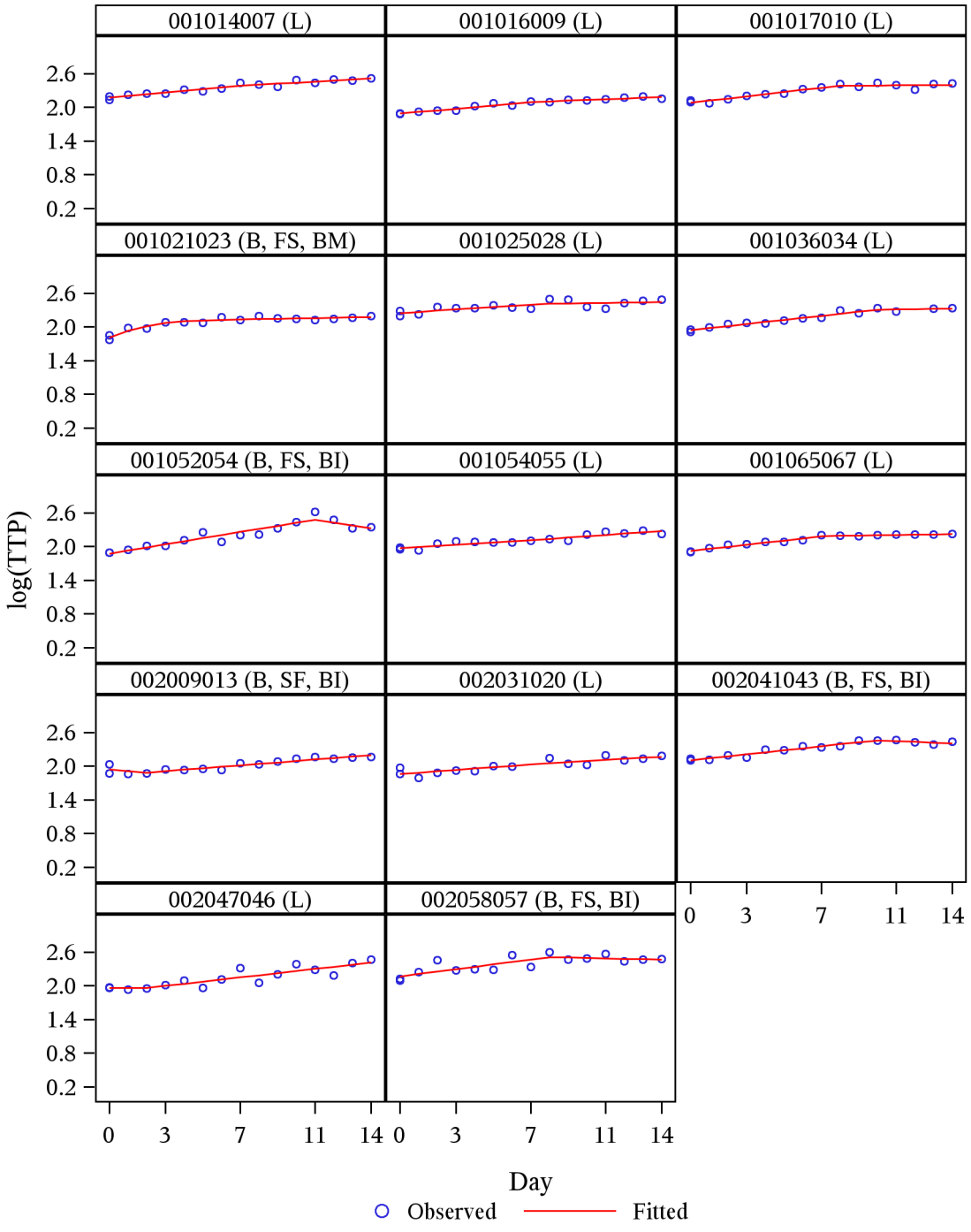


Figure C.57: Observed and Fitted log(TTP), Trial **NC001**, Treatment Group **Pa-Z-M**

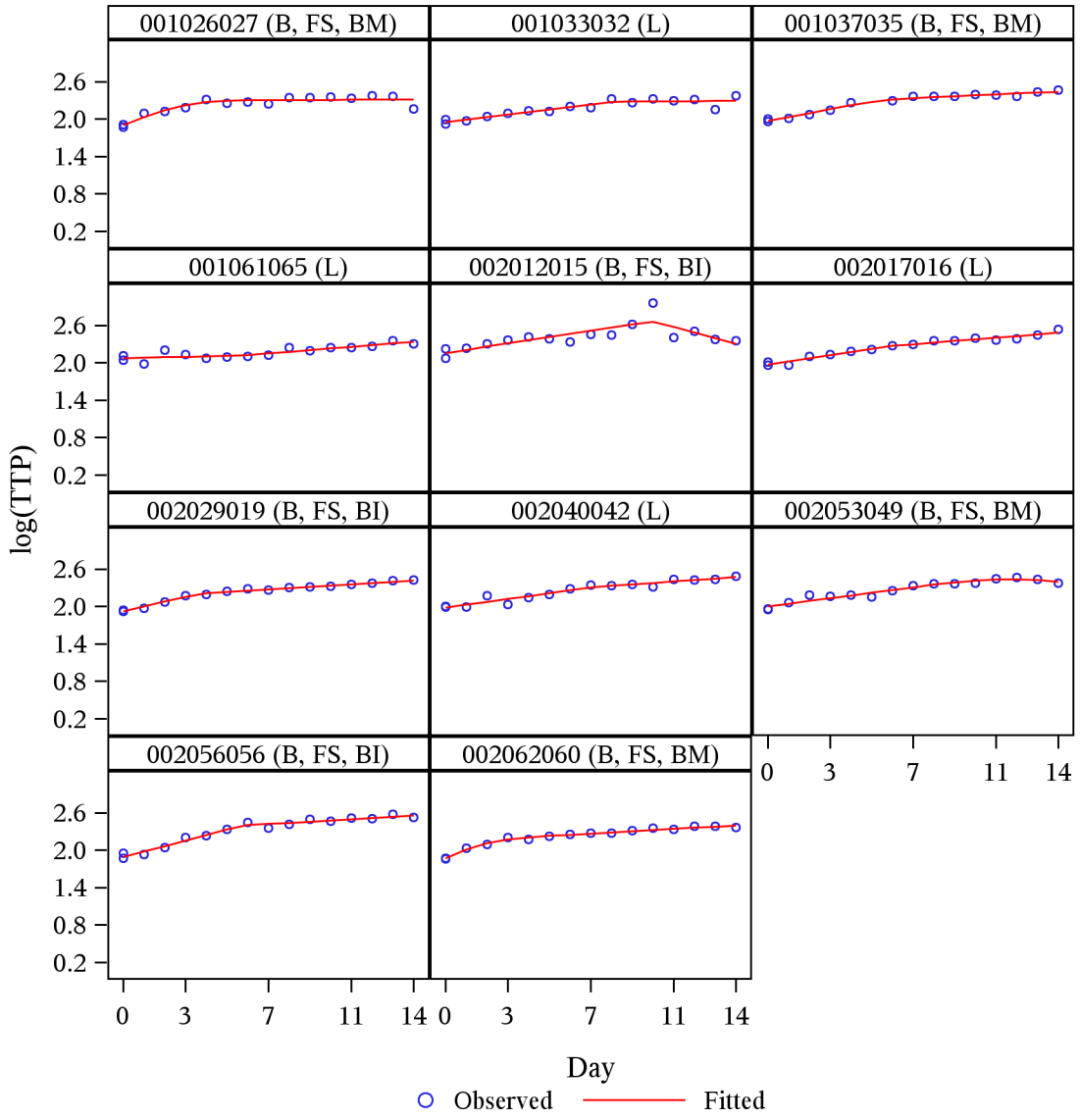


Figure C.58: Observed and Fitted log(TTP), Trial **NC001**, Treatment Group **Rifafour**

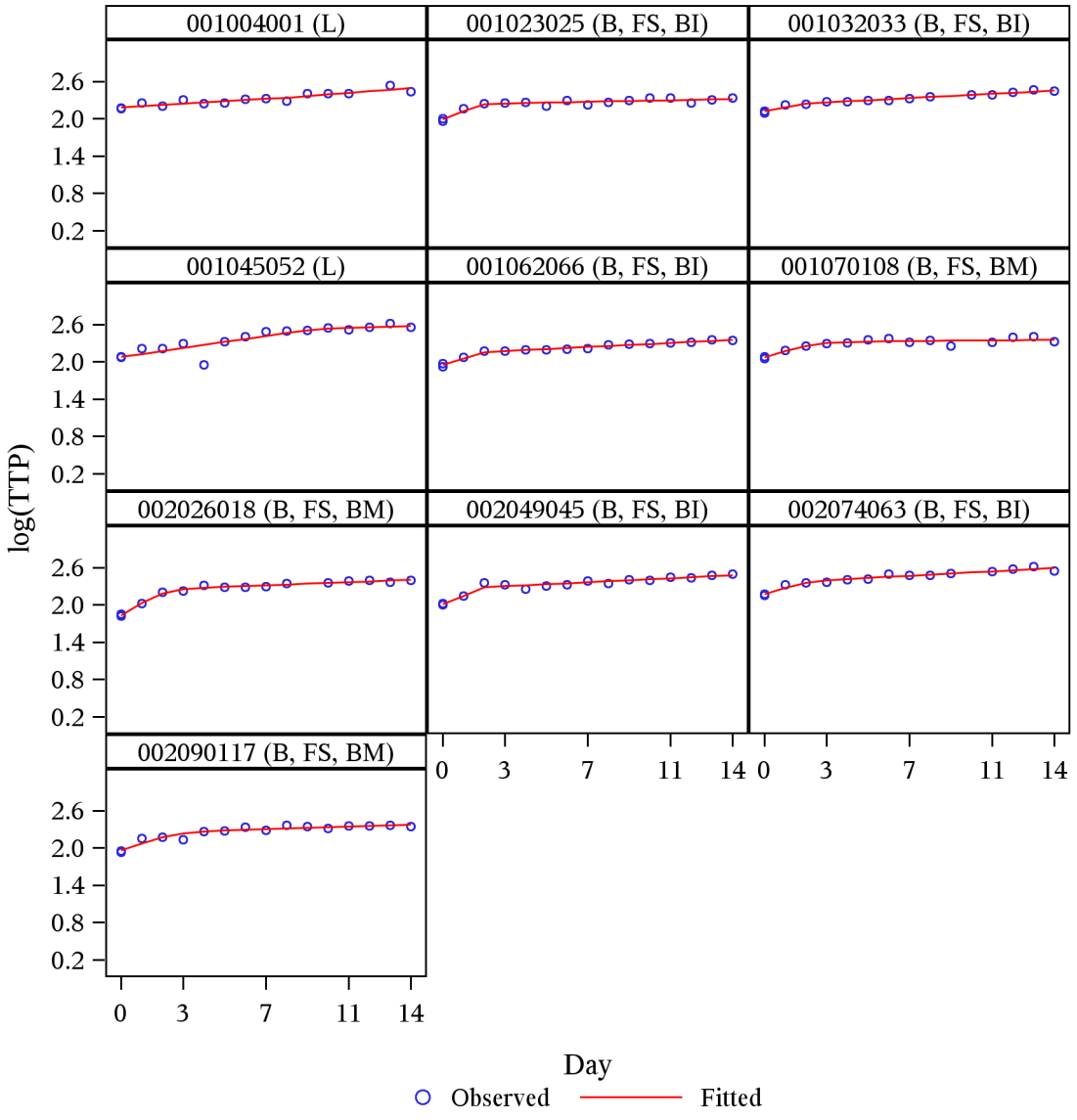


Figure C.59: Observed and Fitted log(TTP), Trial **NC002 (EBA)**, Treatment Group **M-PA100-Z**

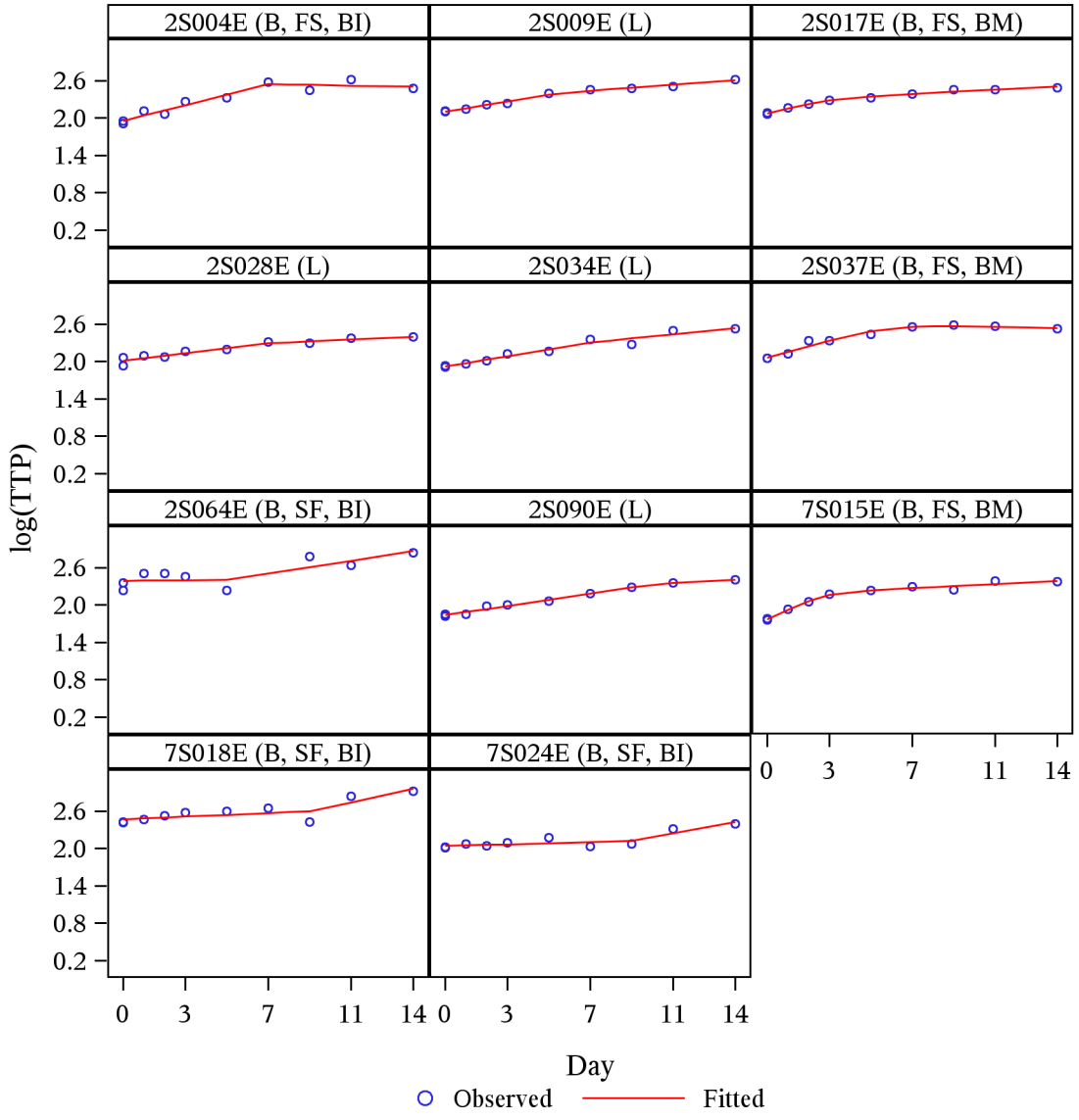


Figure C.60: Observed and Fitted log(TTP), Trial **NC002 (EBA)**, Treatment Group **M-PA200-Z**

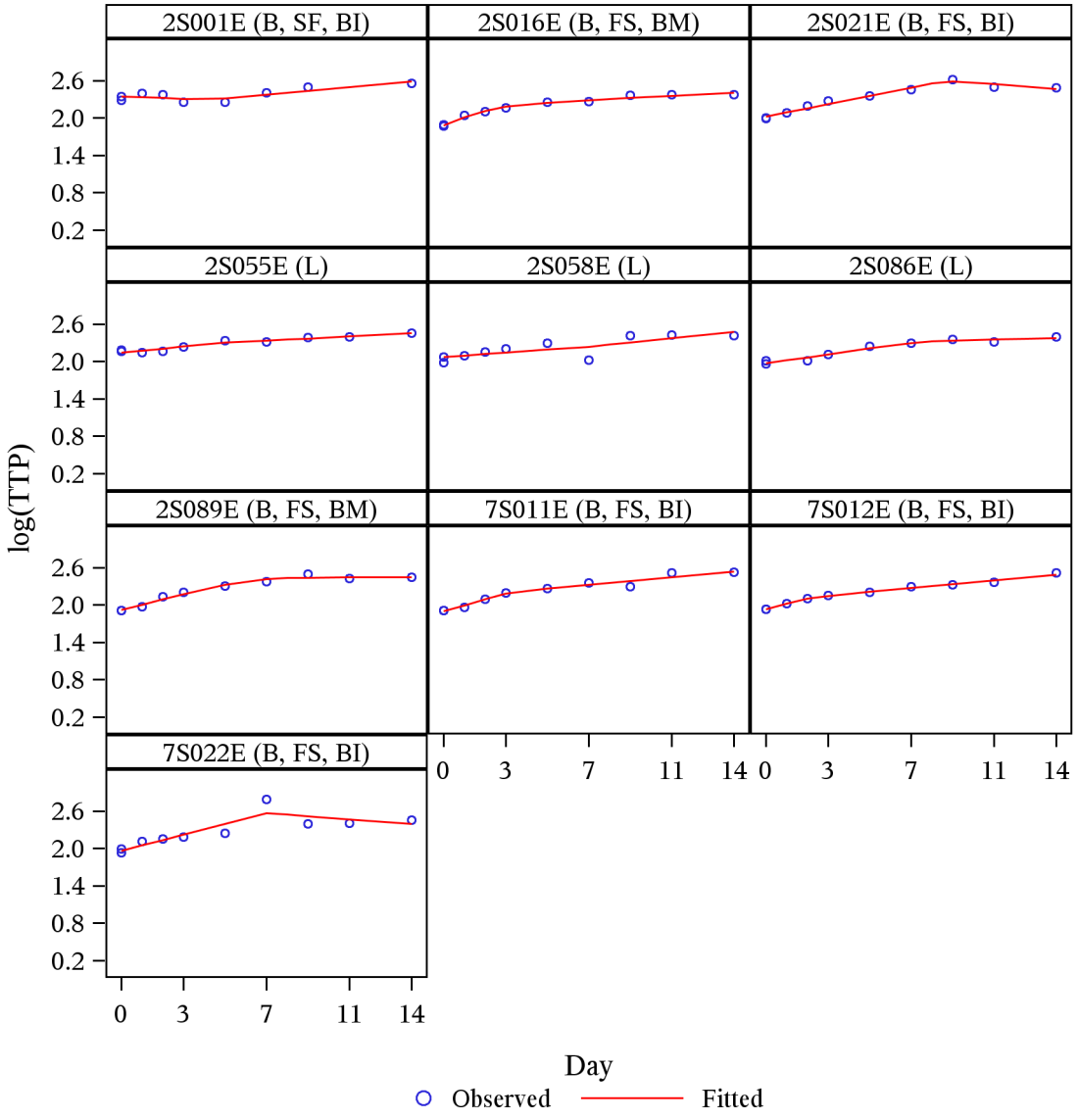


Figure C.61: Observed and Fitted log(TTP), Trial **NC002 (EBA)**, Treatment Group **M-PA200-Z-MDR**

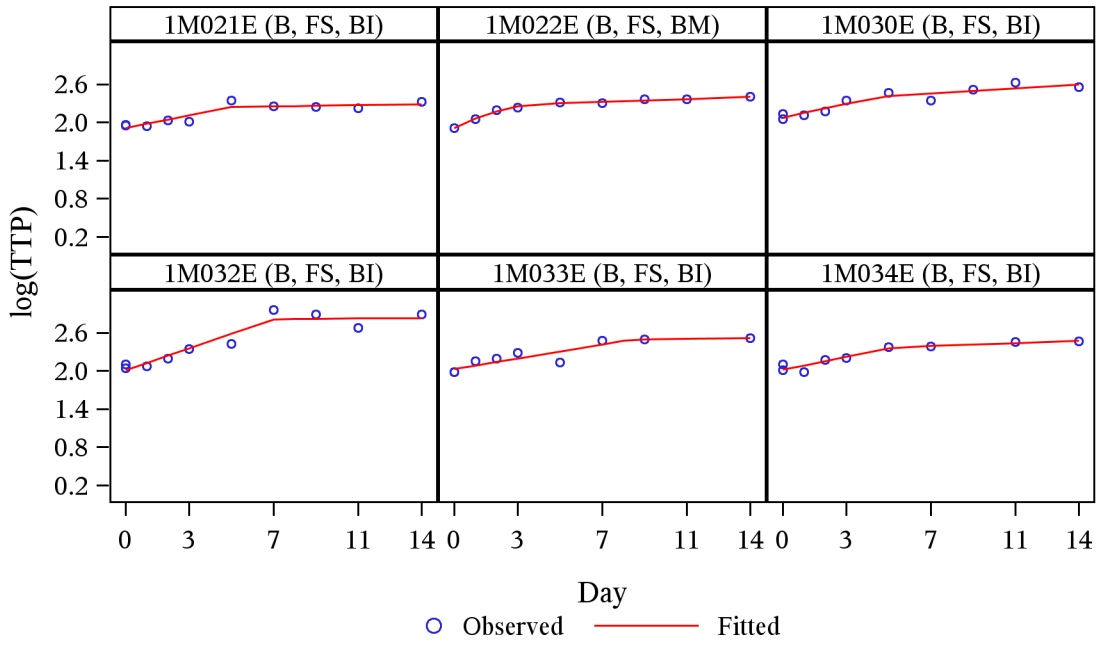


Figure C.62: Observed and Fitted log(TTP), Trial **NC002 (EBA)**, Treatment Group **Rifafour**

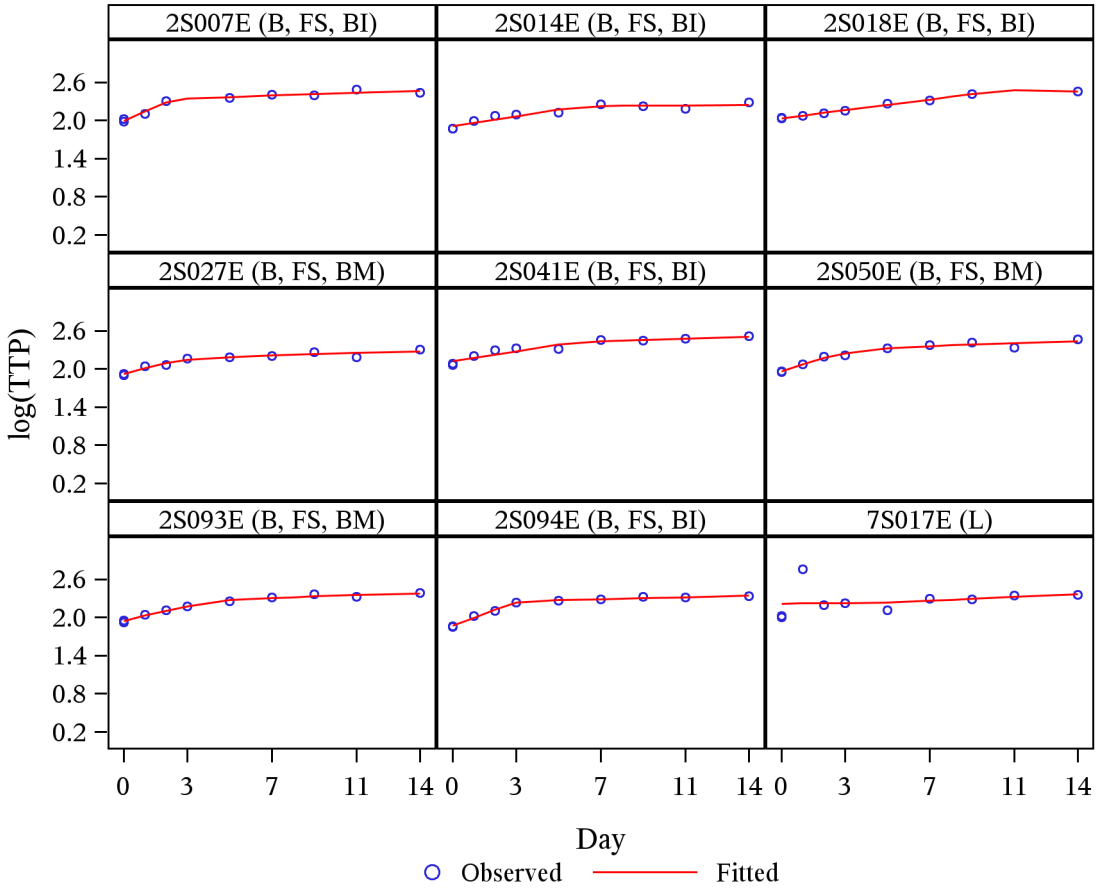


Figure C.63: Observed and Fitted log(TTP), Trial **NC002 ("SSCC")**, Treatment Group **M-PA100-Z**

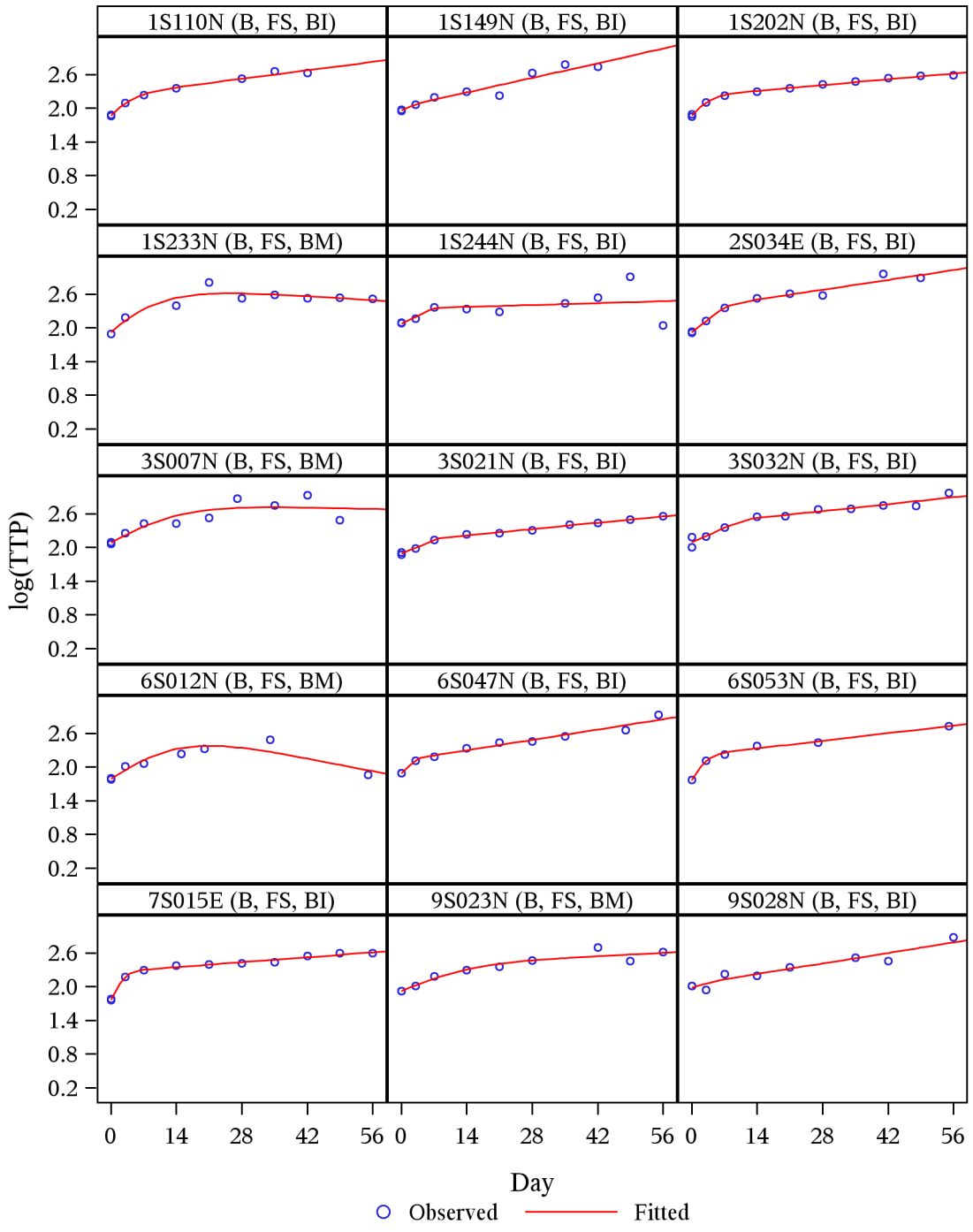


Figure C.64: Observed and Fitted log(TTP), Trial **NC002 ("SSCC")**, Treatment Group **M-PA200-Z**

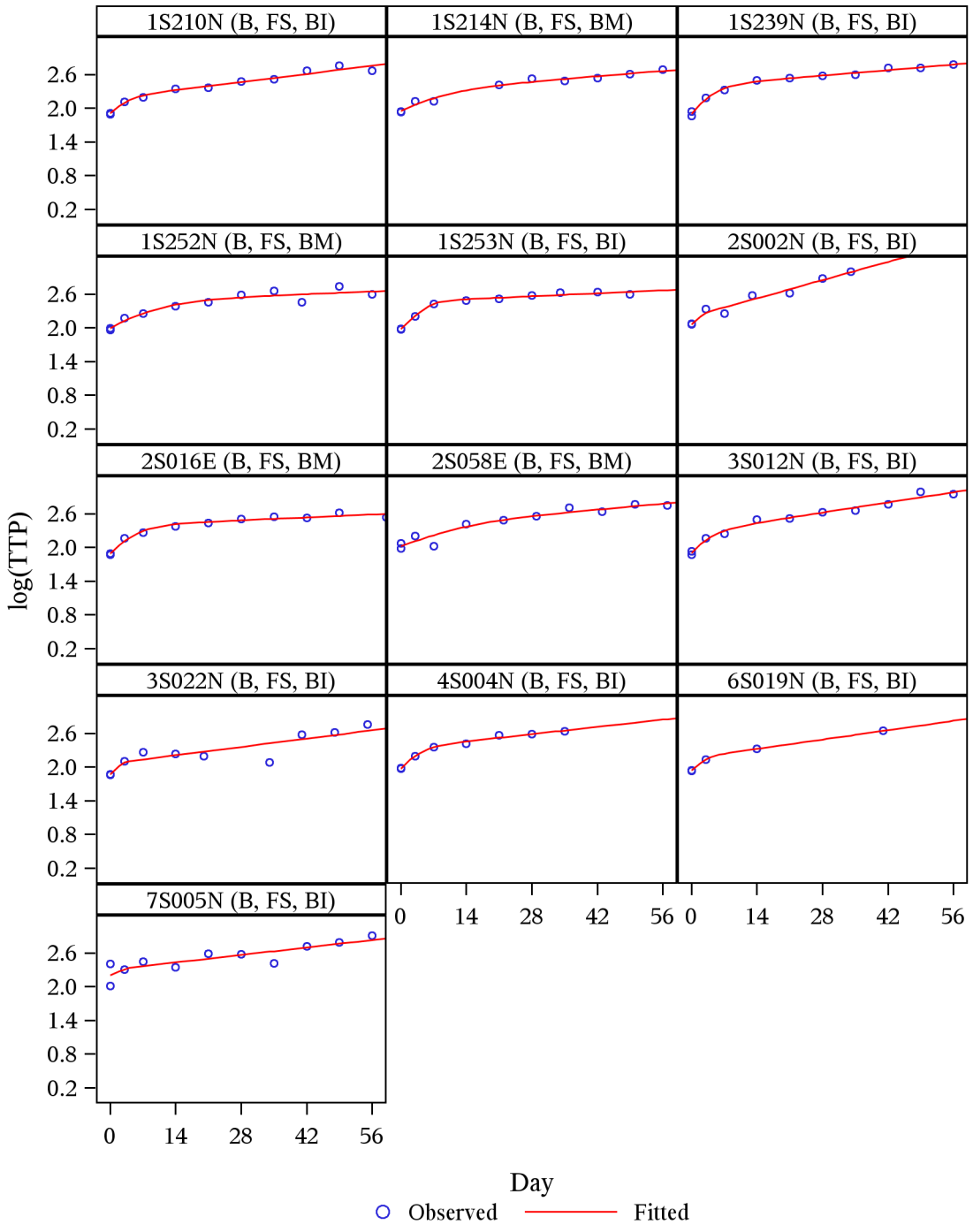


Figure C.65: Observed and Fitted log(TTP), Trial **NC002 ("SSCC")**, Treatment Group **M-PA200-Z-MDR**

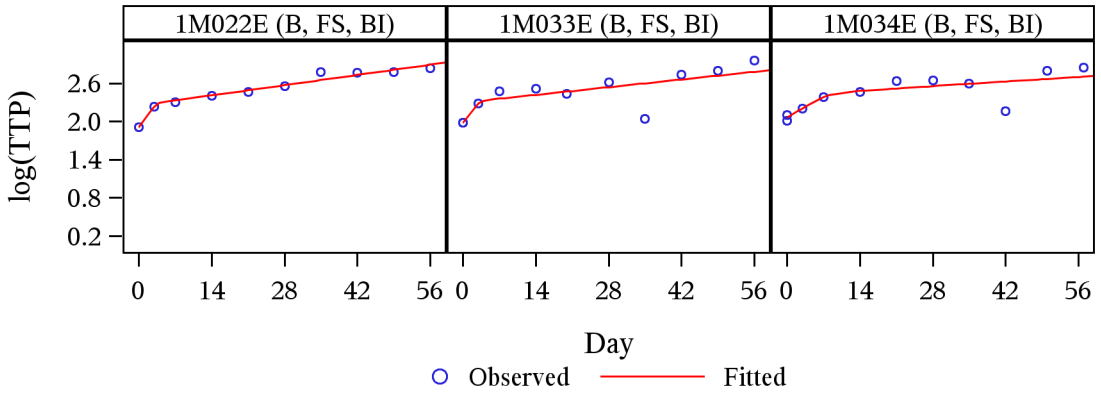


Figure C.66: Observed and Fitted log(TTP), Trial **NC002 ("SSCC")**, Treatment Group **Rifafour**

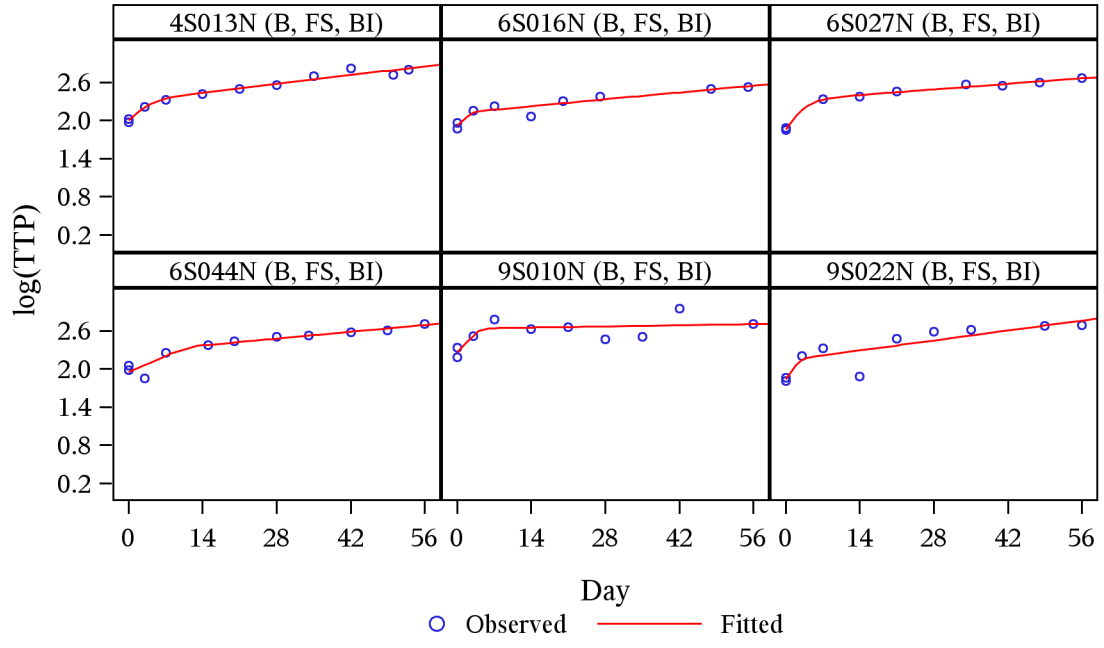


Figure C.67: Observed and Fitted log(TTP), Trial **NC002 ("SSCC")**, Treatment Group **Rifafour**

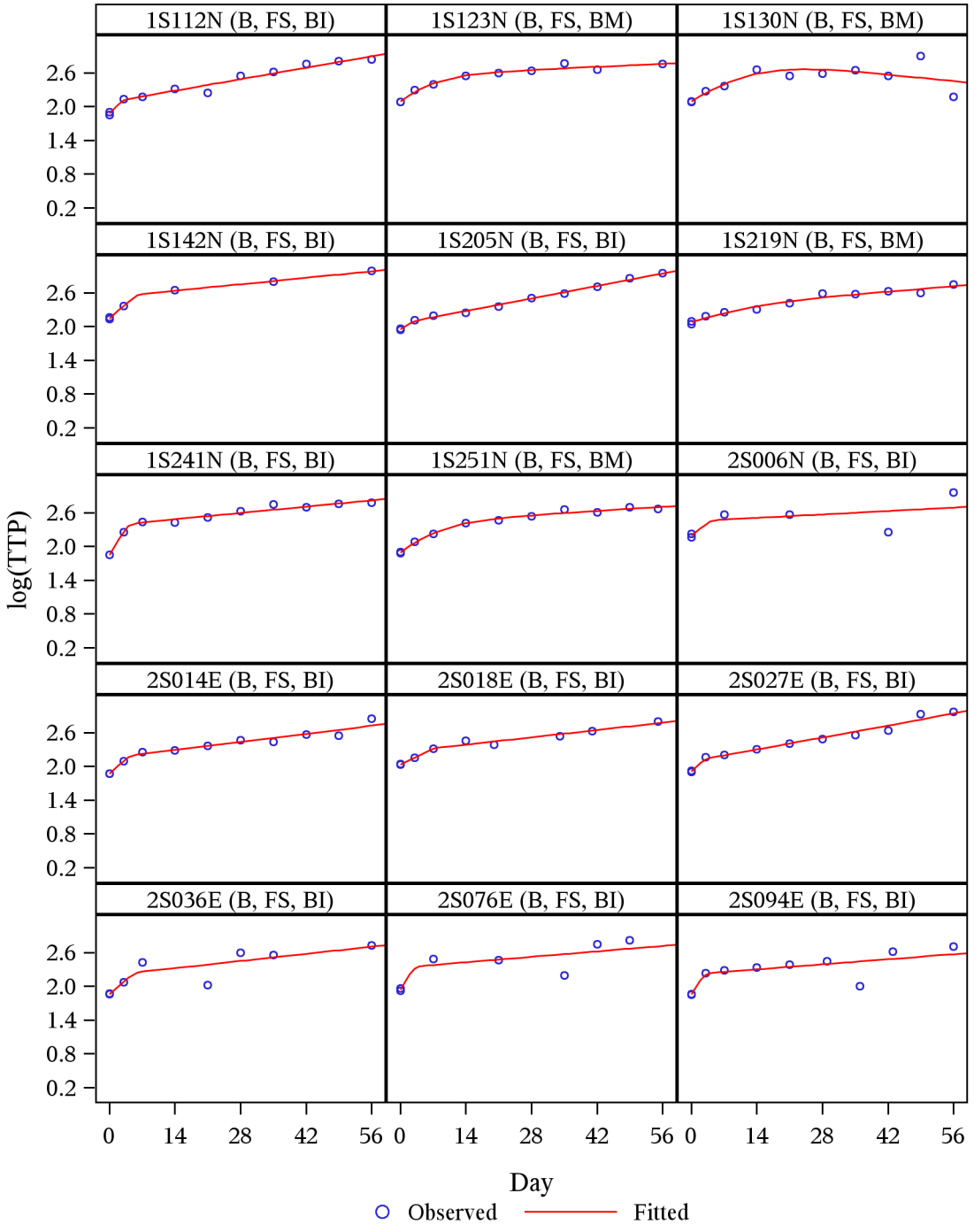


Figure C.68: Observed and Fitted log(TTP), Trial **NC003**, Treatment Group **J-Pa-Z-C**

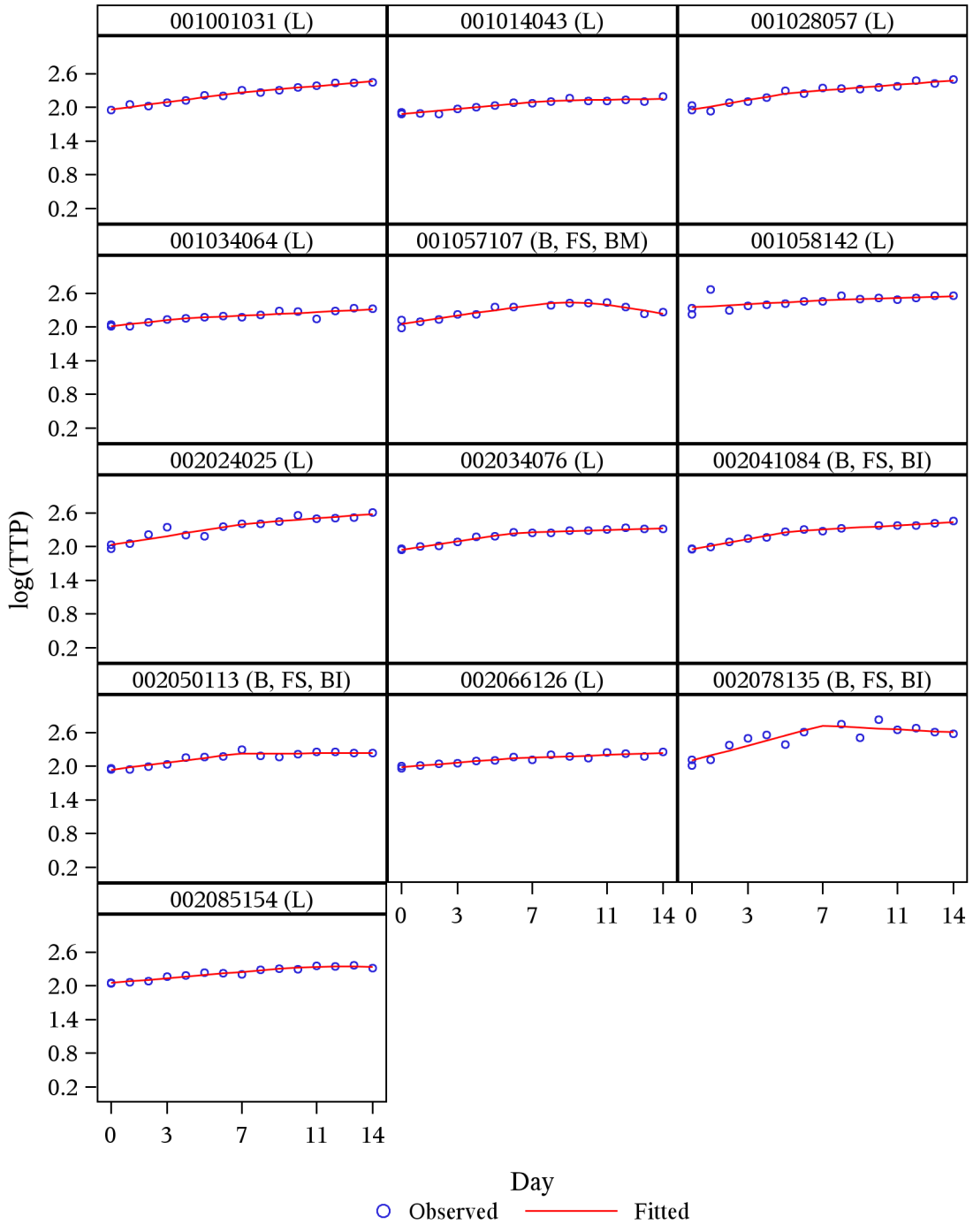


Figure C.69: Observed and Fitted log(TTP), Trial **NC003**, Treatment Group **J-Pa-Z**

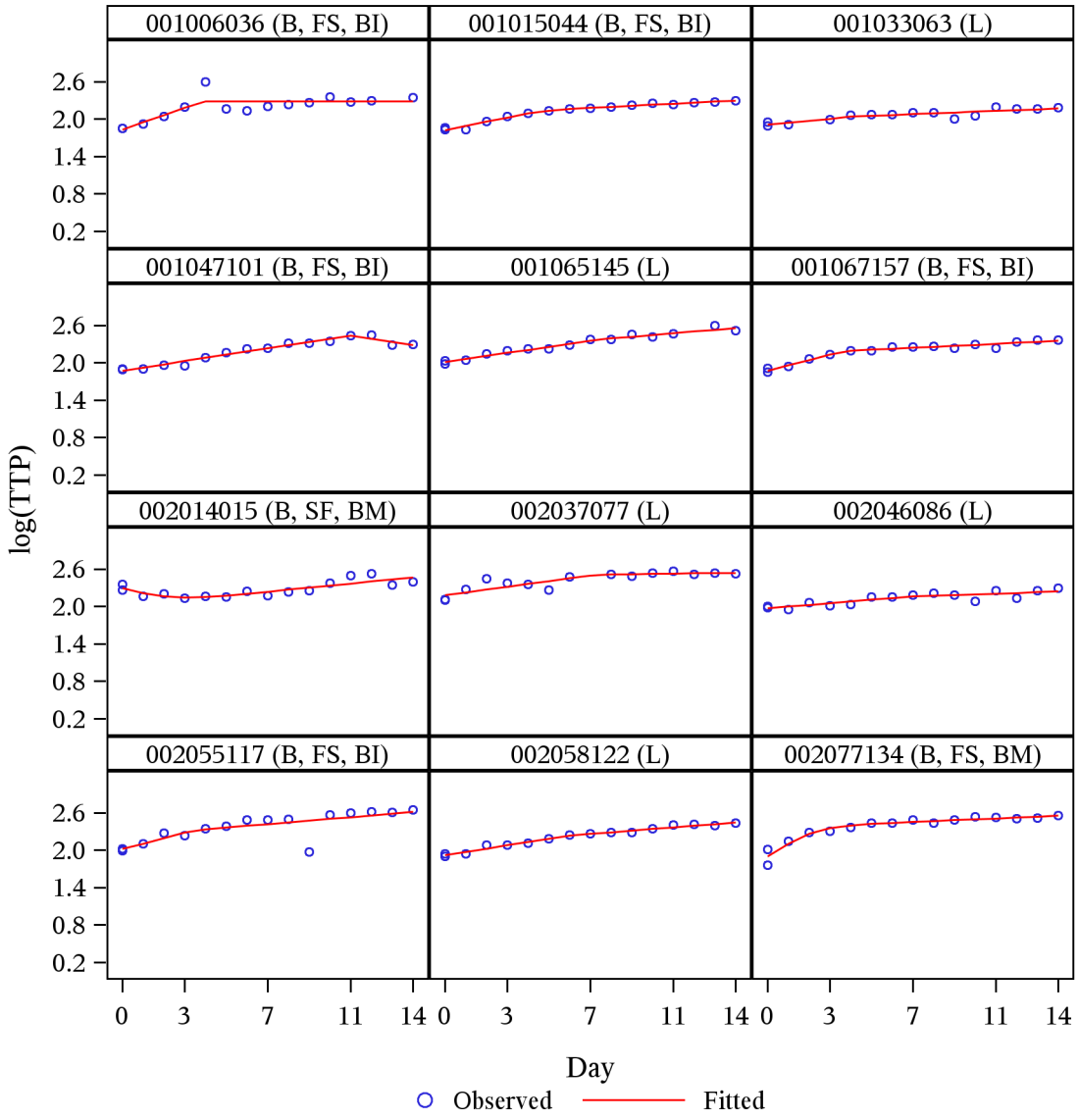


Figure C.70: Observed and Fitted log(TTP), Trial **NC003**, Treatment Group **J-Pa-C**

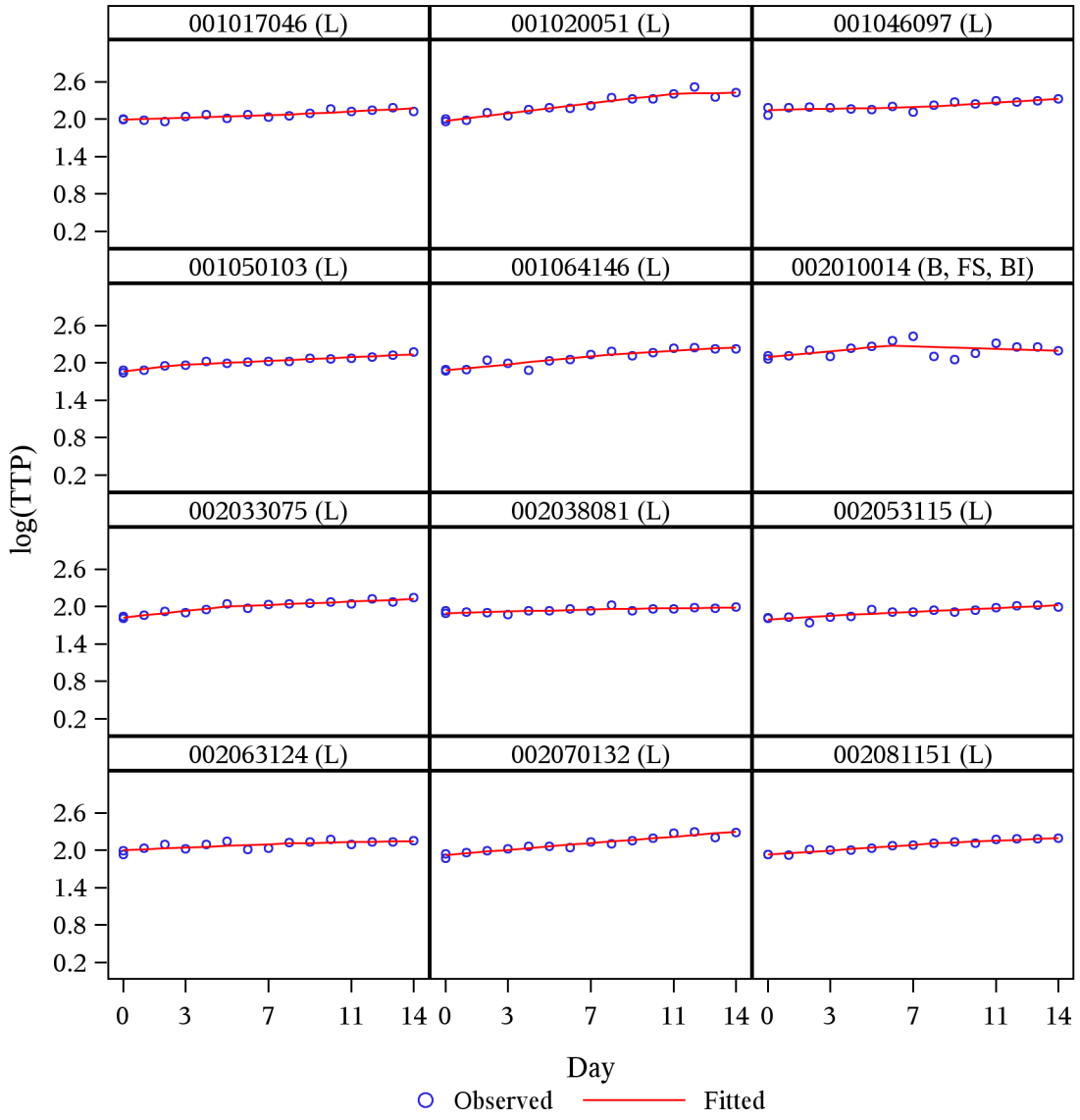


Figure C.71: Observed and Fitted log(TTP), Trial **NC003**, Treatment Group **J-Z-C**

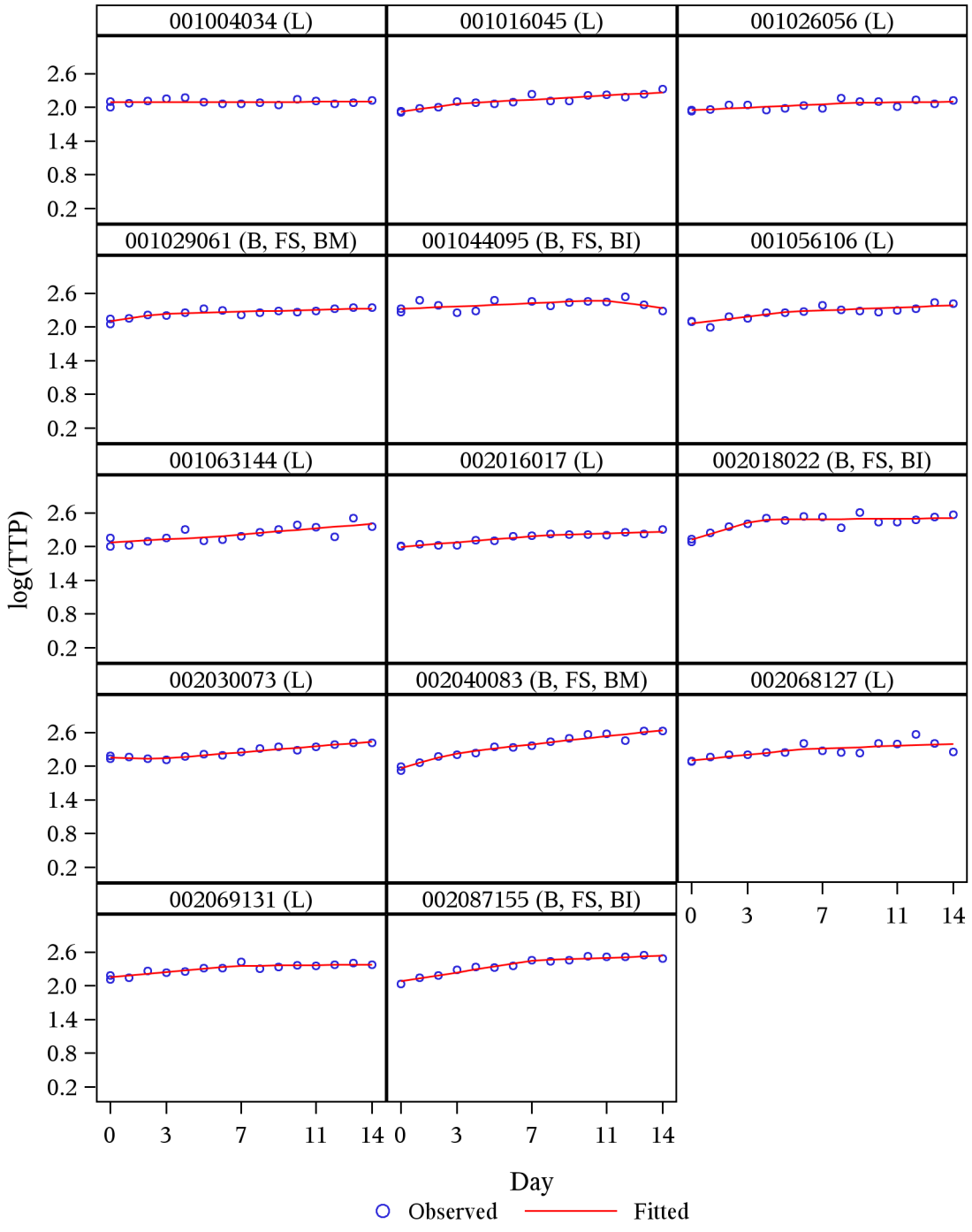


Figure C.72: Observed and Fitted log(TTP), Trial **NC003**, Treatment Group **Z**

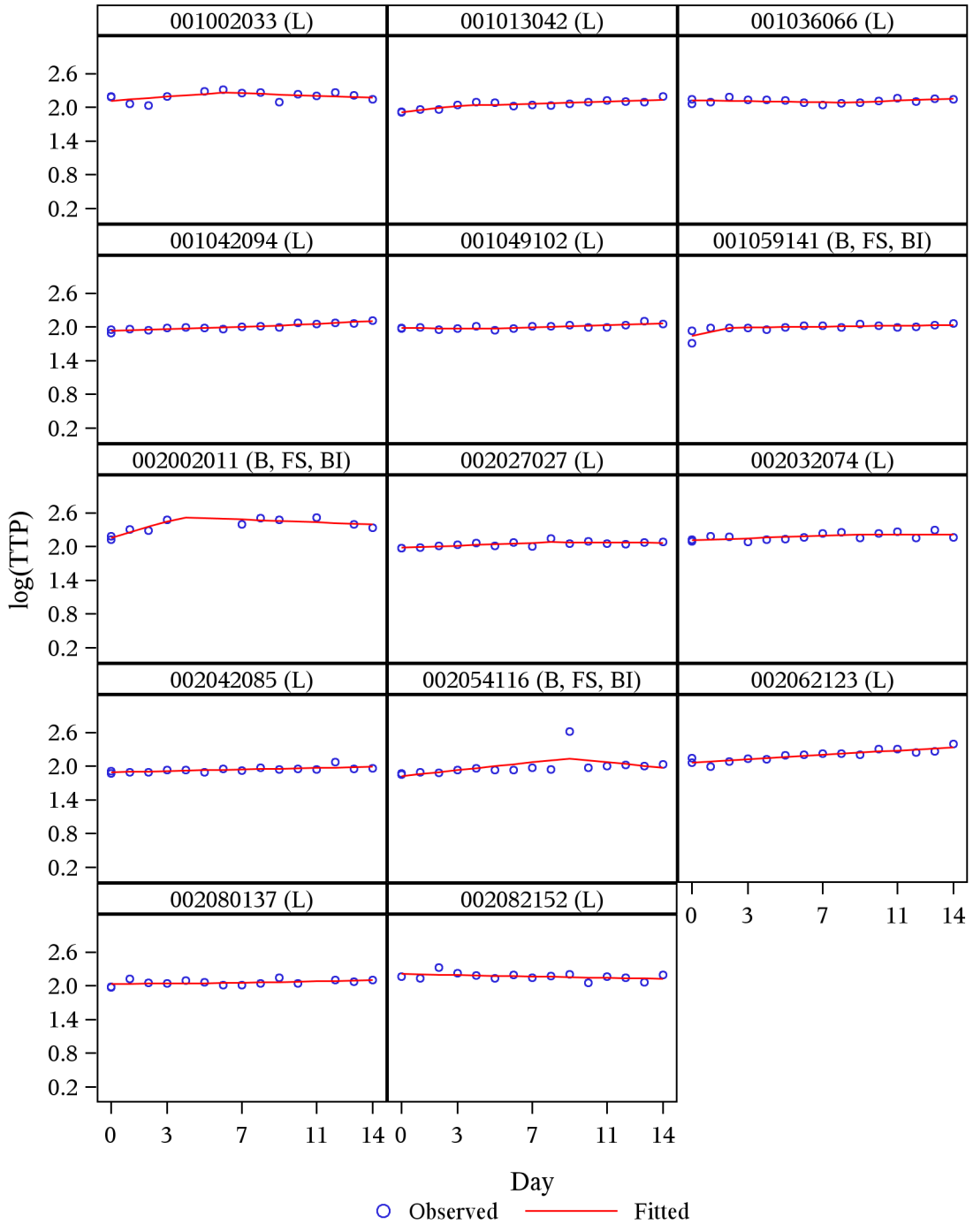


Figure C.73: Observed and Fitted log(TTP), Trial **NC003**, Treatment Group **C**

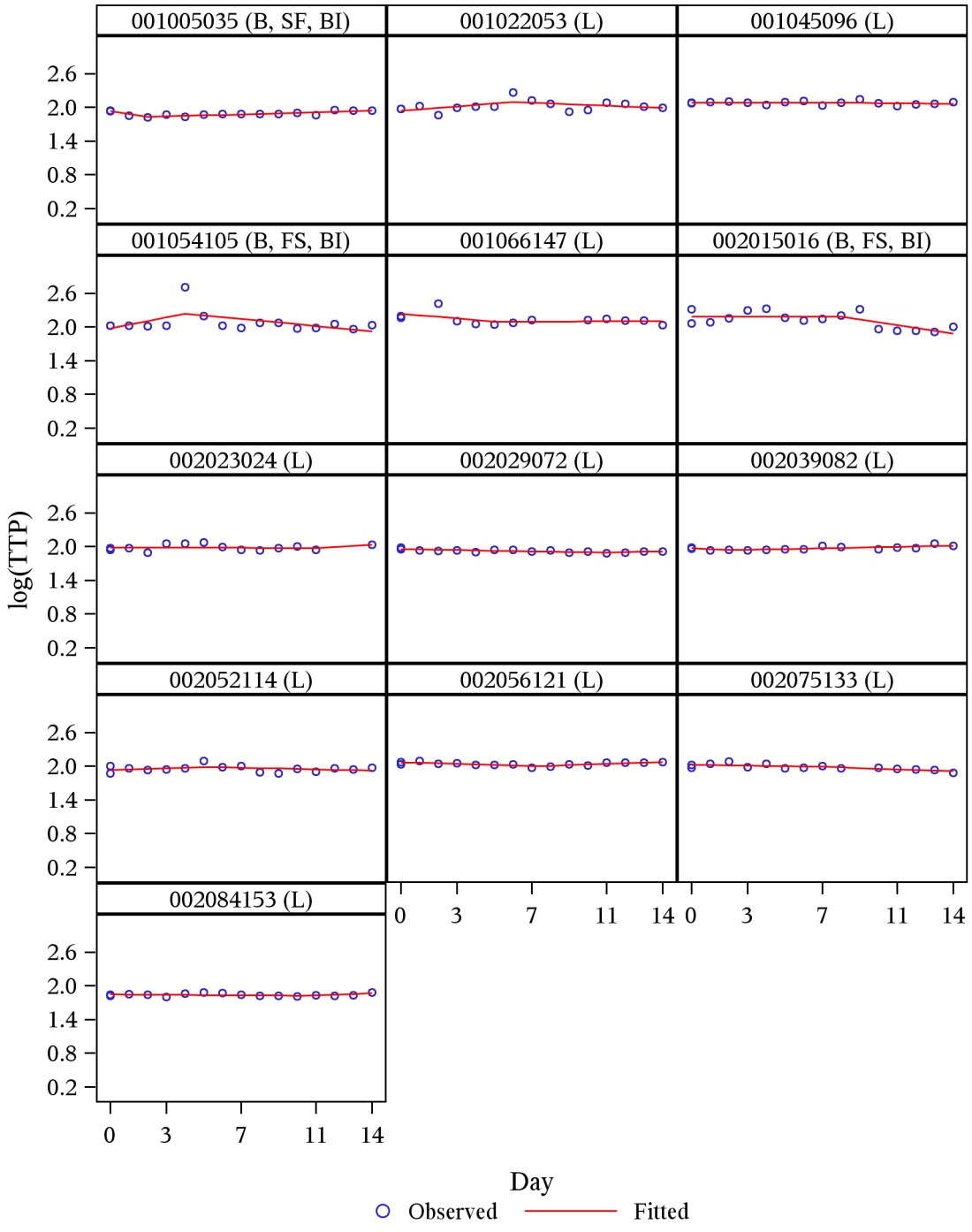
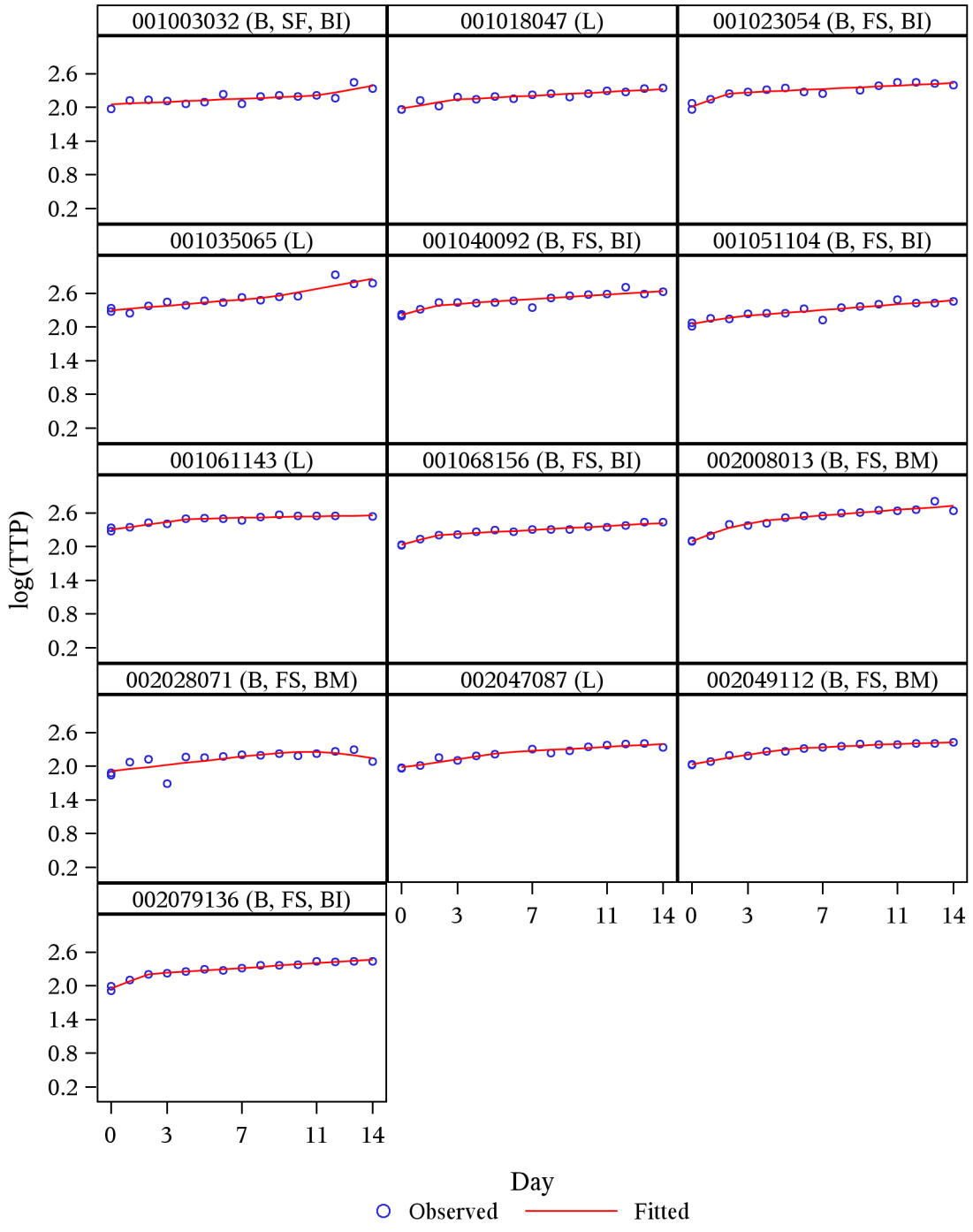


Figure C.74: Observed and Fitted log(TTP), Trial **NC003**, Treatment Group **Rifafour**



Appendix D

Profile Plots

D.1 Colony Forming Unit Count

D.1.1 NC001 Trial

Figure D.1: Observed and Fitted log(CFU) Count, Treatment Group **J**

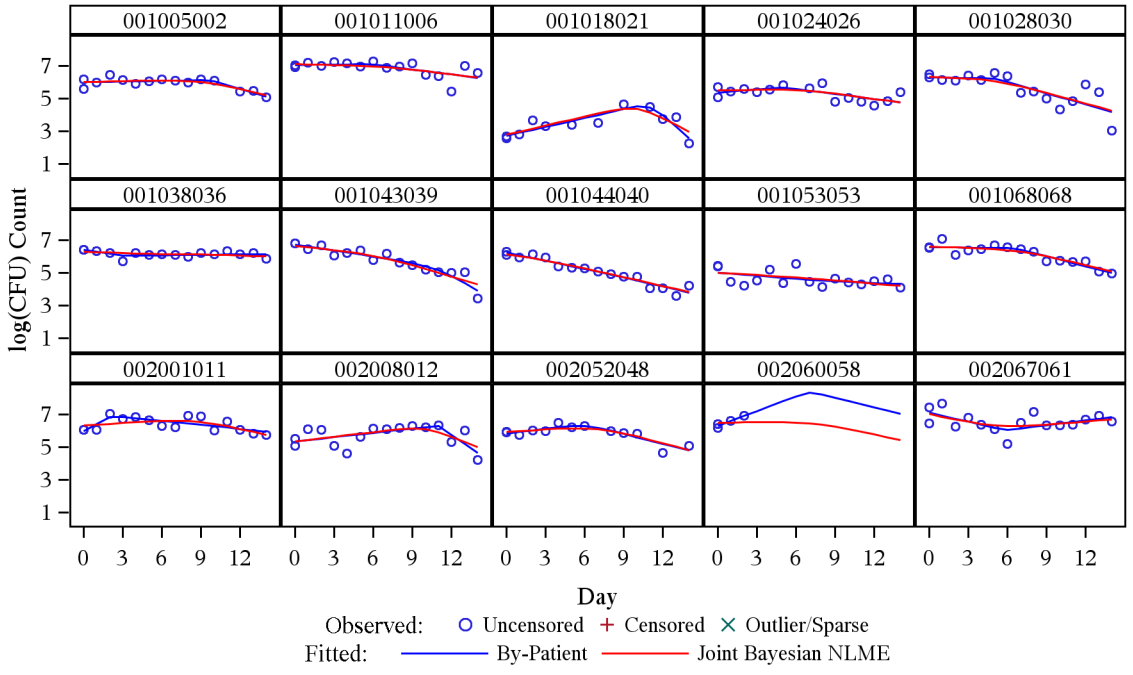


Figure D.2: Observed and Fitted log(CFU) Count, Treatment Group **J-Z**

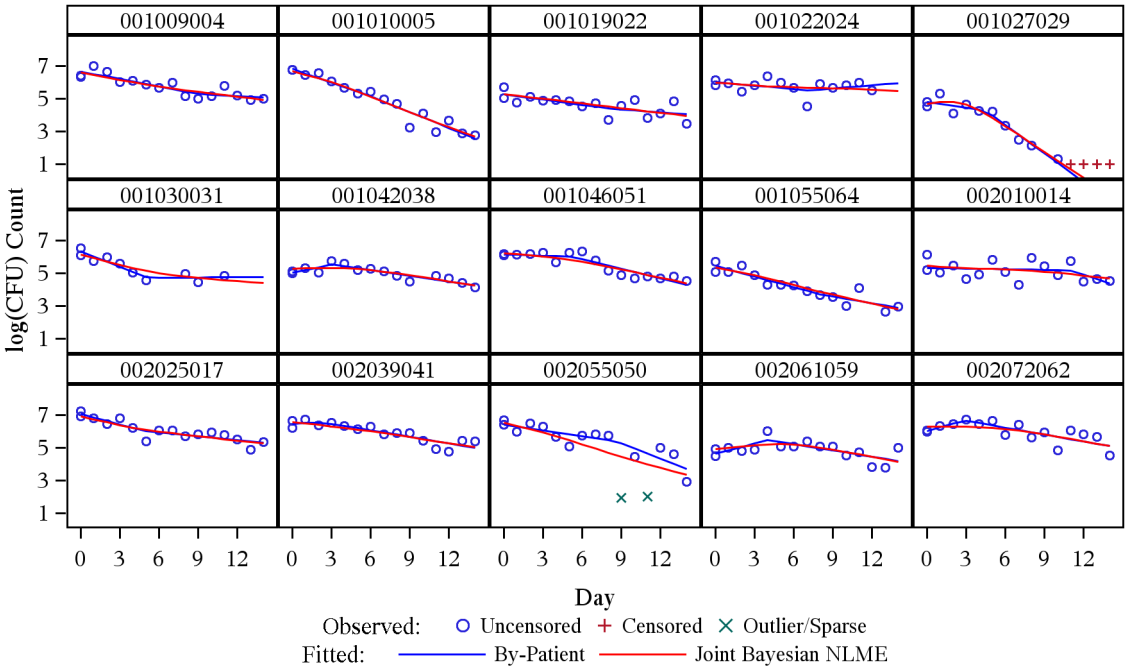


Figure D.3: Observed and Fitted log(CFU) Count, Treatment Group **J-Pa**

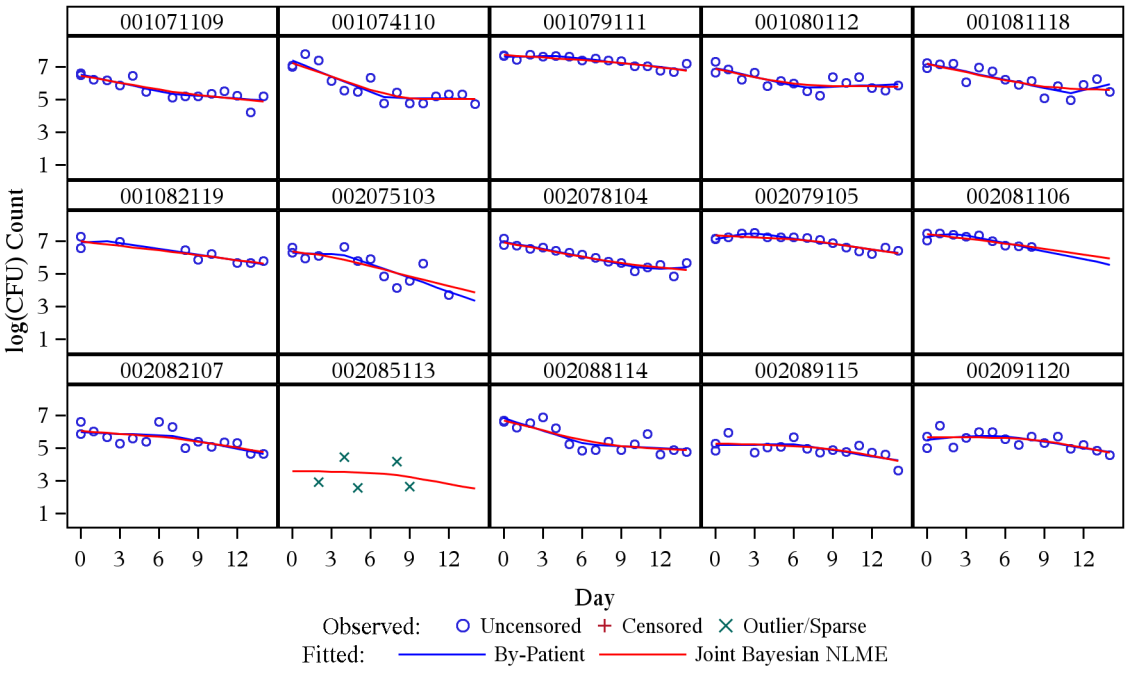


Figure D.4: Observed and Fitted log(CFU) Count, Treatment Group **Pa-Z**

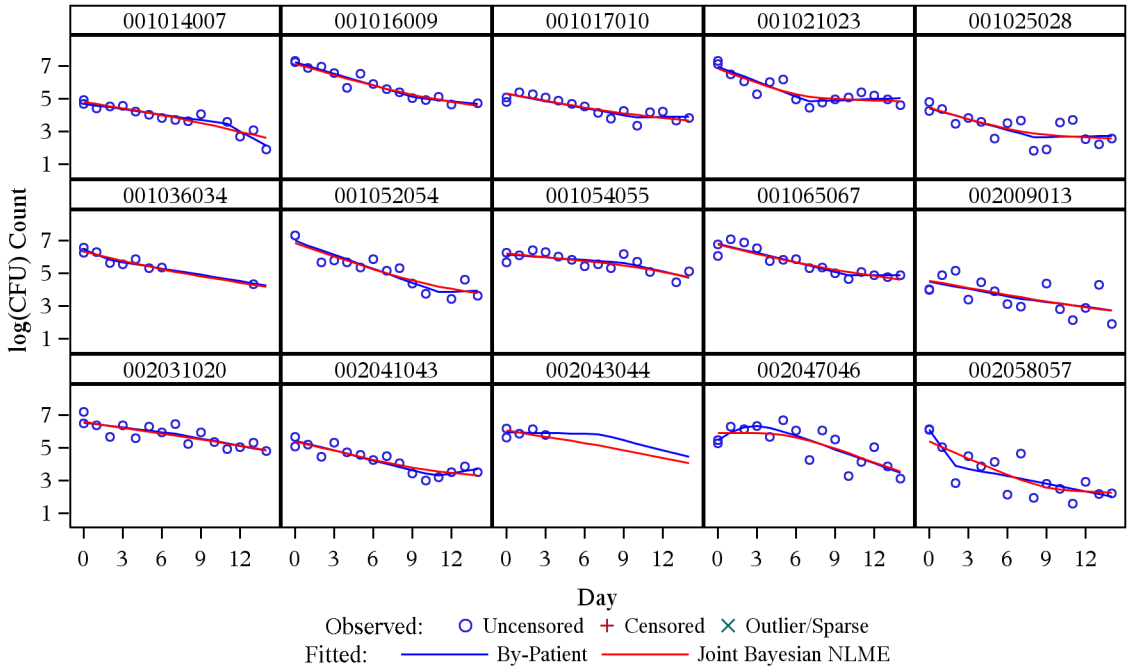


Figure D.5: Observed and Fitted log(CFU) Count, Treatment Group **Pa-Z-M**

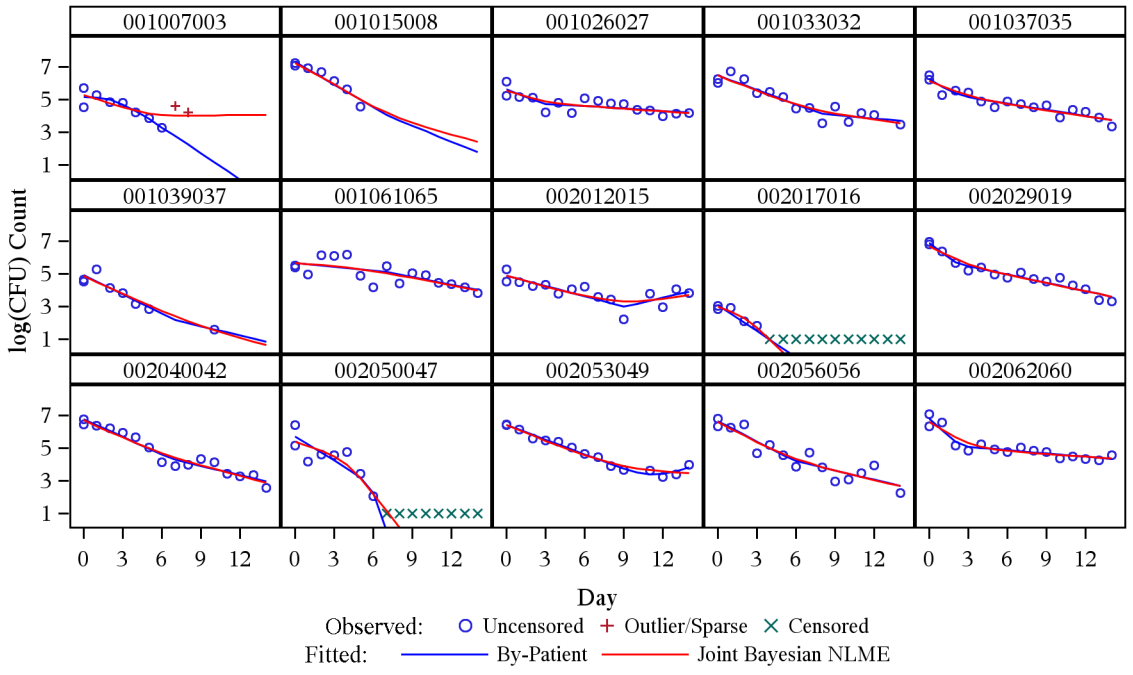
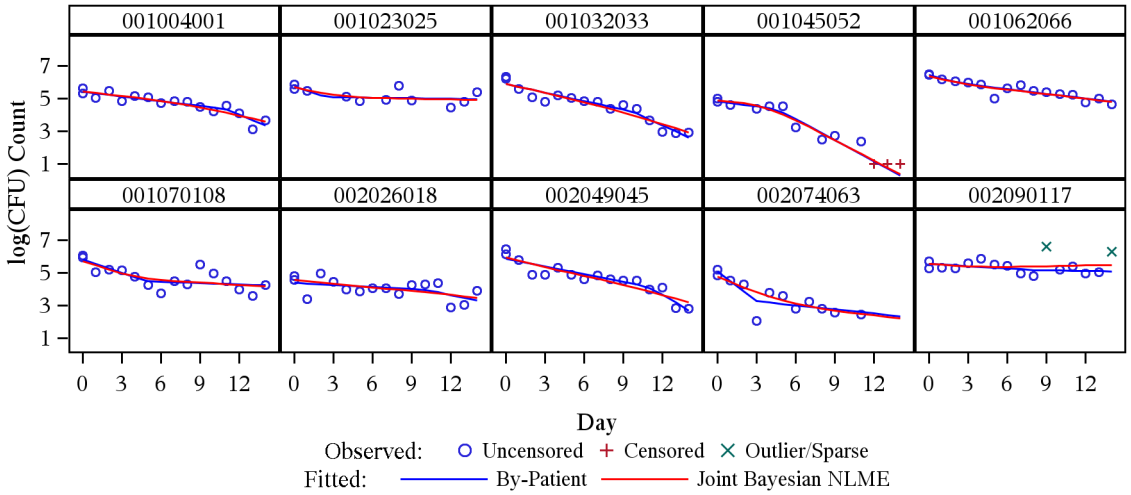


Figure D.6: Observed and Fitted log(CFU) Count, Treatment Group **Rifafour**



D.1.2 NC003 Trial

Figure D.7: Observed and Fitted log(CFU) Count, Treatment Group **J-Pa-Z-C**

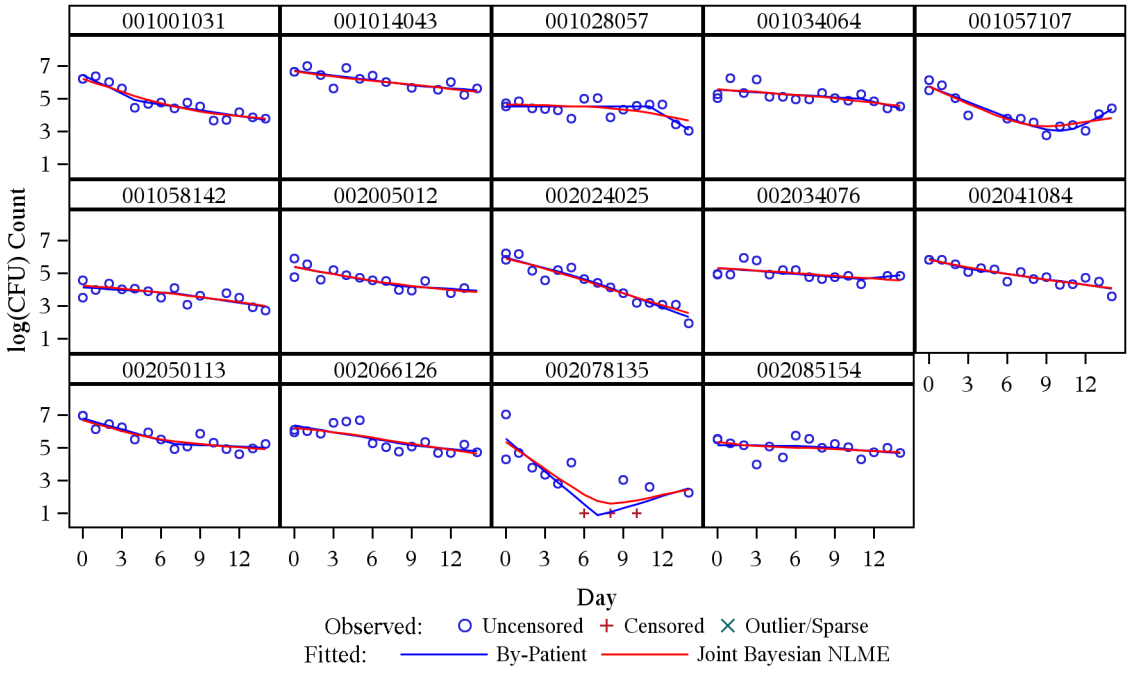


Figure D.8: Observed and Fitted log(CFU) Count, Treatment Group **J-Pa-Z**

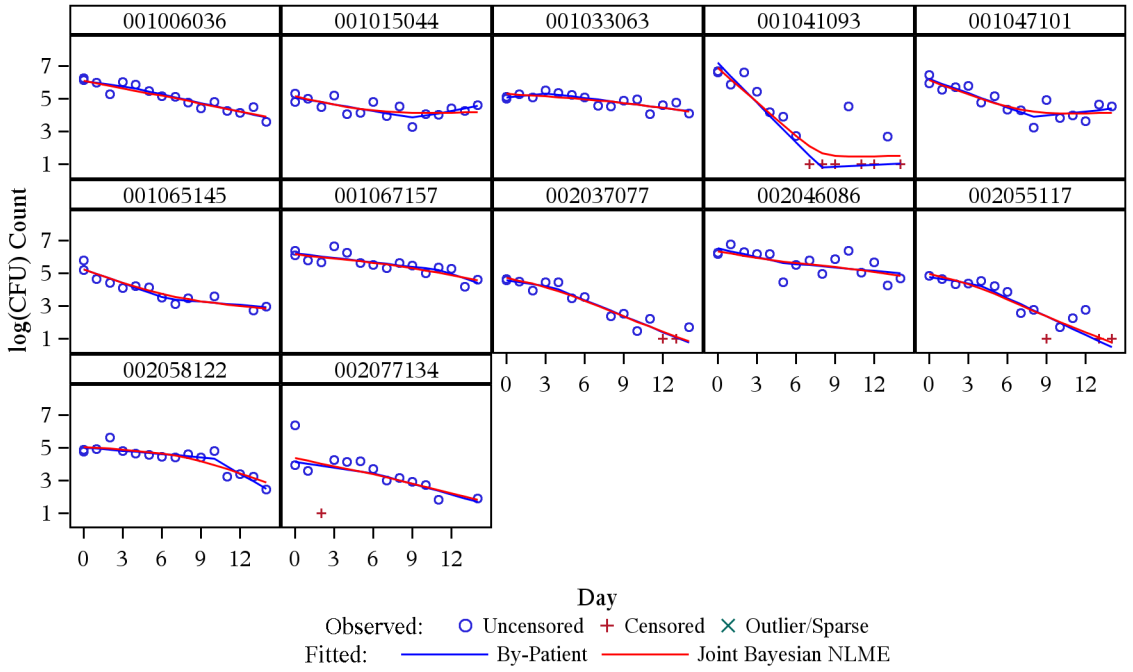


Figure D.9: Observed and Fitted log(CFU) Count, Treatment Group **J-Pa-C**

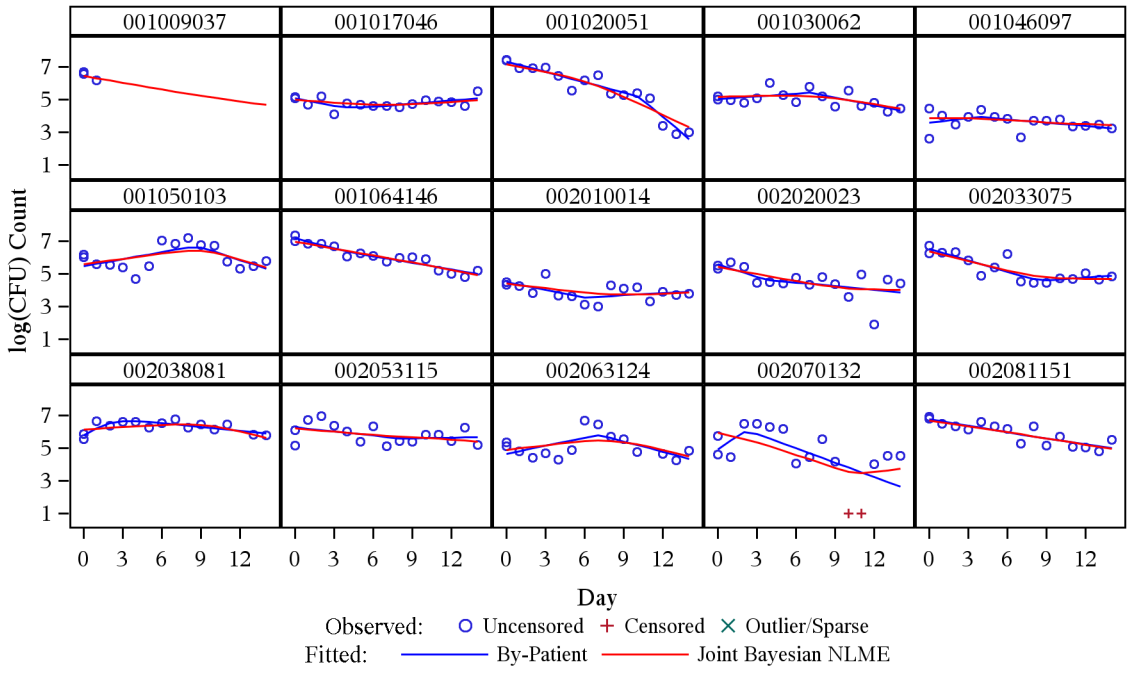


Figure D.10: Observed and Fitted log(CFU) Count, Treatment Group **J-Z-C**

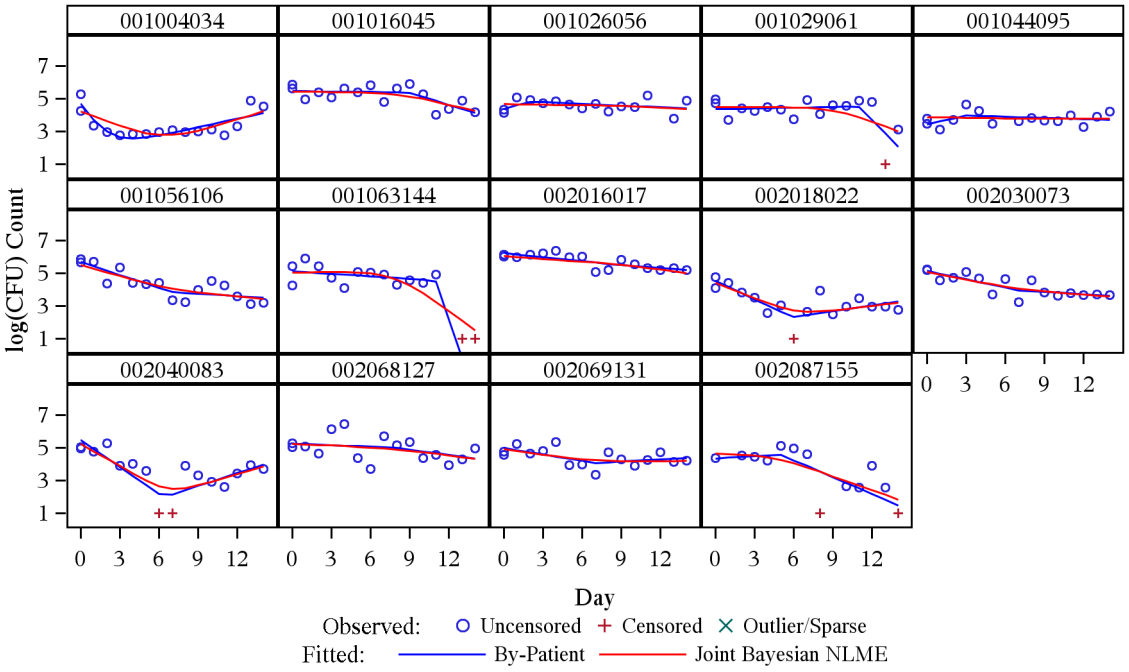


Figure D.11: Observed and Fitted log(CFU) Count, Treatment Group **Z**

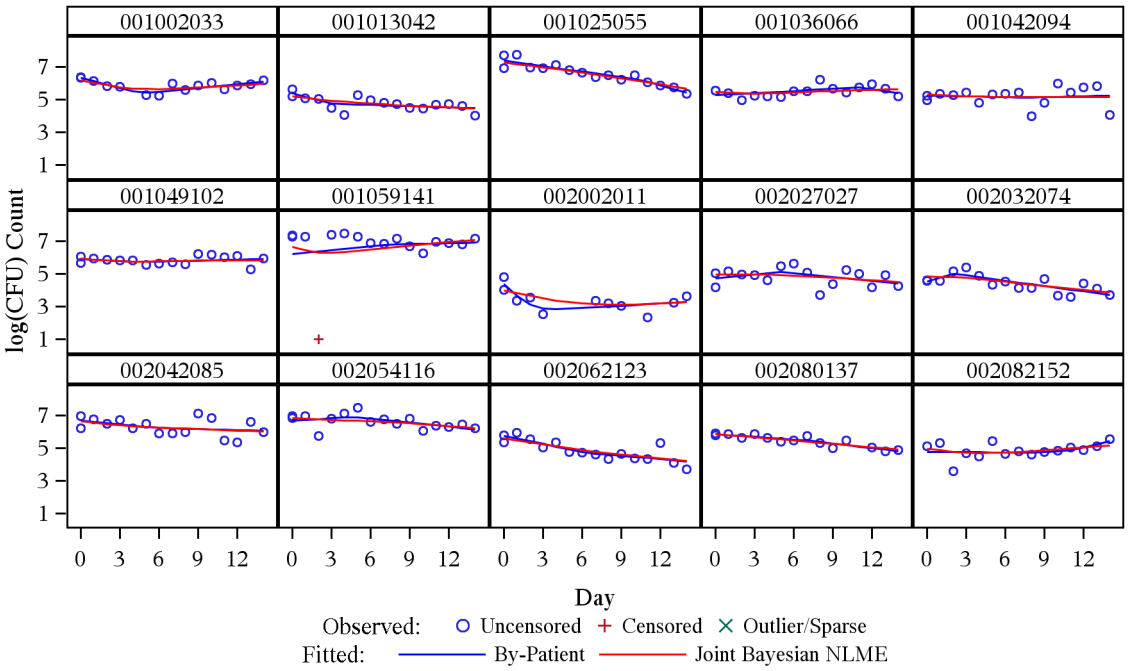


Figure D.12: Observed and Fitted log(CFU) Count, Treatment Group **C**

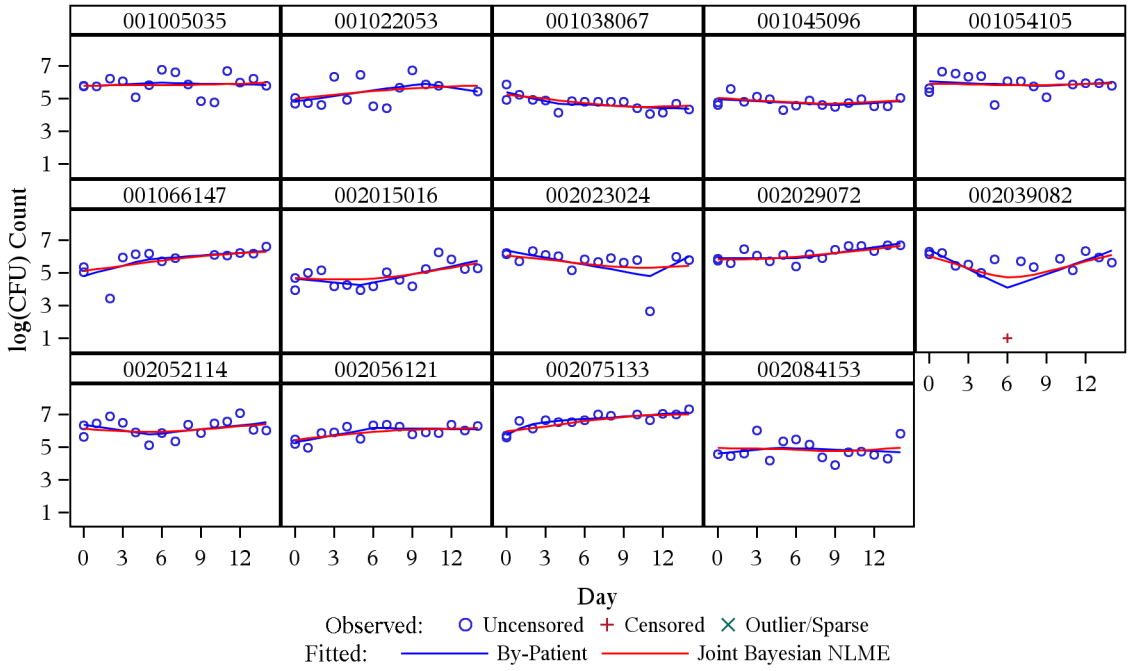
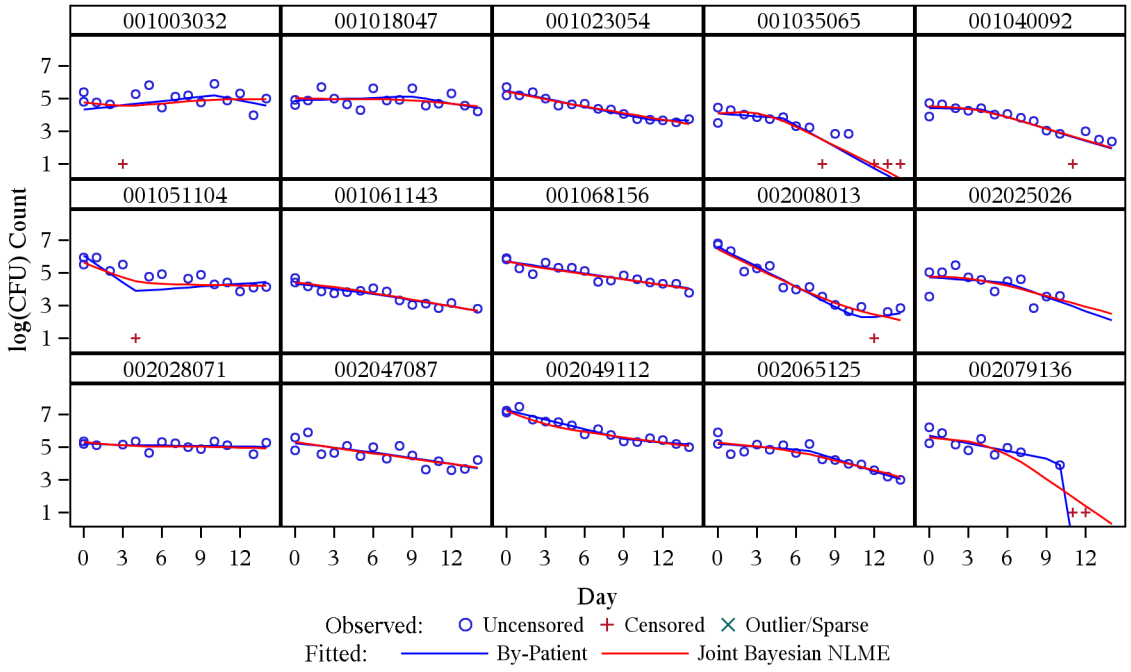


Figure D.13: Observed and Fitted log(CFU) Count, Treatment Group **Rifafour**



D.2 Time to Positivity

D.2.1 NC001 Trial

Figure D.14: Observed and Fitted log(TTP), Treatment Group **J**

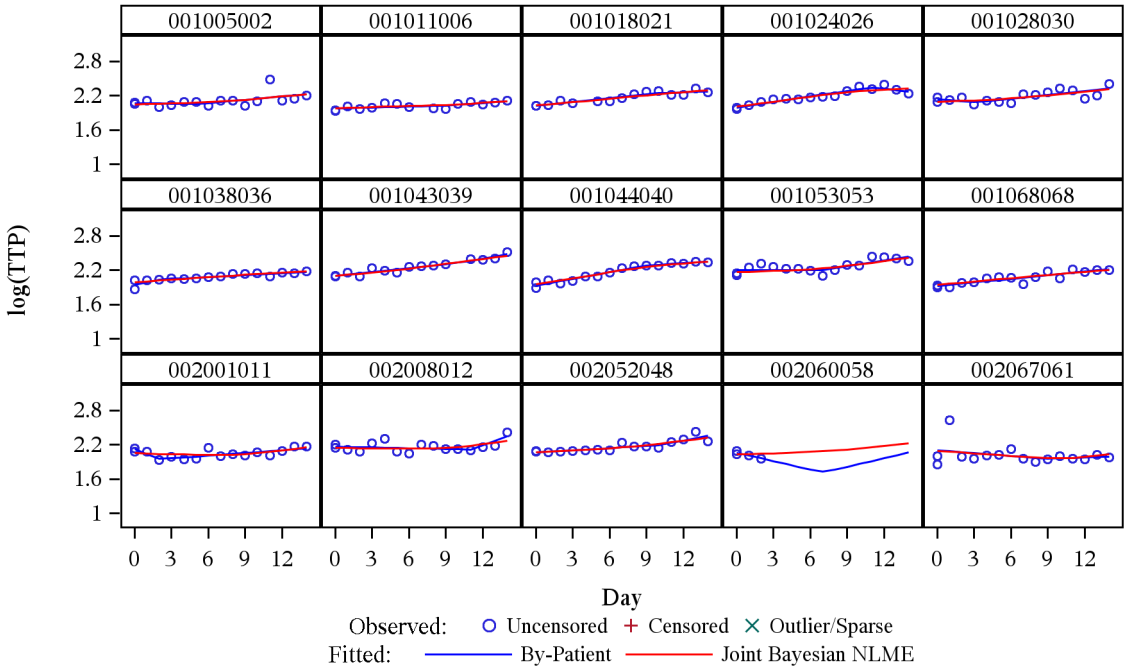


Figure D.15: Observed and Fitted log(TTP), Treatment Group **J-Z**

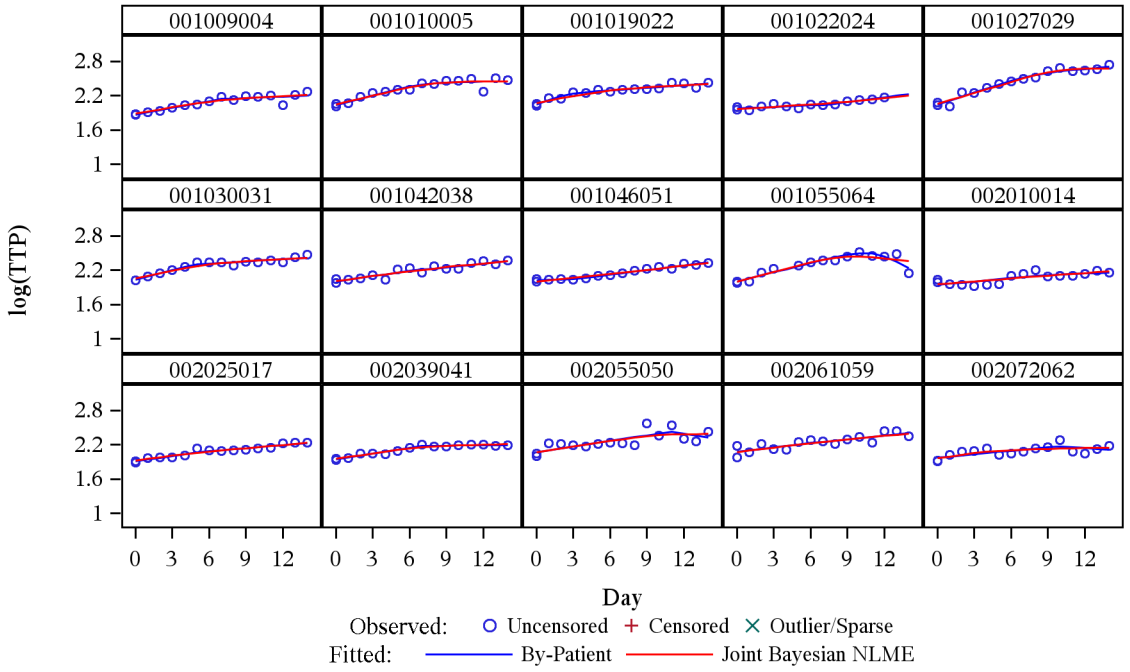


Figure D.16: Observed and Fitted log(TTP), Treatment Group **J-Pa**

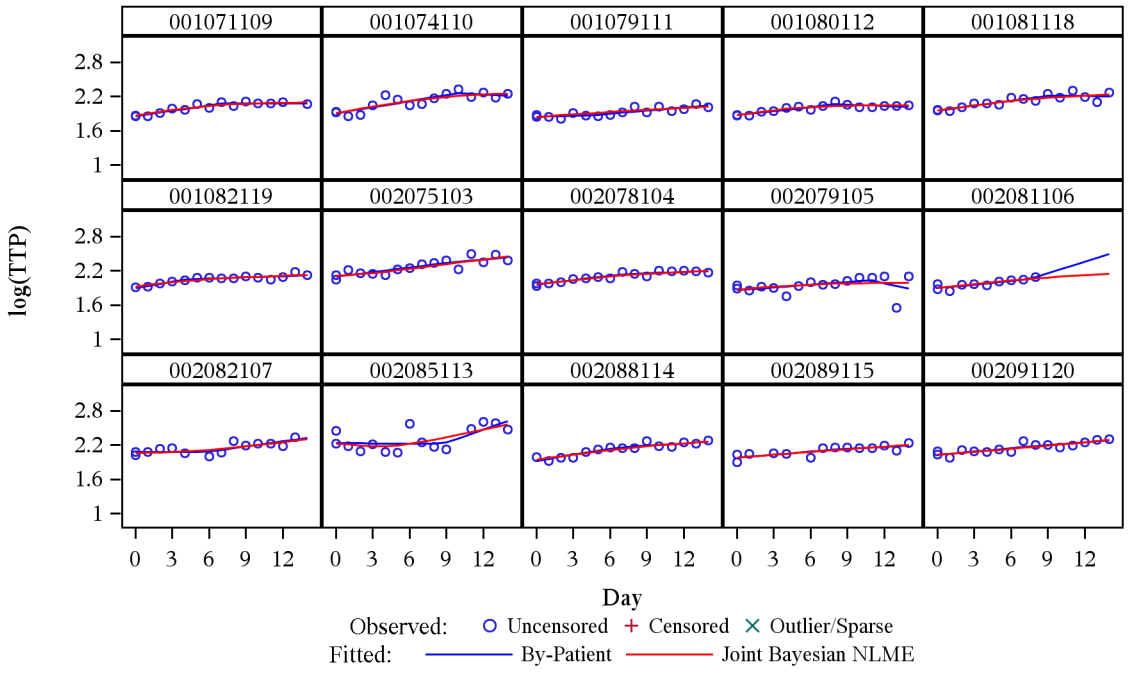


Figure D.17: Observed and Fitted log(TTP), Treatment Group **Pa-Z**

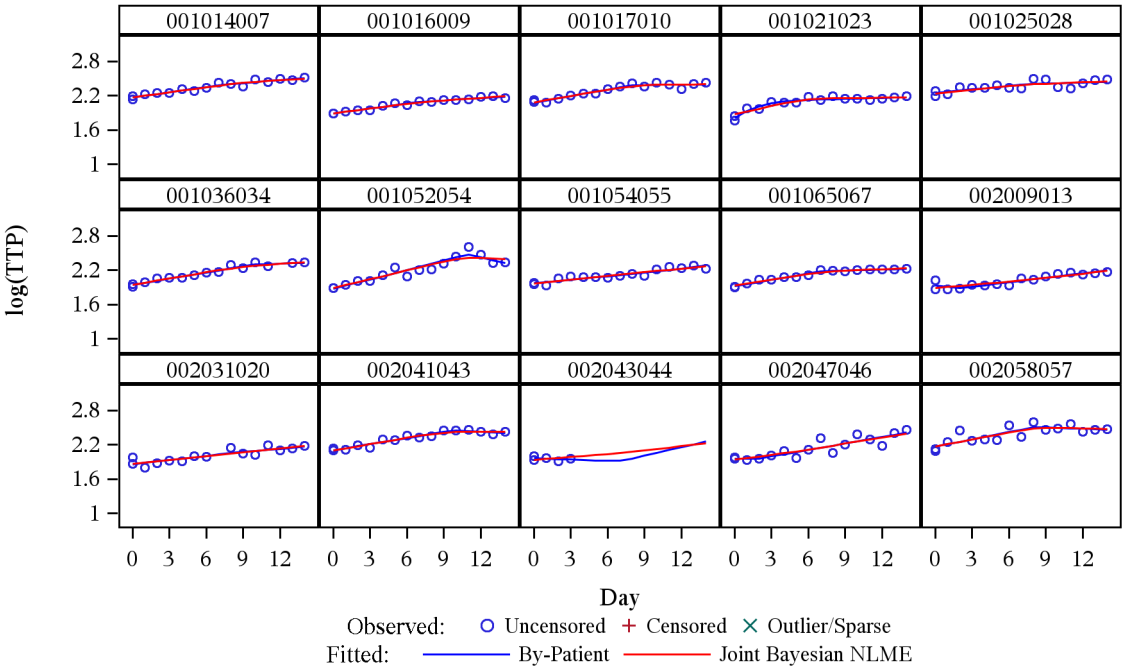


Figure D.18: Observed and Fitted log(TTP), Treatment Group **Pa-Z-M**

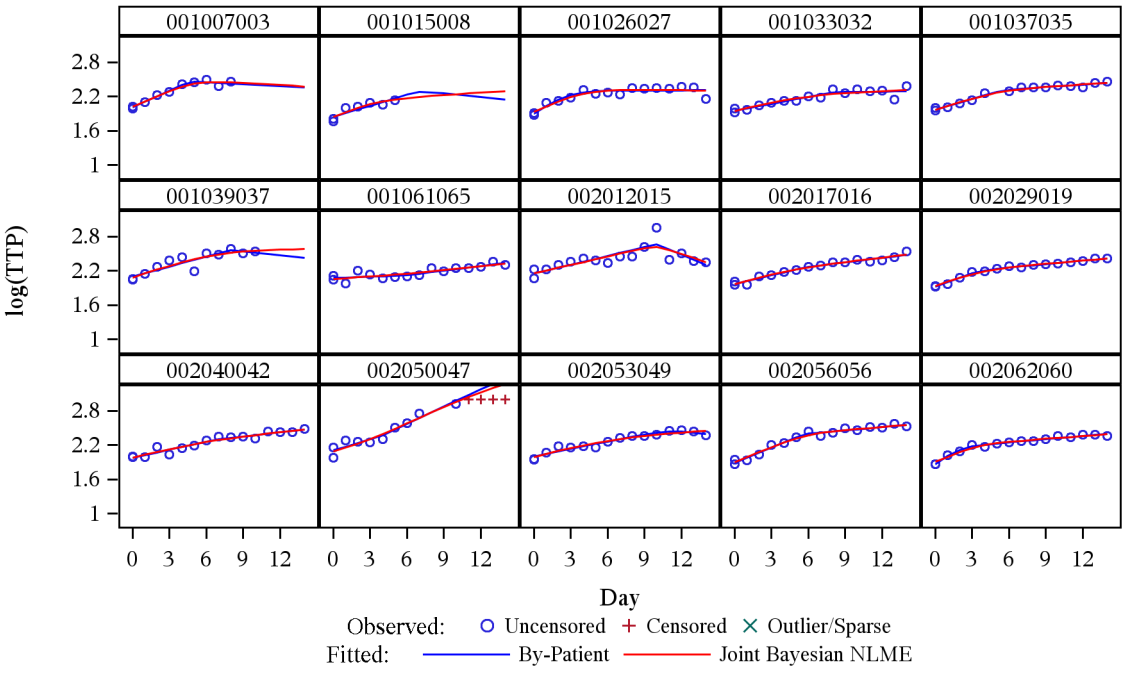
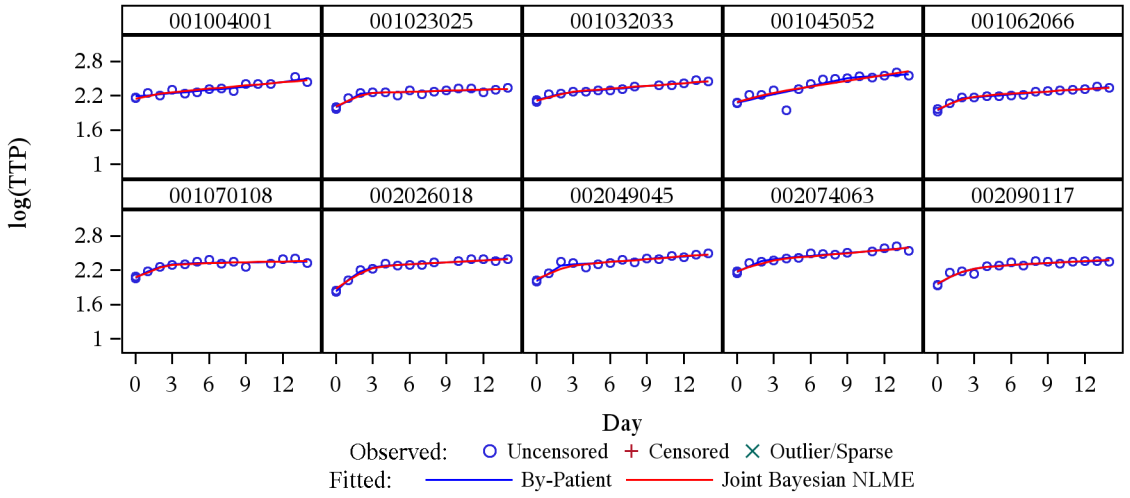


Figure D.19: Observed and Fitted log(TTP), Treatment Group **Rifafour**



D.2.2 NC003 Trial

Figure D.20: Observed and Fitted log(TTP), Treatment Group **J-Pa-Z-C**

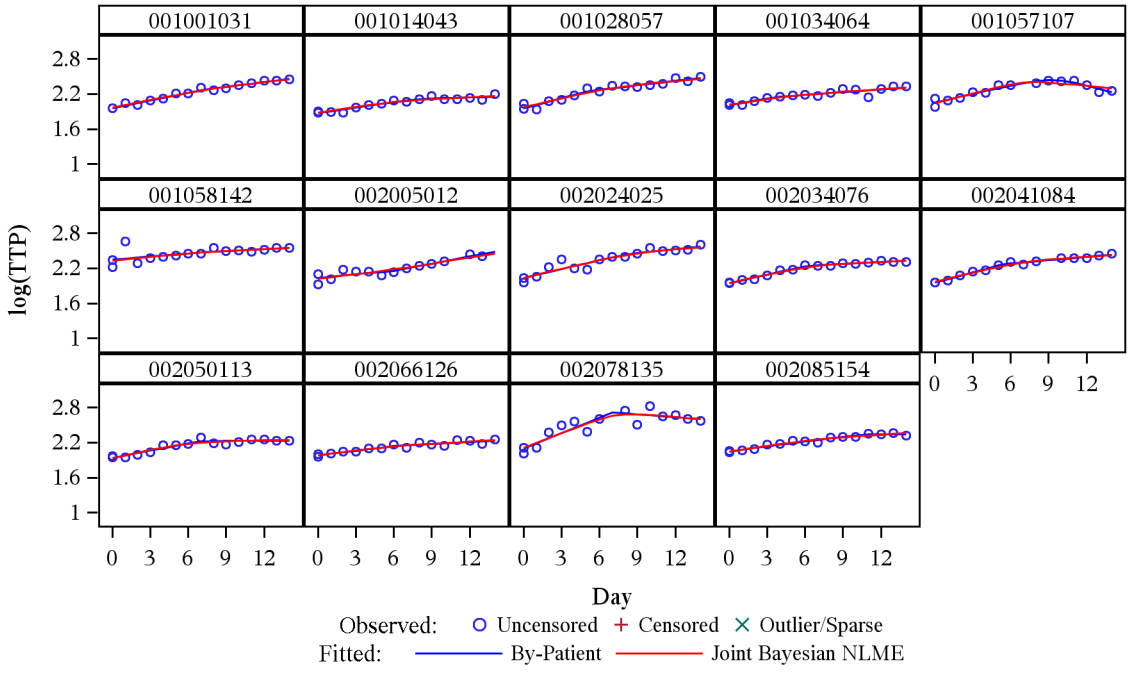


Figure D.21: Observed and Fitted log(TTP), Treatment Group **J-Pa-Z**

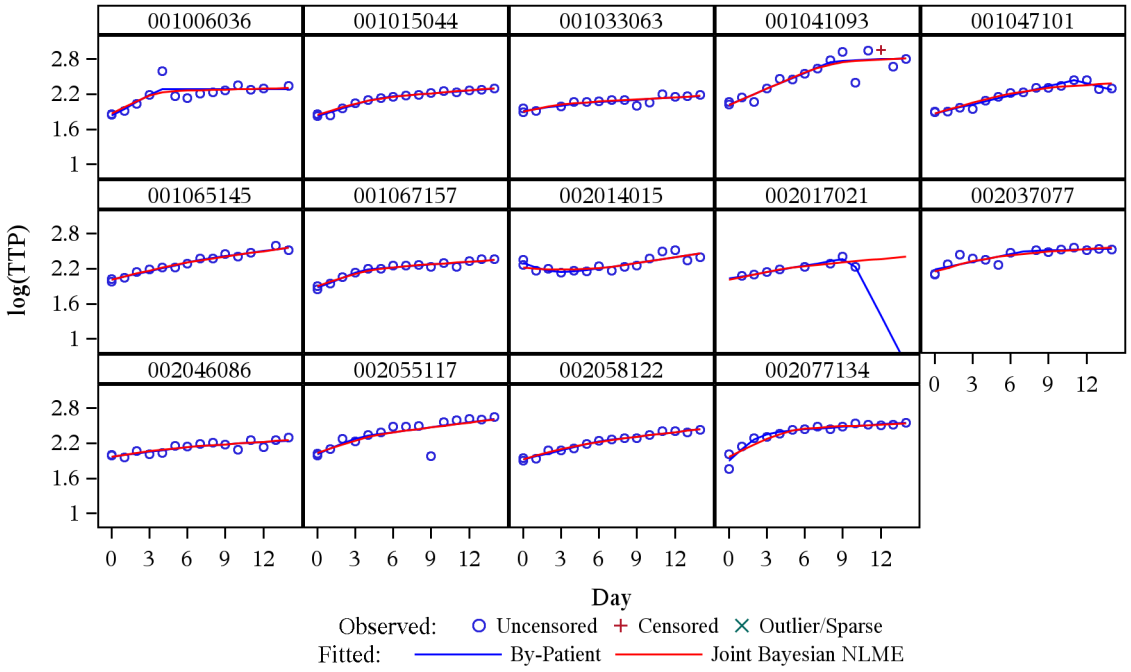


Figure D.22: Observed and Fitted log(TTP), Treatment Group **J-Pa-C**

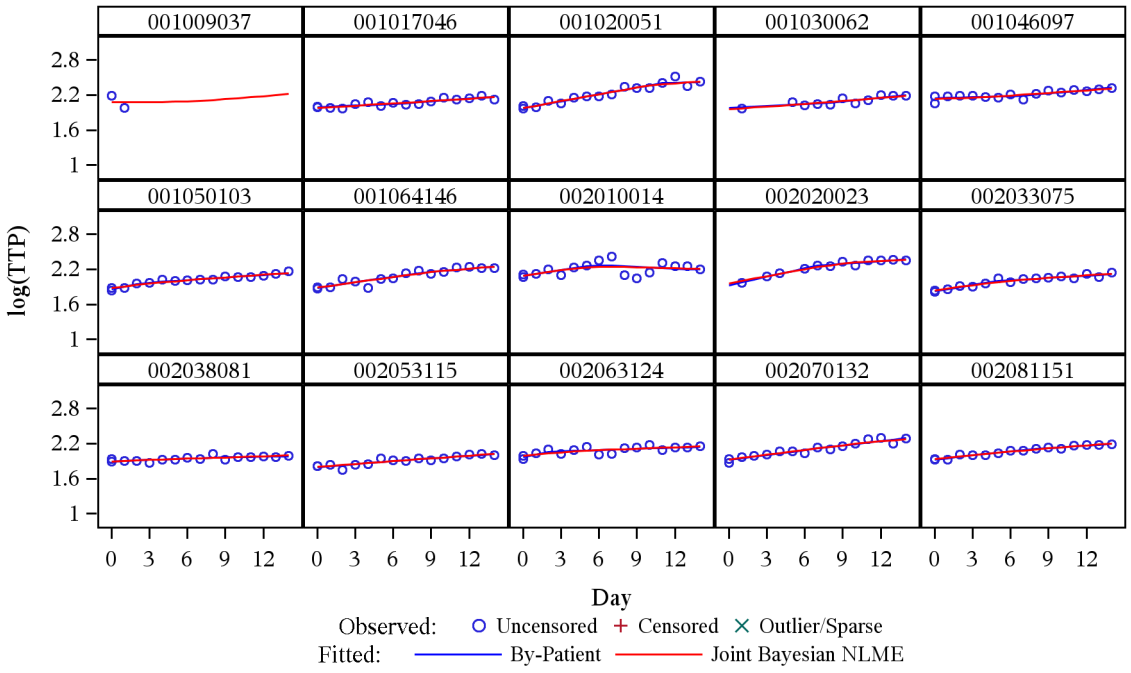


Figure D.23: Observed and Fitted log(TTP), Treatment Group **J-Z-C**

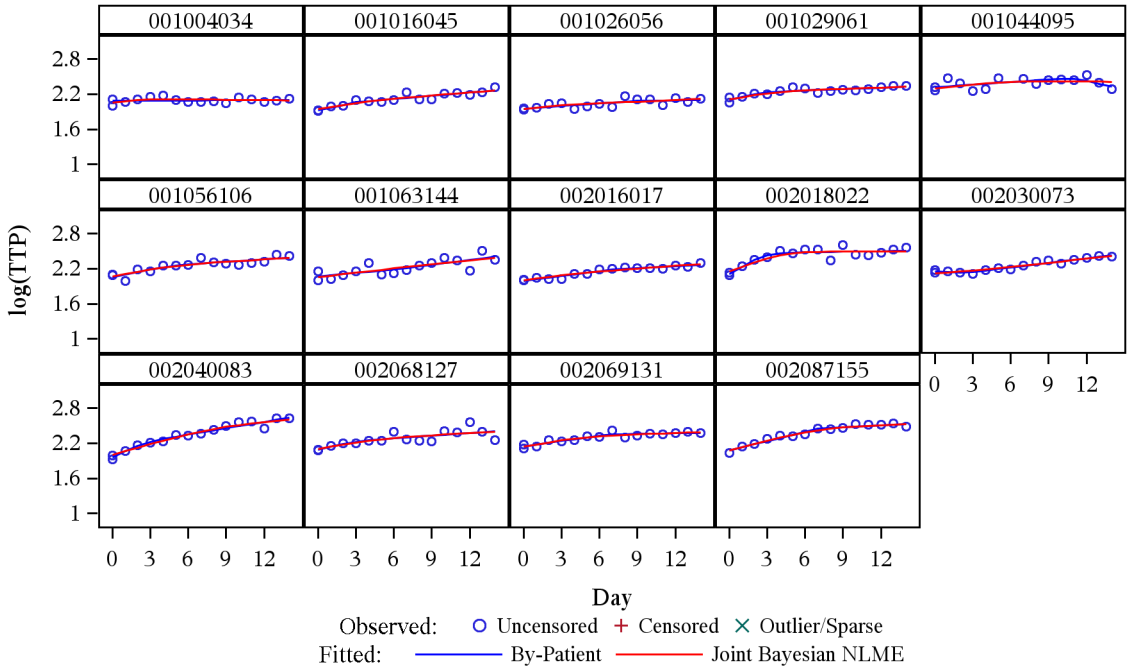


Figure D.24: Observed and Fitted log(TTP), Treatment Group **Z**

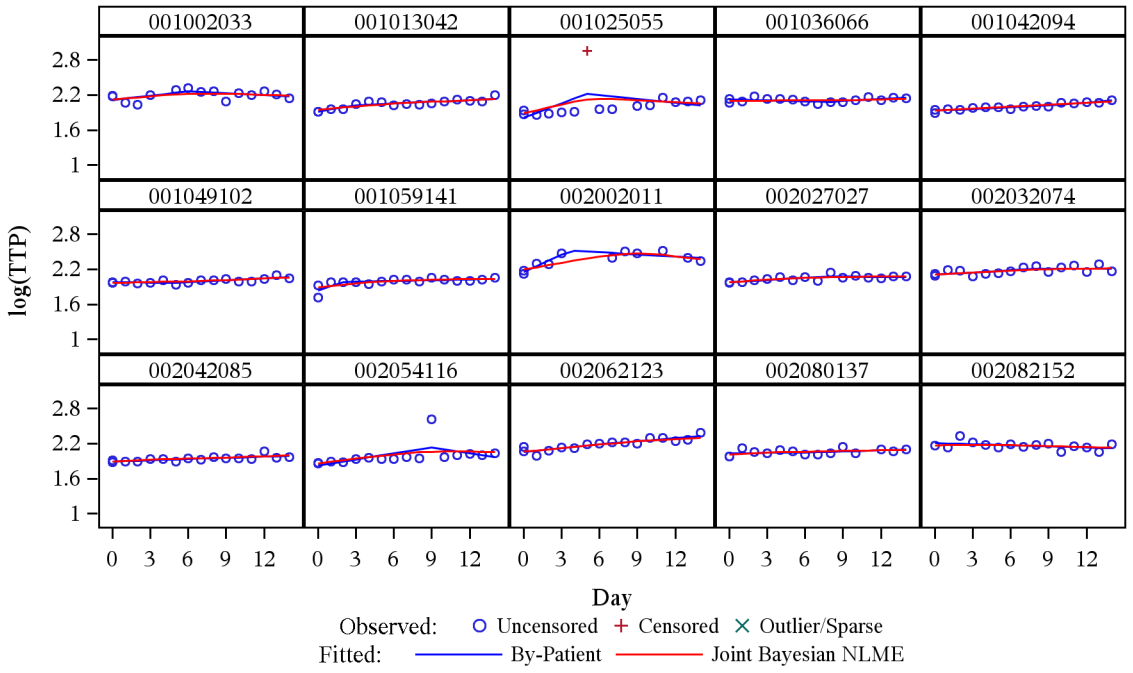


Figure D.25: Observed and Fitted log(TTP), Treatment Group **C**

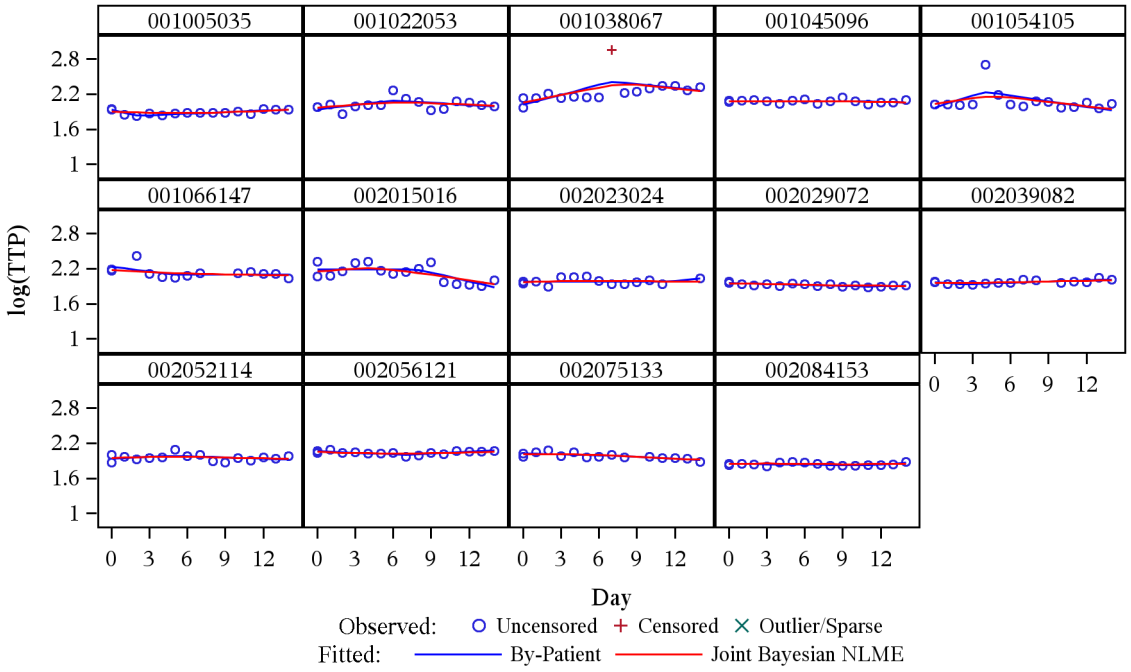
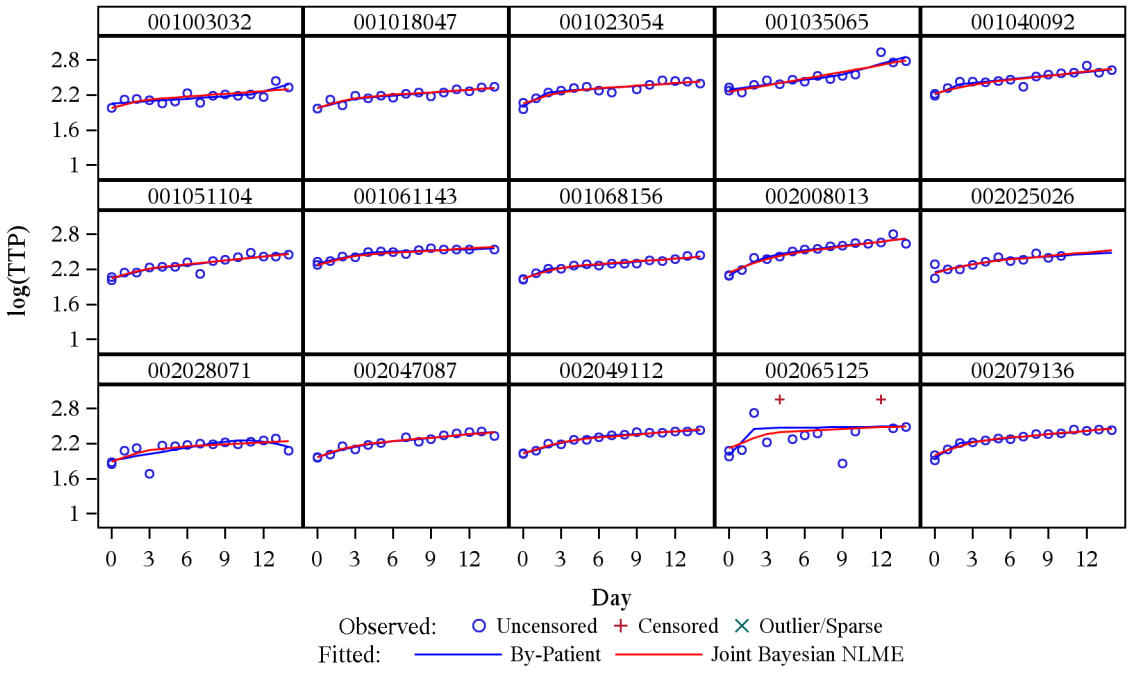


Figure D.26: Observed and Fitted log(TTP), Treatment Group **Rifafour**



Appendix E

Additional Results: Colony Forming Unit Count

E.1 NC001 Trial

E.1.1 Differential Hyperbolic Tangent Regression Model

Model 1.2: **Residuals: Normal**
Random Coefficients: Normal, Fixed Smoothness
Covariance Matrix: "Default" Wishart

Table E.1: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\text{EBA}_j(0-14)$	J (N=15)	15	0.076	[0.017; 0.141]	−0.065	[-0.176; 0.046]
	J-Z (N=15)	15	0.136	[0.067; 0.208]	−0.006	[-0.122; 0.110]
	J-Pa (N=15)	15	0.101	[0.056; 0.146]	−0.040	[-0.143; 0.062]
	Pa-Z (N=15)	15	0.152	[0.099; 0.204]	0.011	[-0.098; 0.119]
	Pa-Z-M (N=15)	15	0.245	[0.086; 0.418]	0.104	[-0.080; 0.298]
	Rifafour (N=10)	10	0.141	[0.048; 0.233]		

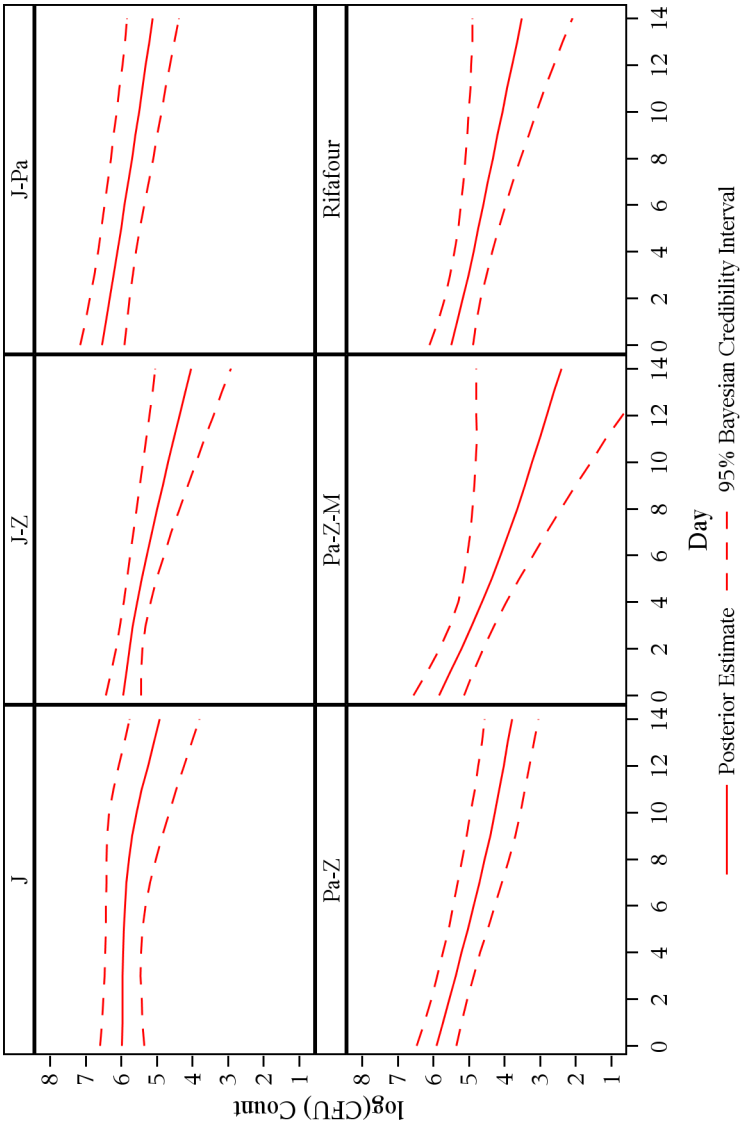
Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table E.1: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
Parameter	**Treatment Group**	**n**	**Posterior Estimate**	**95% BCI**	**Posterior Estimate**	**95% BCI**
$\text{EBA}_j(0-2)$	J (N=15)	15	0.003	[-0.082; 0.086]	−0.157	[-0.328; 0.008]
	J-Z (N=15)	15	0.084	[-0.028; 0.192]	−0.076	[-0.265; 0.104]
	J-Pa (N=15)	15	0.105	[0.020; 0.187]	−0.056	[-0.227; 0.106]
	Pa-Z (N=15)	15	0.179	[0.083; 0.277]	0.019	[-0.160; 0.192]
	Pa-Z-M (N=15)	15	0.316	[0.171; 0.461]	0.155	[-0.056; 0.357]
	Rifafour (N=10)	10	0.160	[0.017; 0.312]		
$\text{EBA}_j(2-14)$	J (N=15)	15	0.088	[0.026; 0.166]	−0.050	[-0.177; 0.084]
	J-Z (N=15)	15	0.144	[0.065; 0.231]	0.006	[-0.130; 0.146]
	J-Pa (N=15)	15	0.101	[0.053; 0.147]	−0.037	[-0.158; 0.082]
	Pa-Z (N=15)	15	0.147	[0.090; 0.201]	0.009	[-0.114; 0.133]
	Pa-Z-M (N=15)	15	0.234	[0.044; 0.439]	0.096	[-0.121; 0.325]
	Rifafour (N=10)	10	0.138	[0.027; 0.247]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.1: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



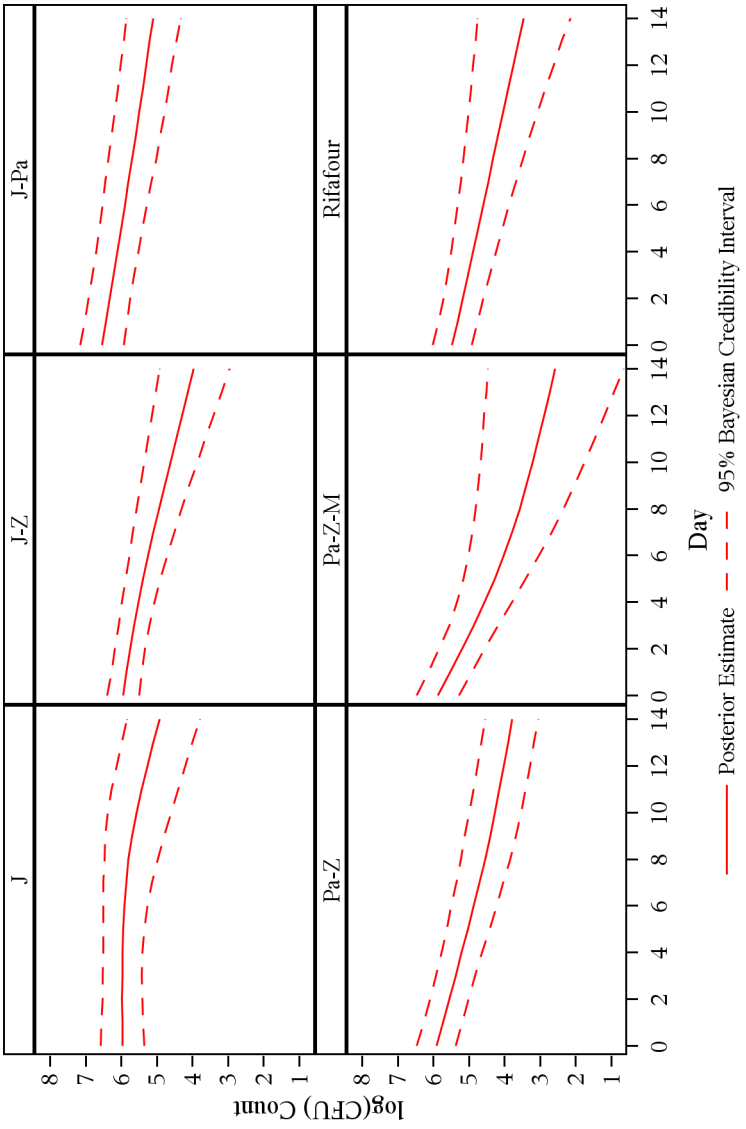
Model 1.3: **Residuals: Normal**
Random Coefficients: Normal
Covariance Matrix: "Frequentist" Wishart

Table E.2: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.075	[0.018; 0.140]	−0.069	[-0.169; 0.033]
	J-Z (N=15)	15	0.142	[0.079; 0.206]	−0.002	[-0.106; 0.102]
	J-Pa (N=15)	15	0.103	[0.065; 0.141]	−0.041	[-0.132; 0.049]
	Pa-Z (N=15)	15	0.152	[0.108; 0.196]	0.008	[-0.086; 0.101]
	Pa-Z-M (N=15)	15	0.235	[0.110; 0.363]	0.092	[-0.055; 0.242]
	Rifafour (N=10)	10	0.144	[0.063; 0.227]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	−0.001	[-0.075; 0.072]	−0.154	[-0.289; -0.029]
	J-Z (N=15)	15	0.098	[0.011; 0.181]	−0.054	[-0.196; 0.077]
	J-Pa (N=15)	15	0.108	[0.033; 0.181]	−0.045	[-0.181; 0.078]
	Pa-Z (N=15)	15	0.179	[0.100; 0.261]	0.027	[-0.112; 0.156]
	Pa-Z-M (N=15)	15	0.340	[0.221; 0.461]	0.187	[0.025; 0.344]
	Rifafour (N=10)	10	0.153	[0.052; 0.268]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.087	[0.028; 0.165]	−0.055	[-0.162; 0.060]
	J-Z (N=15)	15	0.150	[0.083; 0.219]	0.007	[-0.104; 0.120]
	J-Pa (N=15)	15	0.102	[0.063; 0.141]	−0.040	[-0.138; 0.057]
	Pa-Z (N=15)	15	0.147	[0.099; 0.192]	0.005	[-0.096; 0.105]
	Pa-Z-M (N=15)	15	0.218	[0.083; 0.353]	0.076	[-0.082; 0.235]
	Rifafour (N=10)	10	0.142	[0.053; 0.233]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.2: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



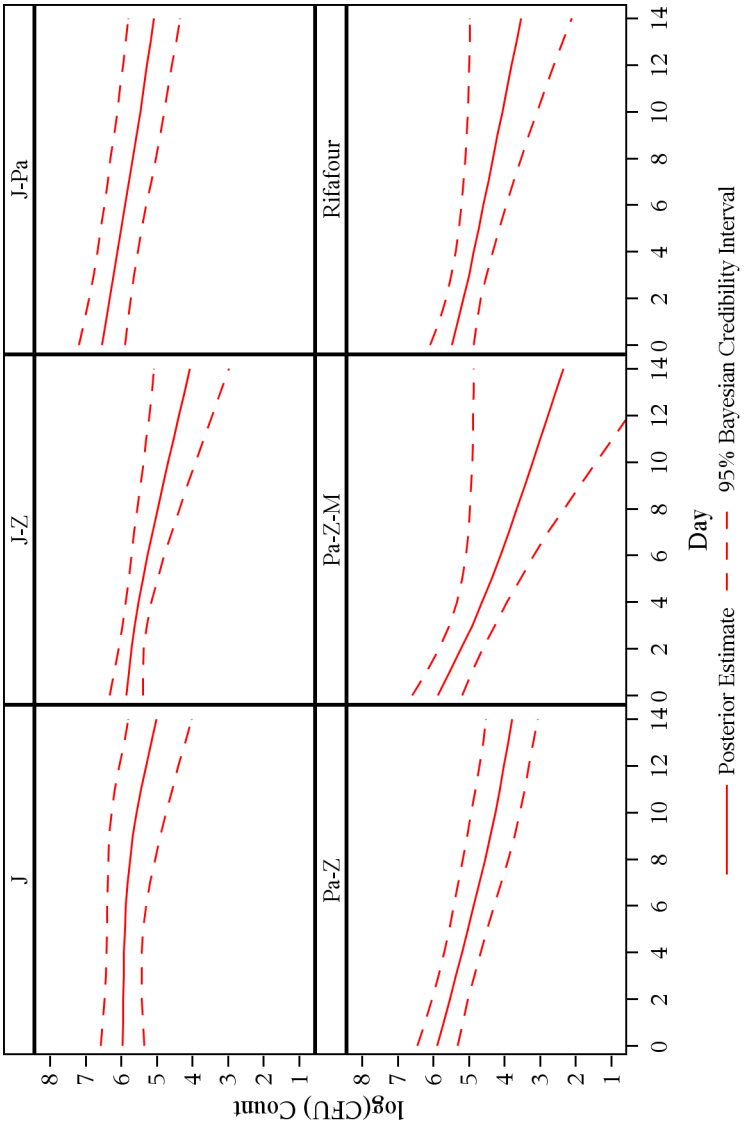
Model 1.4: Residuals: Skew Normal
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.3: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\text{EBA}_j(0-14)$	J (N=15)	15	0.068	[0.012; 0.128]	−0.070	[-0.181; 0.042]
	J-Z (N=15)	15	0.127	[0.059; 0.199]	−0.011	[-0.128; 0.106]
	J-Pa (N=15)	15	0.104	[0.059; 0.150]	−0.034	[-0.140; 0.072]
	Pa-Z (N=15)	15	0.151	[0.097; 0.202]	0.012	[-0.096; 0.121]
	Pa-Z-M (N=15)	15	0.252	[0.085; 0.438]	0.114	[-0.080; 0.321]
	Rifafour (N=10)	10	0.139	[0.042; 0.234]		
$\text{EBA}_j(0-2)$	J (N=15)	15	0.006	[-0.080; 0.091]	−0.154	[-0.326; 0.013]
	J-Z (N=15)	15	0.071	[-0.045; 0.182]	−0.089	[-0.277; 0.094]
	J-Pa (N=15)	15	0.110	[0.024; 0.194]	−0.051	[-0.220; 0.115]
	Pa-Z (N=15)	15	0.175	[0.080; 0.271]	0.015	[-0.162; 0.185]
	Pa-Z-M (N=15)	15	0.331	[0.180; 0.482]	0.170	[-0.040; 0.379]
	Rifafour (N=10)	10	0.160	[0.017; 0.311]		
$\text{EBA}_j(2-14)$	J (N=15)	15	0.079	[0.021; 0.148]	−0.056	[-0.183; 0.075]
	J-Z (N=15)	15	0.137	[0.056; 0.222]	0.002	[-0.135; 0.141]
	J-Pa (N=15)	15	0.103	[0.056; 0.150]	−0.032	[-0.152; 0.092]
	Pa-Z (N=15)	15	0.146	[0.090; 0.200]	0.011	[-0.112; 0.137]
	Pa-Z-M (N=15)	15	0.239	[0.039; 0.458]	0.104	[-0.122; 0.348]
	Rifafour (N=10)	10	0.135	[0.020; 0.245]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.3: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



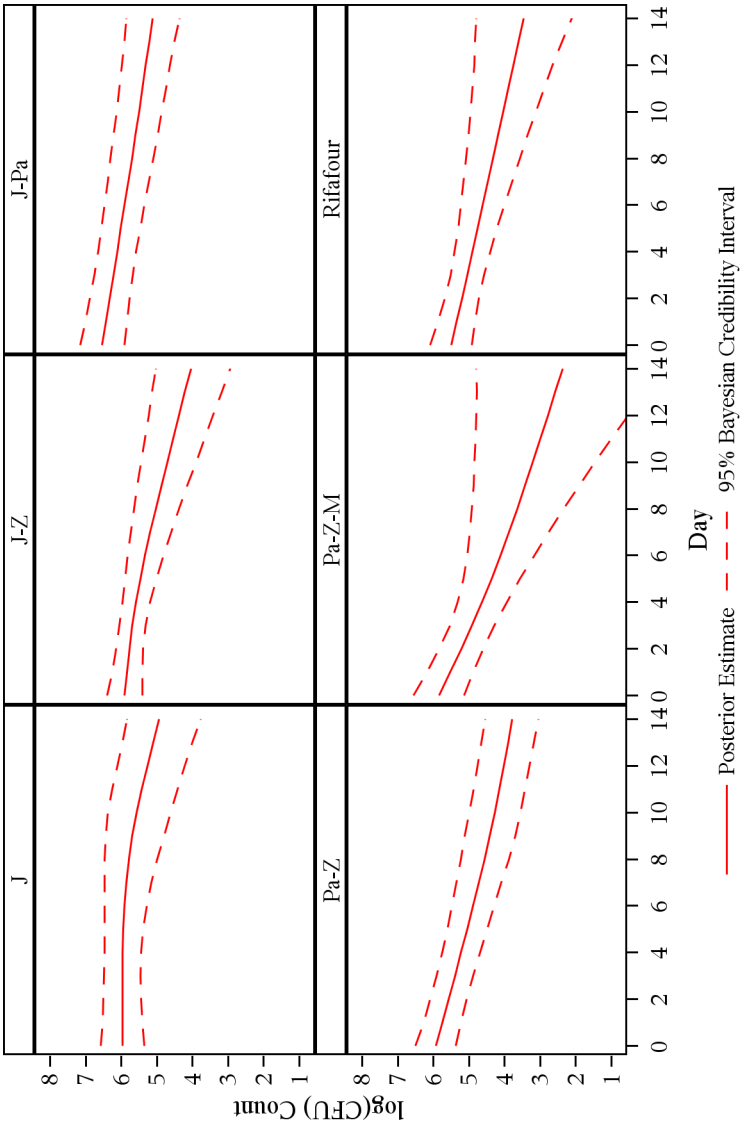
Model 1.5: Residuals: Student t
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.4: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.074	[0.010; 0.145]	−0.073	[-0.185; 0.042]
	J-Z (N=15)	15	0.133	[0.065; 0.204]	−0.013	[-0.128; 0.101]
	J-Pa (N=15)	15	0.101	[0.056; 0.146]	−0.045	[-0.147; 0.055]
	Pa-Z (N=15)	15	0.154	[0.100; 0.207]	0.007	[-0.098; 0.113]
	Pa-Z-M (N=15)	15	0.248	[0.087; 0.430]	0.102	[-0.082; 0.304]
	Rifafour (N=10)	10	0.146	[0.055; 0.238]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	–0.002	[-0.086; 0.084]	−0.156	[-0.316; 0.000]
	J-Z (N=15)	15	0.069	[-0.038; 0.170]	−0.085	[-0.254; 0.081]
	J-Pa (N=15)	15	0.105	[0.019; 0.187]	−0.049	[-0.210; 0.105]
	Pa-Z (N=15)	15	0.179	[0.079; 0.277]	0.025	[-0.142; 0.187]
	Pa-Z-M (N=15)	15	0.313	[0.164; 0.460]	0.159	[-0.040; 0.355]
	Rifafour (N=10)	10	0.154	[0.021; 0.290]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.086	[0.019; 0.170]	−0.059	[-0.185; 0.075]
	J-Z (N=15)	15	0.144	[0.066; 0.229]	−0.001	[-0.132; 0.133]
	J-Pa (N=15)	15	0.100	[0.053; 0.148]	−0.044	[-0.160; 0.072]
	Pa-Z (N=15)	15	0.149	[0.093; 0.203]	0.004	[-0.114; 0.124]
	Pa-Z-M (N=15)	15	0.238	[0.046; 0.455]	0.093	[-0.124; 0.330]
	Rifafour (N=10)	10	0.145	[0.037; 0.251]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.4: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



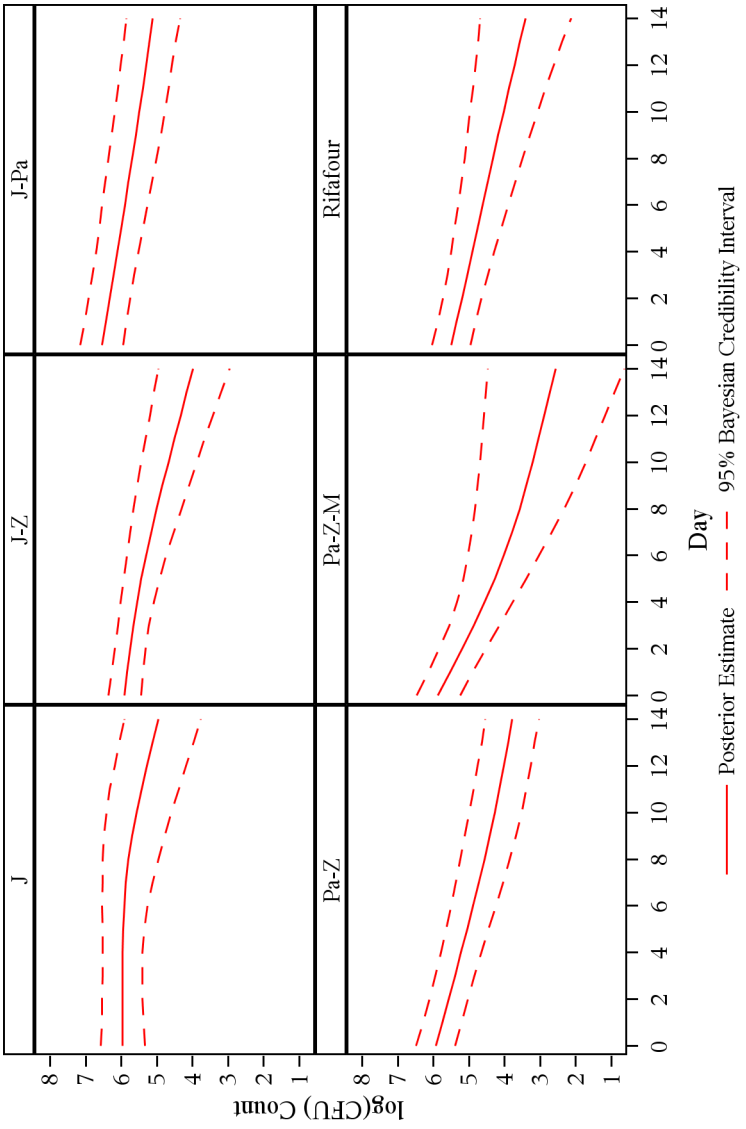
Model 1.6: **Residuals: Student t**
Random Coefficients: Normal
Covariance Matrix: "Frequentist" Wishart

Table E.5: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.072	[0.012; 0.141]	−0.077	[-0.180; 0.028]
	J-Z (N=15)	15	0.137	[0.073; 0.203]	−0.011	[-0.114; 0.092]
	J-Pa (N=15)	15	0.102	[0.064; 0.141]	−0.046	[-0.138; 0.043]
	Pa-Z (N=15)	15	0.153	[0.110; 0.198]	0.005	[-0.089; 0.097]
	Pa-Z-M (N=15)	15	0.236	[0.109; 0.364]	0.087	[-0.063; 0.238]
	Rifafour (N=10)	10	0.149	[0.067; 0.232]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	–0.006	[-0.081; 0.069]	−0.157	[-0.279; -0.041]
	J-Z (N=15)	15	0.079	[0.000; 0.155]	−0.072	[-0.196; 0.047]
	J-Pa (N=15)	15	0.108	[0.033; 0.183]	−0.042	[-0.167; 0.075]
	Pa-Z (N=15)	15	0.180	[0.098; 0.261]	0.029	[-0.097; 0.150]
	Pa-Z-M (N=15)	15	0.341	[0.221; 0.463]	0.190	[0.037; 0.343]
	Rifafour (N=10)	10	0.151	[0.060; 0.248]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.085	[0.021; 0.166]	−0.063	[-0.176; 0.055]
	J-Z (N=15)	15	0.147	[0.079; 0.218]	−0.001	[-0.113; 0.111]
	J-Pa (N=15)	15	0.101	[0.061; 0.141]	−0.047	[-0.146; 0.049]
	Pa-Z (N=15)	15	0.149	[0.102; 0.194]	0.001	[-0.100; 0.101]
	Pa-Z-M (N=15)	15	0.218	[0.083; 0.355]	0.070	[-0.091; 0.232]
	Rifafour (N=10)	10	0.148	[0.059; 0.239]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.5: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



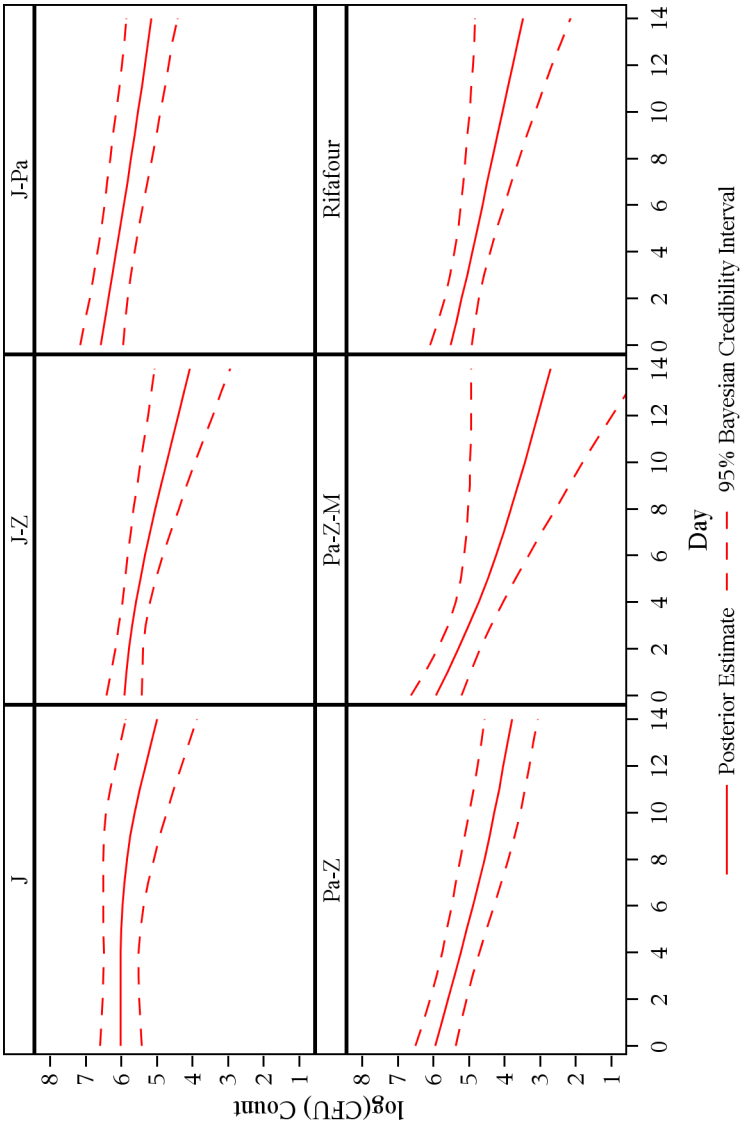
Model 1.7: **Residuals: Student t**
Random Coefficients: Student t
Covariance Matrix: "Default" Wishart

Table E.6: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.073	[0.011; 0.143]	−0.071	[-0.182; 0.043]
	J-Z (N=15)	15	0.131	[0.064; 0.204]	−0.013	[-0.128; 0.103]
	J-Pa (N=15)	15	0.101	[0.057; 0.145]	−0.043	[-0.145; 0.058]
	Pa-Z (N=15)	15	0.153	[0.101; 0.207]	0.008	[-0.096; 0.113]
	Pa-Z-M (N=15)	15	0.230	[0.080; 0.400]	0.085	[-0.091; 0.275]
	Rifafour (N=10)	10	0.145	[0.052; 0.237]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	0.000	[-0.088; 0.085]	−0.154	[-0.315; 0.003]
	J-Z (N=15)	15	0.070	[-0.036; 0.174]	−0.084	[-0.256; 0.081]
	J-Pa (N=15)	15	0.106	[0.020; 0.187]	−0.048	[-0.206; 0.107]
	Pa-Z (N=15)	15	0.179	[0.081; 0.277]	0.024	[-0.141; 0.189]
	Pa-Z-M (N=15)	15	0.314	[0.170; 0.457]	0.160	[-0.036; 0.355]
	Rifafour (N=10)	10	0.154	[0.021; 0.290]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.086	[0.020; 0.167]	−0.058	[-0.182; 0.074]
	J-Z (N=15)	15	0.142	[0.065; 0.227]	−0.002	[-0.132; 0.134]
	J-Pa (N=15)	15	0.101	[0.054; 0.147]	−0.043	[-0.158; 0.076]
	Pa-Z (N=15)	15	0.149	[0.093; 0.202]	0.006	[-0.112; 0.125]
	Pa-Z-M (N=15)	15	0.216	[0.040; 0.417]	0.073	[-0.131; 0.293]
	Rifafour (N=10)	10	0.143	[0.035; 0.248]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.6: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



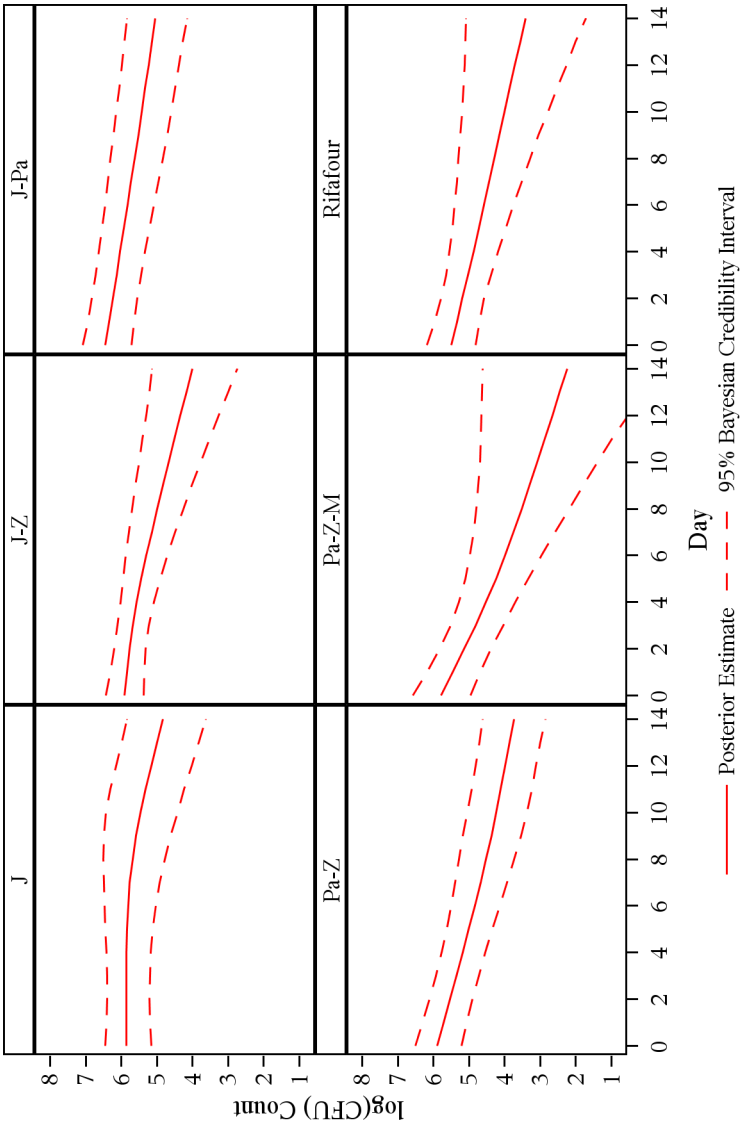
Model 1.8: **Residuals: Student t**
Random Coefficients: Skew Normal
Covariance Matrix: "Default" Wishart

Table E.7: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.073	[0.002; 0.151]	−0.076	[-0.213; 0.059]
	J-Z (N=15)	15	0.136	[0.059; 0.219]	−0.014	[-0.152; 0.125]
	J-Pa (N=15)	15	0.101	[0.051; 0.151]	−0.049	[-0.176; 0.077]
	Pa-Z (N=15)	15	0.153	[0.094; 0.213]	0.004	[-0.125; 0.135]
	Pa-Z-M (N=15)	15	0.254	[0.089; 0.434]	0.105	[-0.097; 0.318]
	Rifafour (N=10)	10	0.149	[0.034; 0.267]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	–0.005	[-0.104; 0.094]	−0.165	[-0.358; 0.027]
	J-Z (N=15)	15	0.073	[-0.046; 0.189]	−0.087	[-0.292; 0.115]
	J-Pa (N=15)	15	0.104	[0.013; 0.192]	−0.055	[-0.247; 0.134]
	Pa-Z (N=15)	15	0.178	[0.071; 0.287]	0.018	[-0.182; 0.216]
	Pa-Z-M (N=15)	15	0.332	[0.163; 0.510]	0.172	[-0.068; 0.412]
	Rifafour (N=10)	10	0.160	[-0.007; 0.329]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.086	[0.012; 0.176]	−0.062	[-0.213; 0.092]
	J-Z (N=15)	15	0.146	[0.059; 0.244]	−0.001	[-0.157; 0.158]
	J-Pa (N=15)	15	0.100	[0.047; 0.153]	−0.048	[-0.188; 0.093]
	Pa-Z (N=15)	15	0.149	[0.086; 0.210]	0.002	[-0.141; 0.146]
	Pa-Z-M (N=15)	15	0.241	[0.048; 0.446]	0.093	[-0.139; 0.339]
	Rifafour (N=10)	10	0.148	[0.018; 0.278]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.7: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



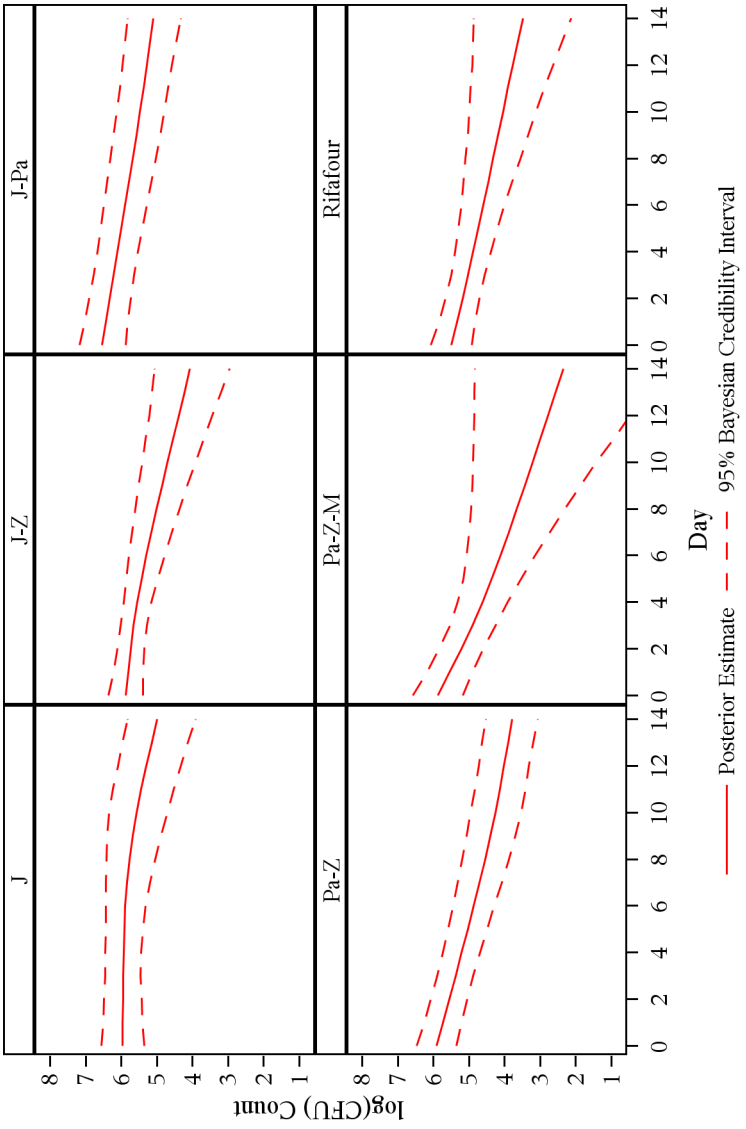
Model 1.9: Residuals: Skew Student t
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.8: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.069	[0.010; 0.135]	−0.074	[-0.184; 0.041]
	J-Z (N=15)	15	0.129	[0.062; 0.199]	−0.014	[-0.128; 0.102]
	J-Pa (N=15)	15	0.103	[0.058; 0.149]	−0.040	[-0.142; 0.064]
	Pa-Z (N=15)	15	0.152	[0.099; 0.204]	0.009	[-0.096; 0.117]
	Pa-Z-M (N=15)	15	0.252	[0.085; 0.436]	0.109	[-0.082; 0.314]
	Rifafour (N=10)	10	0.143	[0.049; 0.236]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	0.003	[-0.084; 0.090]	−0.154	[-0.316; 0.006]
	J-Z (N=15)	15	0.068	[-0.039; 0.174]	−0.088	[-0.263; 0.082]
	J-Pa (N=15)	15	0.109	[0.023; 0.192]	−0.048	[-0.213; 0.110]
	Pa-Z (N=15)	15	0.177	[0.081; 0.272]	0.020	[-0.147; 0.186]
	Pa-Z-M (N=15)	15	0.330	[0.181; 0.481]	0.173	[-0.028; 0.375]
	Rifafour (N=10)	10	0.157	[0.019; 0.298]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.080	[0.019; 0.158]	−0.060	[-0.185; 0.074]
	J-Z (N=15)	15	0.139	[0.062; 0.224]	−0.002	[-0.133; 0.137]
	J-Pa (N=15)	15	0.102	[0.055; 0.149]	−0.038	[-0.154; 0.082]
	Pa-Z (N=15)	15	0.148	[0.092; 0.200]	0.007	[-0.112; 0.130]
	Pa-Z-M (N=15)	15	0.238	[0.043; 0.456]	0.098	[-0.124; 0.339]
	Rifafour (N=10)	10	0.141	[0.030; 0.248]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.8: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



E.1.2 Other Regression Models

E.1.2.1 Linear Regression Model

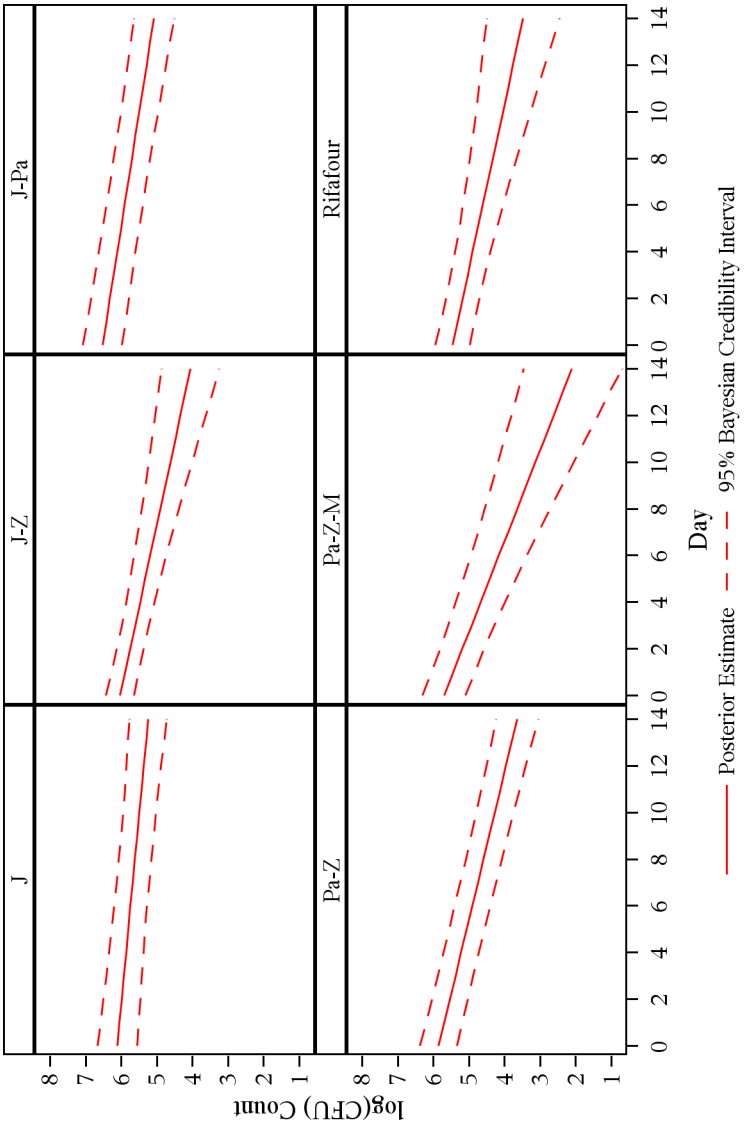
Model 2.1: **Residuals: Normal**
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.9: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J (N=15)	15	6.115	[5.550; 6.670]
	J-Z (N=15)	15	6.033	[5.639; 6.425]
	J-Pa (N=15)	15	6.528	[5.976; 7.080]
	Pa-Z (N=15)	15	5.852	[5.333; 6.378]
	Pa-Z-M (N=15)	15	5.698	[5.094; 6.301]
	Rifafour (N=10)	10	5.463	[4.980; 5.945]
$\boldsymbol{\lambda_j}$	J (N=15)	15	0.062	[0.019; 0.104]
	J-Z (N=15)	15	0.141	[0.081; 0.201]
	J-Pa (N=15)	15	0.103	[0.071; 0.136]
	Pa-Z (N=15)	15	0.158	[0.121; 0.194]
	Pa-Z-M (N=15)	15	0.256	[0.166; 0.351]
	Rifafour (N=10)	10	0.142	[0.067; 0.216]

Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.9: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



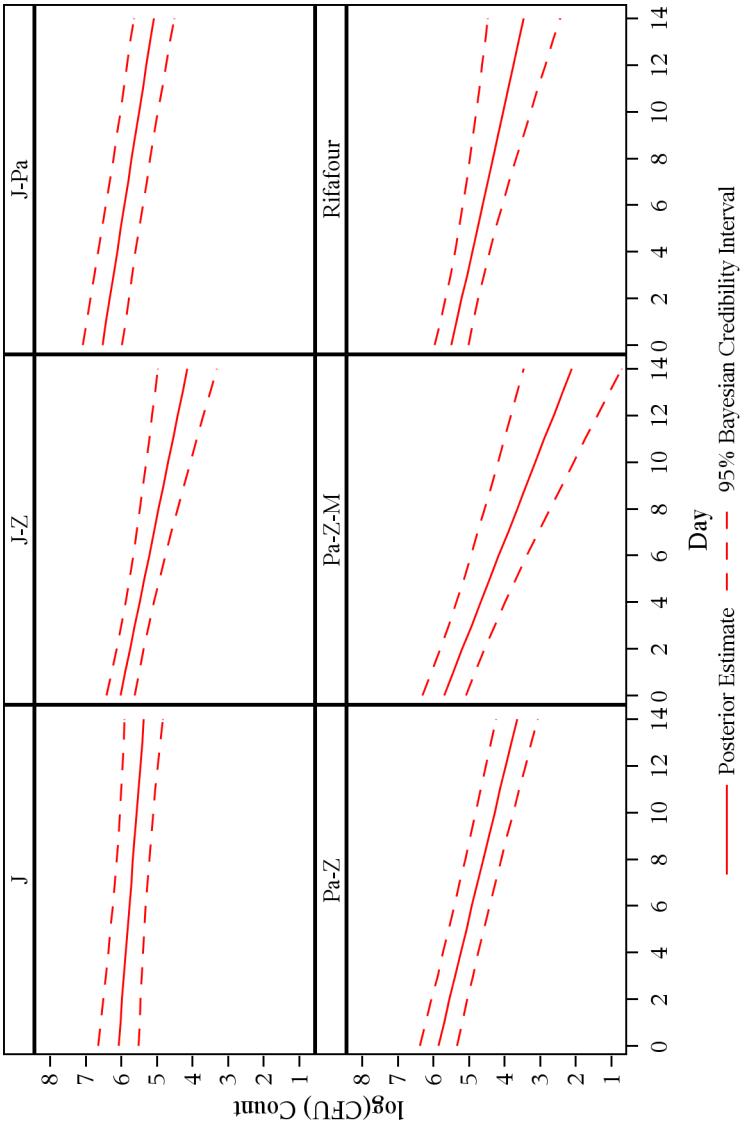
Model 2.2: Residuals: Student t
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.10: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J (N=15)	15	6.080	[5.511; 6.650]
	J-Z (N=15)	15	6.024	[5.626; 6.415]
	J-Pa (N=15)	15	6.532	[5.976; 7.086]
	Pa-Z (N=15)	15	5.862	[5.333; 6.385]
	Pa-Z-M (N=15)	15	5.697	[5.087; 6.311]
	Rifafour (N=10)	10	5.491	[5.010; 5.966]
$\boldsymbol{\lambda_j}$	J (N=15)	15	0.051	[0.007; 0.095]
	J-Z (N=15)	15	0.134	[0.074; 0.194]
	J-Pa (N=15)	15	0.103	[0.070; 0.136]
	Pa-Z (N=15)	15	0.158	[0.121; 0.195]
	Pa-Z-M (N=15)	15	0.256	[0.165; 0.351]
	Rifafour (N=10)	10	0.145	[0.072; 0.219]

Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.10: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



E.1.2.2 Conventional Bilinear Regression Model

Model 3.1: Residuals: Normal
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.11: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.076	[0.017; 0.143]	−0.066	[-0.177; 0.046]
	J-Z (N=15)	15	0.134	[0.066; 0.207]	−0.008	[-0.125; 0.108]
	J-Pa (N=15)	15	0.101	[0.057; 0.145]	−0.042	[-0.146; 0.062]
	Pa-Z (N=15)	15	0.152	[0.100; 0.202]	0.009	[-0.097; 0.115]
	Pa-Z-M (N=15)	15	0.242	[0.083; 0.409]	0.100	[-0.088; 0.288]
	Rifafour (N=10)	10	0.143	[0.050; 0.237]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	0.006	[-0.077; 0.090]	−0.160	[-0.342; 0.008]
	J-Z (N=15)	15	0.084	[-0.032; 0.195]	−0.082	[-0.279; 0.103]
	J-Pa (N=15)	15	0.104	[0.021; 0.184]	−0.062	[-0.244; 0.104]
	Pa-Z (N=15)	15	0.177	[0.084; 0.272]	0.011	[-0.175; 0.185]
	Pa-Z-M (N=15)	15	0.322	[0.180; 0.463]	0.155	[-0.058; 0.359]
	Rifafour (N=10)	10	0.167	[0.019; 0.330]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.088	[0.027; 0.167]	−0.051	[-0.176; 0.083]
	J-Z (N=15)	15	0.143	[0.065; 0.229]	0.004	[-0.131; 0.142]
	J-Pa (N=15)	15	0.101	[0.055; 0.147]	−0.038	[-0.158; 0.083]
	Pa-Z (N=15)	15	0.147	[0.092; 0.199]	0.008	[-0.114; 0.132]
	Pa-Z-M (N=15)	15	0.229	[0.040; 0.426]	0.090	[-0.129; 0.312]
	Rifafour (N=10)	10	0.139	[0.026; 0.248]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table E.12: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J (N=15)	15	5.982	[5.368; 6.597]
	J-Z (N=15)	15	5.939	[5.442; 6.436]
	J-Pa (N=15)	15	6.532	[5.893; 7.152]
	Pa-Z (N=15)	15	5.913	[5.359; 6.465]
	Pa-Z-M (N=15)	15	5.847	[5.129; 6.565]
	Rifafour (N=10)	10	5.497	[4.893; 6.099]
$\boldsymbol{\beta_{1j}}$	J (N=15)	15	0.087	[0.040; 0.136]
	J-Z (N=15)	15	0.121	[0.060; 0.181]
	J-Pa (N=15)	15	0.100	[0.059; 0.141]
	Pa-Z (N=15)	15	0.148	[0.100; 0.196]
	Pa-Z-M (N=15)	15	0.259	[0.135; 0.387]
	Rifafour (N=10)	10	0.152	[0.072; 0.236]
$\boldsymbol{\lambda_{1j}}$	J (N=15)	15	0.006	[-0.077; 0.090]
	J-Z (N=15)	15	0.084	[-0.032; 0.195]
	J-Pa (N=15)	15	0.104	[0.021; 0.184]
	Pa-Z (N=15)	15	0.177	[0.084; 0.272]
	Pa-Z-M (N=15)	15	0.322	[0.180; 0.463]
	Rifafour (N=10)	10	0.167	[0.019; 0.330]
$\boldsymbol{\beta_{2j}}$	J (N=15)	15	0.080	[0.002; 0.162]
	J-Z (N=15)	15	0.037	[-0.054; 0.129]
	J-Pa (N=15)	15	−0.004	[-0.076; 0.070]
	Pa-Z (N=15)	15	−0.030	[-0.113; 0.053]
	Pa-Z-M (N=15)	15	−0.063	[-0.222; 0.102]
	Rifafour (N=10)	10	−0.014	[-0.139; 0.107]
$\boldsymbol{\lambda_{2j}}$	J (N=15)	15	0.167	[0.071; 0.272]
	J-Z (N=15)	15	0.158	[0.053; 0.261]
	J-Pa (N=15)	15	0.096	[0.012; 0.184]
	Pa-Z (N=15)	15	0.118	[0.016; 0.213]
	Pa-Z-M (N=15)	15	0.196	[-0.054; 0.456]
	Rifafour (N=10)	10	0.138	[-0.003; 0.284]

Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.11: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time

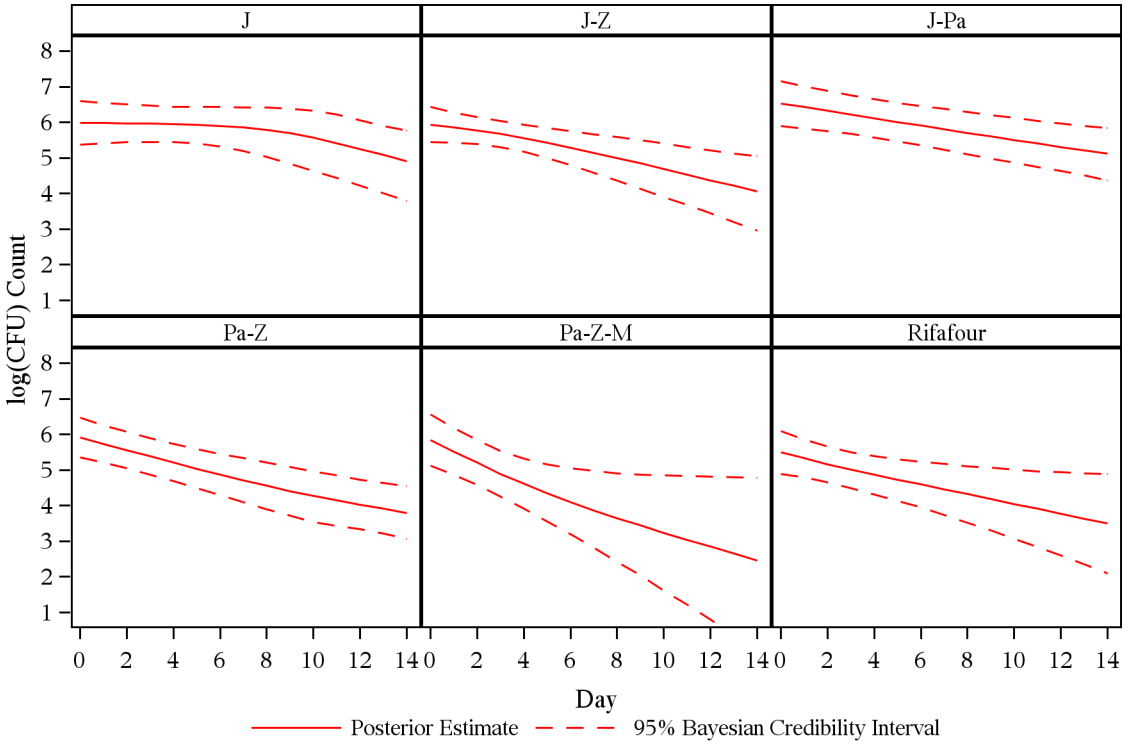


Table E.12: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
κ_j	J (N=15)	15	7.875	[3.037; 10.860]
	J-Z (N=15)	15	4.743	[2.079; 10.260]
	J-Pa (N=15)	15	7.575	[2.688; 10.820]
	Pa-Z (N=15)	15	7.664	[2.530; 10.860]
	Pa-Z-M (N=15)	15	4.824	[2.108; 9.905]
	Rifafour (N=10)	10	4.557	[2.062; 10.180]

Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

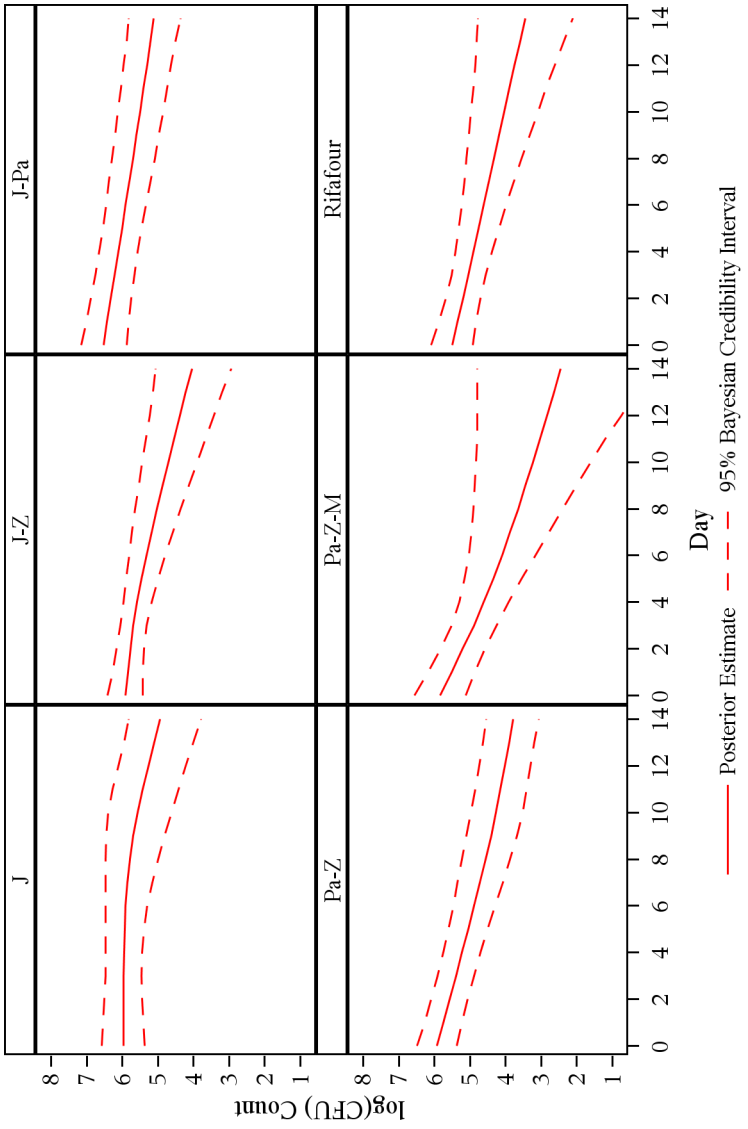
Model 3.2: Residuals: Student t
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.13: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{EBA_j(0-14)}$	J (N=15)	15	0.074	[0.011; 0.145]	−0.073	[-0.183; 0.043]
	J-Z (N=15)	15	0.133	[0.066; 0.204]	−0.014	[-0.127; 0.101]
	J-Pa (N=15)	15	0.101	[0.057; 0.146]	−0.046	[-0.147; 0.057]
	Pa-Z (N=15)	15	0.153	[0.102; 0.206]	0.006	[-0.099; 0.111]
	Pa-Z-M (N=15)	15	0.243	[0.084; 0.410]	0.096	[-0.086; 0.285]
	Rifafour (N=10)	10	0.147	[0.054; 0.238]		
$\mathbf{EBA_j(0-2)}$	J (N=15)	15	0.001	[-0.083; 0.086]	−0.155	[-0.318; 0.003]
	J-Z (N=15)	15	0.071	[-0.036; 0.174]	−0.085	[-0.256; 0.083]
	J-Pa (N=15)	15	0.105	[0.020; 0.185]	−0.051	[-0.215; 0.107]
	Pa-Z (N=15)	15	0.178	[0.083; 0.272]	0.022	[-0.146; 0.187]
	Pa-Z-M (N=15)	15	0.321	[0.178; 0.468]	0.166	[-0.034; 0.363]
	Rifafour (N=10)	10	0.156	[0.023; 0.296]		
$\mathbf{EBA_j(2-14)}$	J (N=15)	15	0.086	[0.021; 0.170]	−0.059	[-0.184; 0.076]
	J-Z (N=15)	15	0.144	[0.066; 0.227]	−0.002	[-0.134; 0.133]
	J-Pa (N=15)	15	0.101	[0.054; 0.147]	−0.045	[-0.159; 0.073]
	Pa-Z (N=15)	15	0.149	[0.095; 0.201]	0.004	[-0.115; 0.121]
	Pa-Z-M (N=15)	15	0.229	[0.042; 0.427]	0.084	[-0.128; 0.306]
	Rifafour (N=10)	10	0.145	[0.037; 0.251]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.12: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



E.2 NC002 ("SSCC") Trial

Differential Hyperbolic Tangent Regression Model

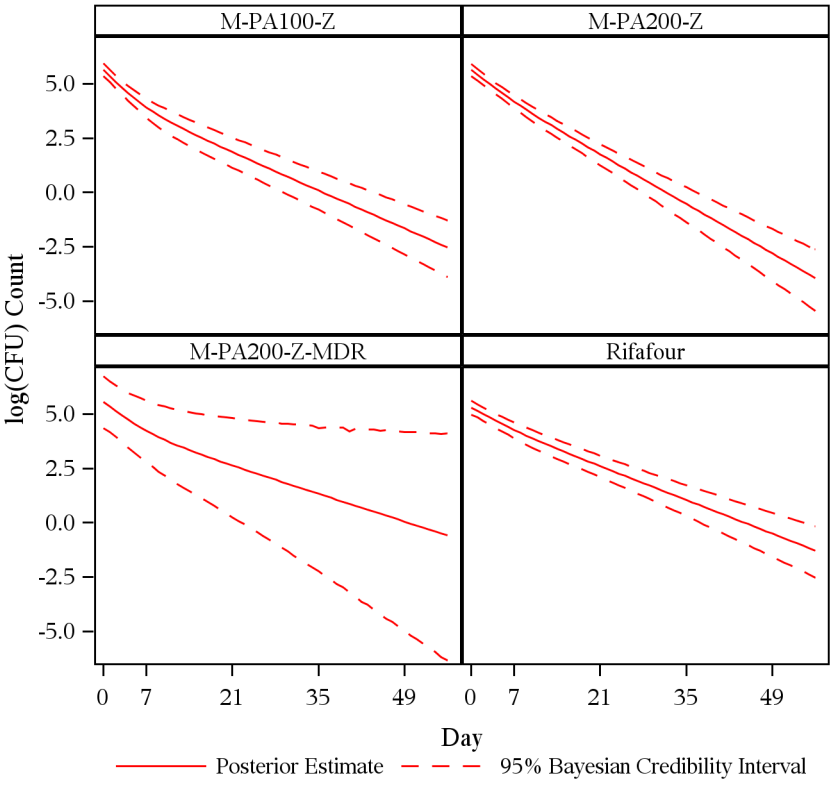
Model 1.6: **Residuals: Student t**
Random Coefficients: Normal
Covariance Matrix: "Frequentist" Wishart

Table E.14: Posterior Estimates and Corresponding 95% BCIs for $\text{BA}_j(t_1 - t_2)$

					Difference vs Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\text{BA}_j(0-56)$	M-PA100-Z (N=60)	56	0.146	[0.123; 0.170]	0.028	[-0.003; 0.060]
	M-PA200-Z (N=61)	54	0.171	[0.147; 0.197]	0.053	[0.022; 0.087]
	M-PA200-Z-MDR (N=26)	9	0.110	[0.036; 0.203]	−0.008	[-0.084; 0.085]
	Rifafour (N=59)	54	0.118	[0.096; 0.140]		
$\text{BA}_j(7-56)$	M-PA100-Z (N=60)	56	0.132	[0.106; 0.159]	0.018	[-0.017; 0.054]
	M-PA200-Z (N=61)	54	0.166	[0.138; 0.197]	0.052	[0.016; 0.091]
	M-PA200-Z-MDR (N=26)	9	0.098	[0.019; 0.200]	−0.015	[-0.098; 0.088]
	Rifafour (N=59)	54	0.113	[0.090; 0.139]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{BA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.13: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



E.3 NC003 Trial

E.3.1 Differential Hyperbolic Tangent Regression Model

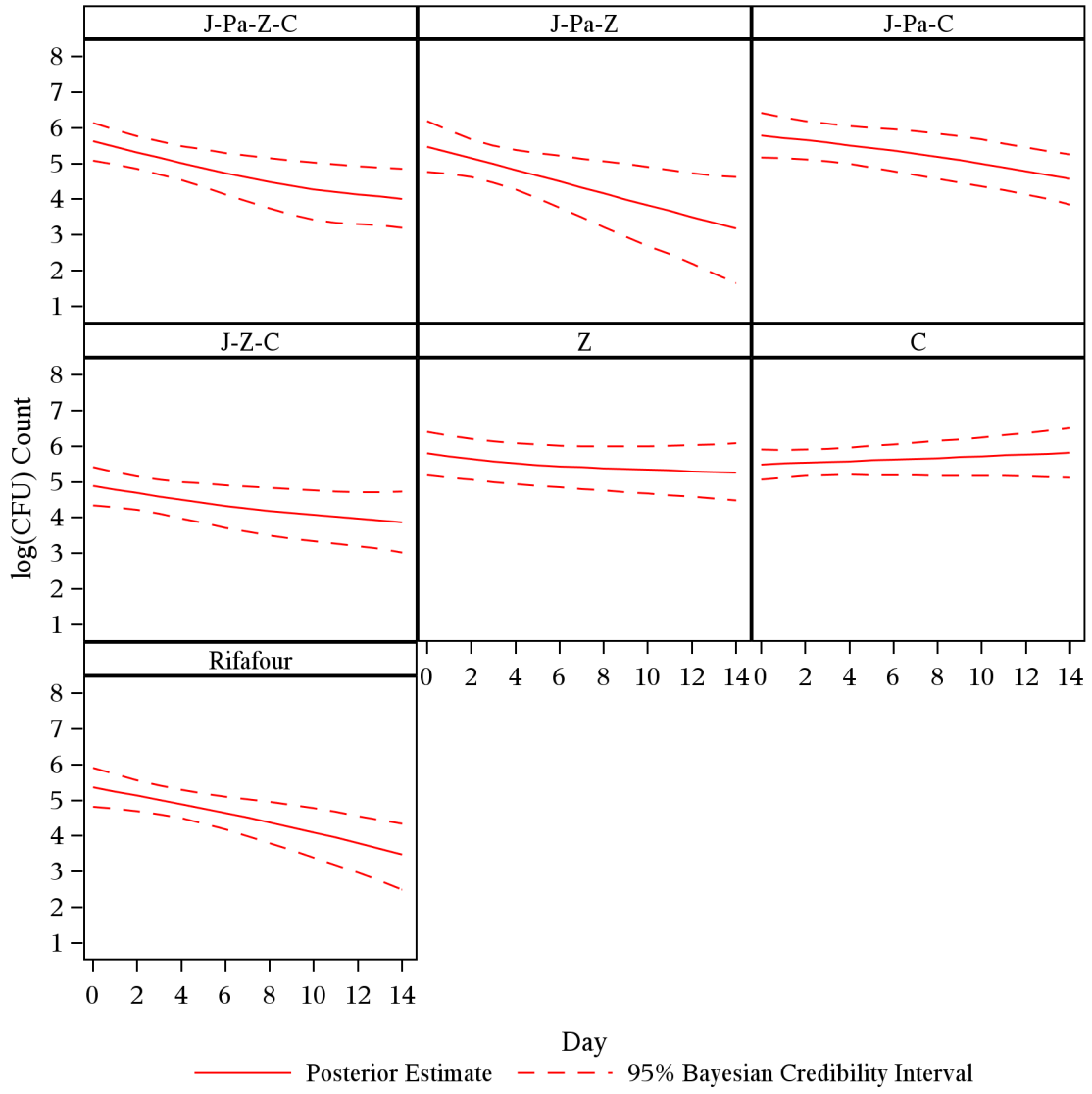
Model 1.5: **Residuals: Student t**
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.15: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\text{EBA}_j(0-14)$	J-Pa-Z-C (N=14)	14	0.115	[0.053; 0.178]	−0.019	[-0.113; 0.073]
	J-Pa-Z (N=14)	12	0.164	[0.063; 0.276]	0.029	[-0.095; 0.158]
	J-Pa-C (N=15)	15	0.087	[0.024; 0.151]	−0.047	[-0.142; 0.046]
	J-Z-C (N=14)	14	0.073	[0.004; 0.142]	−0.062	[-0.160; 0.035]
	Z (N=15)	15	0.038	[-0.012; 0.087]	−0.096	[-0.183; -0.013]
	C (N=15)	14	−0.023	[-0.070; 0.023]	−0.157	[-0.243; -0.075]
	Rifafour (N=15)	15	0.134	[0.066; 0.206]		
$\text{EBA}_j(0-2)$	J-Pa-Z-C (N=14)	14	0.153	[0.050; 0.265]	0.037	[-0.113; 0.190]
	J-Pa-Z (N=14)	12	0.161	[-0.016; 0.339]	0.045	[-0.160; 0.252]
	J-Pa-C (N=15)	15	0.069	[-0.042; 0.177]	−0.047	[-0.201; 0.104]
	J-Z-C (N=14)	14	0.099	[-0.024; 0.224]	−0.017	[-0.179; 0.150]
	Z (N=15)	15	0.079	[-0.006; 0.170]	−0.037	[-0.173; 0.105]
	C (N=15)	14	−0.023	[-0.121; 0.073]	−0.140	[-0.284; 0.006]
	Rifafour (N=15)	15	0.116	[0.006; 0.223]		
$\text{EBA}_j(2-14)$	J-Pa-Z-C (N=14)	14	0.109	[0.041; 0.171]	−0.029	[-0.129; 0.066]
	J-Pa-Z (N=14)	12	0.164	[0.051; 0.292]	0.027	[-0.110; 0.168]
	J-Pa-C (N=15)	15	0.090	[0.025; 0.160]	−0.047	[-0.147; 0.051]
	J-Z-C (N=14)	14	0.068	[-0.009; 0.143]	−0.069	[-0.178; 0.034]
	Z (N=15)	15	0.031	[-0.029; 0.089]	−0.106	[-0.203; -0.015]
	C (N=15)	14	−0.023	[-0.076; 0.030]	−0.160	[-0.253; -0.072]
	Rifafour (N=15)	15	0.137	[0.066; 0.214]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.14: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



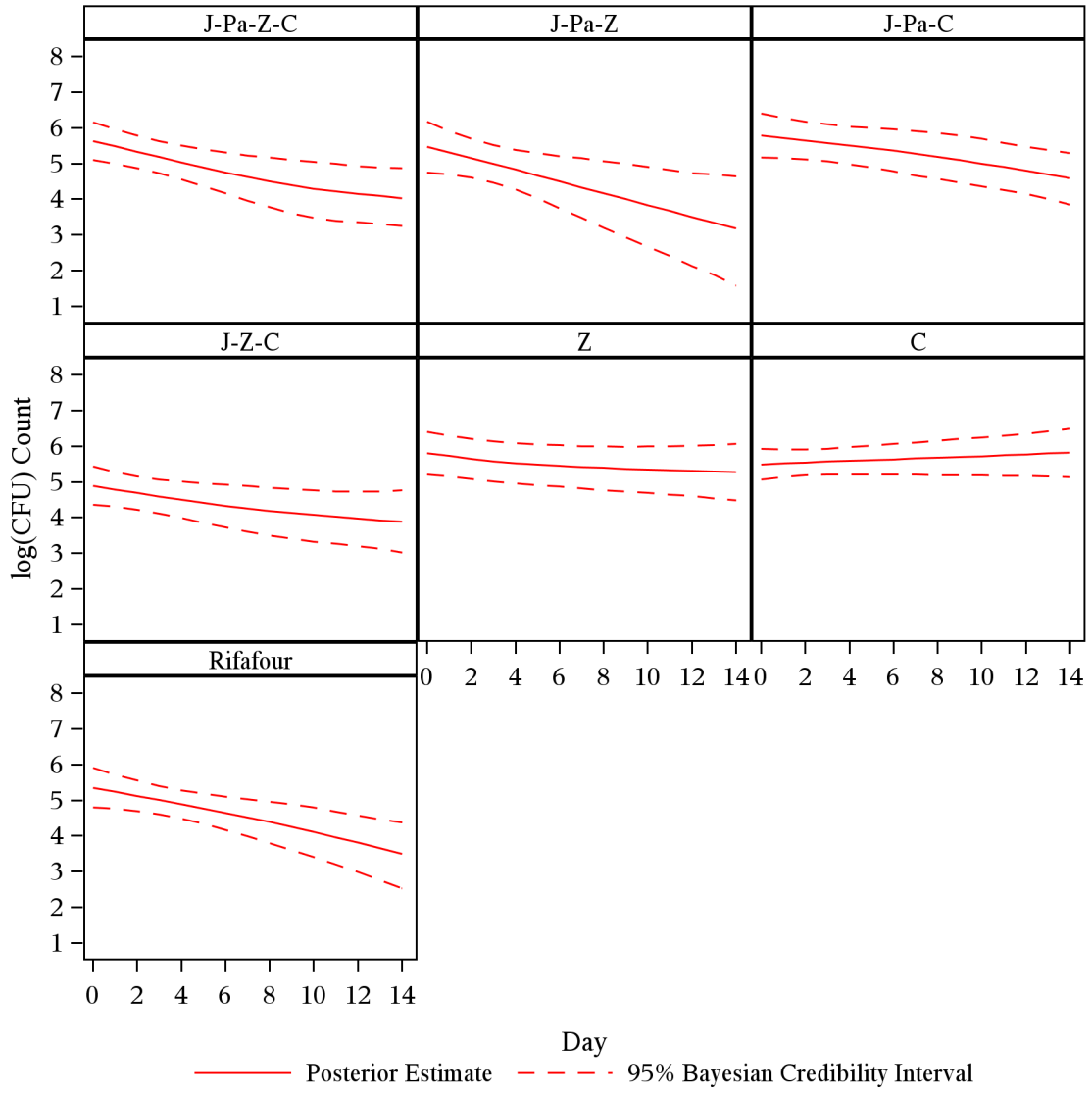
Model 1.7: **Residuals: Student t**
Random Coefficients: Student t
Covariance Matrix: "Default" Wishart

Table E.16: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{EBA_j(0-14)}$	J-Pa-Z-C (N=14)	14	0.114	[0.053; 0.177]	−0.018	[-0.113; 0.074]
	J-Pa-Z (N=14)	12	0.163	[0.060; 0.280]	0.031	[-0.096; 0.164]
	J-Pa-C (N=15)	15	0.086	[0.022; 0.148]	−0.047	[-0.142; 0.046]
	J-Z-C (N=14)	14	0.072	[0.004; 0.142]	−0.060	[-0.159; 0.037]
	Z (N=15)	15	0.038	[-0.012; 0.087]	−0.094	[-0.180; -0.009]
	C (N=15)	14	–0.023	[-0.069; 0.023]	−0.156	[-0.241; -0.074]
	Rifafour (N=15)	15	0.133	[0.064; 0.204]		
$\mathbf{EBA_j(0-2)}$	J-Pa-Z-C (N=14)	14	0.151	[0.048; 0.261]	0.036	[-0.113; 0.187]
	J-Pa-Z (N=14)	12	0.157	[-0.022; 0.336]	0.042	[-0.165; 0.250]
	J-Pa-C (N=15)	15	0.069	[-0.042; 0.179]	−0.046	[-0.198; 0.110]
	J-Z-C (N=14)	14	0.099	[-0.022; 0.226]	−0.016	[-0.179; 0.150]
	Z (N=15)	15	0.079	[-0.007; 0.170]	−0.036	[-0.172; 0.102]
	C (N=15)	14	–0.025	[-0.126; 0.072]	−0.140	[-0.284; 0.004]
	Rifafour (N=15)	15	0.115	[0.008; 0.221]		
$\mathbf{EBA_j(2-14)}$	J-Pa-Z-C (N=14)	14	0.108	[0.040; 0.170]	−0.027	[-0.128; 0.065]
	J-Pa-Z (N=14)	12	0.164	[0.050; 0.295]	0.029	[-0.111; 0.177]
	J-Pa-C (N=15)	15	0.088	[0.023; 0.157]	−0.047	[-0.147; 0.051]
	J-Z-C (N=14)	14	0.068	[-0.011; 0.143]	−0.068	[-0.175; 0.037]
	Z (N=15)	15	0.031	[-0.029; 0.088]	−0.104	[-0.200; -0.012]
	C (N=15)	14	–0.023	[-0.075; 0.030]	−0.158	[-0.251; -0.073]
	Rifafour (N=15)	15	0.135	[0.065; 0.211]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.15: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



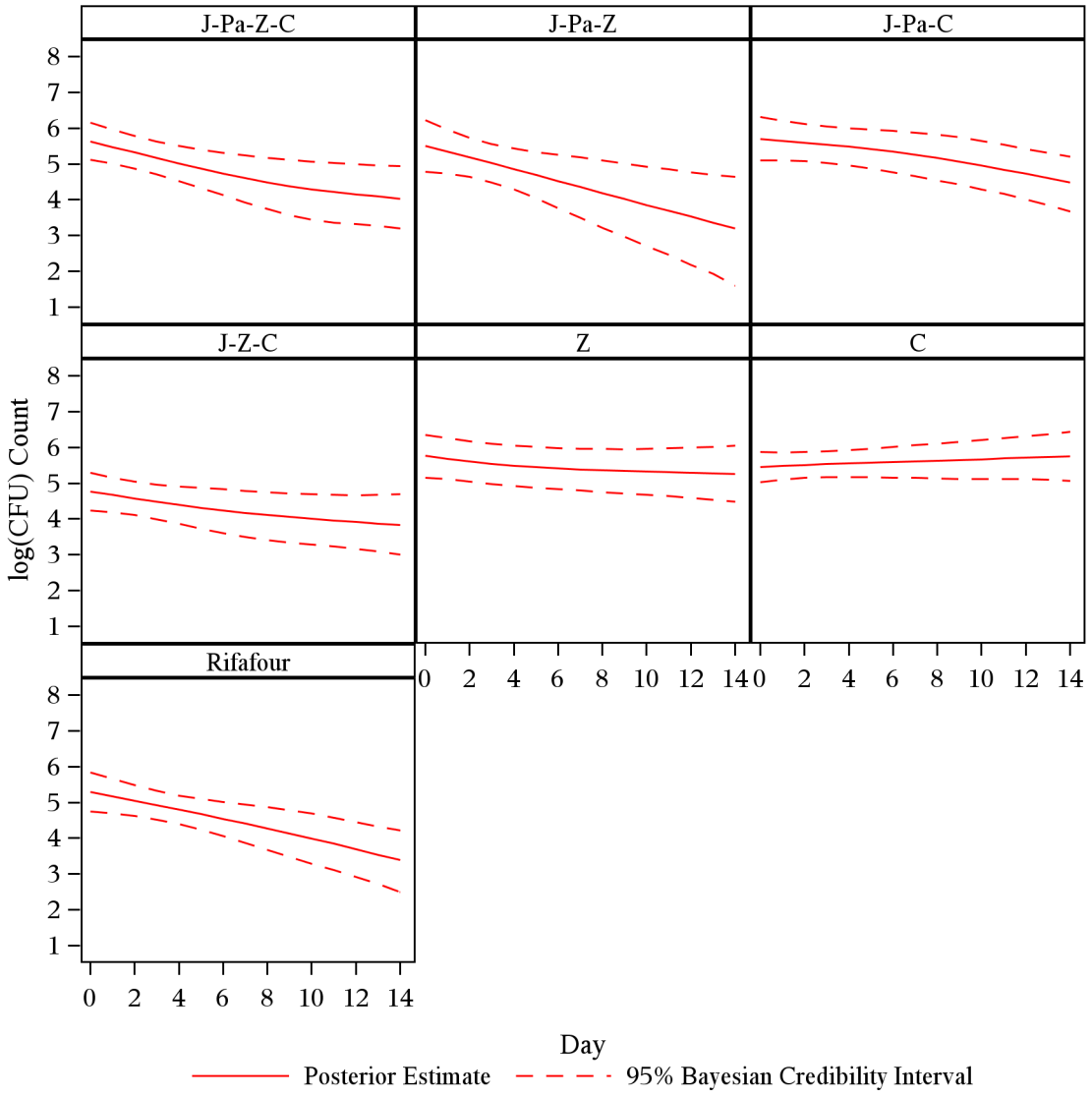
Model 1.9: Residuals: Skew Student t
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.17: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		**Posterior**		**Posterior**	
Parameter	**Group**	**n**	**Estimate**	**95% BCI**	**Estimate**	**95% BCI**
$\mathbf{EBA_j(0-14)}$	J-Pa-Z-C (N=14)	14	0.114	[0.050; 0.178]	−0.022	[-0.116; 0.070]
	J-Pa-Z (N=14)	12	0.165	[0.061; 0.280]	0.028	[-0.098; 0.163]
	J-Pa-C (N=15)	15	0.087	[0.025; 0.151]	−0.050	[-0.141; 0.043]
	J-Z-C (N=14)	14	0.067	[0.001; 0.133]	−0.069	[-0.165; 0.024]
	Z (N=15)	15	0.036	[-0.015; 0.085]	−0.100	[-0.186; -0.017]
	C (N=15)	14	–0.021	[-0.069; 0.026]	−0.158	[-0.240; -0.076]
	Rifafour (N=15)	15	0.137	[0.069; 0.207]		
$\mathbf{EBA_j(0-2)}$	J-Pa-Z-C (N=14)	14	0.158	[0.051; 0.273]	0.033	[-0.118; 0.188]
	J-Pa-Z (N=14)	12	0.161	[-0.023; 0.343]	0.036	[-0.176; 0.245]
	J-Pa-C (N=15)	15	0.054	[-0.058; 0.164]	−0.071	[-0.221; 0.081]
	J-Z-C (N=14)	14	0.096	[-0.030; 0.226]	−0.028	[-0.191; 0.138]
	Z (N=15)	15	0.076	[-0.011; 0.168]	−0.049	[-0.185; 0.090]
	C (N=15)	14	–0.025	[-0.128; 0.073]	−0.150	[-0.298; -0.006]
	Rifafour (N=15)	15	0.125	[0.017; 0.231]		
$\mathbf{EBA_j(2-14)}$	J-Pa-Z-C (N=14)	14	0.107	[0.033; 0.170]	−0.031	[-0.132; 0.063]
	J-Pa-Z (N=14)	12	0.165	[0.050; 0.296]	0.027	[-0.108; 0.173]
	J-Pa-C (N=15)	15	0.092	[0.028; 0.165]	−0.046	[-0.141; 0.053]
	J-Z-C (N=14)	14	0.062	[-0.015; 0.134]	−0.076	[-0.180; 0.022]
	Z (N=15)	15	0.030	[-0.032; 0.086]	−0.109	[-0.202; -0.020]
	C (N=15)	14	–0.021	[-0.074; 0.032]	−0.159	[-0.246; -0.075]
	Rifafour (N=15)	15	0.139	[0.071; 0.210]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.16: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



E.3.2 Other Regression Models

E.3.2.1 Linear Regression Model

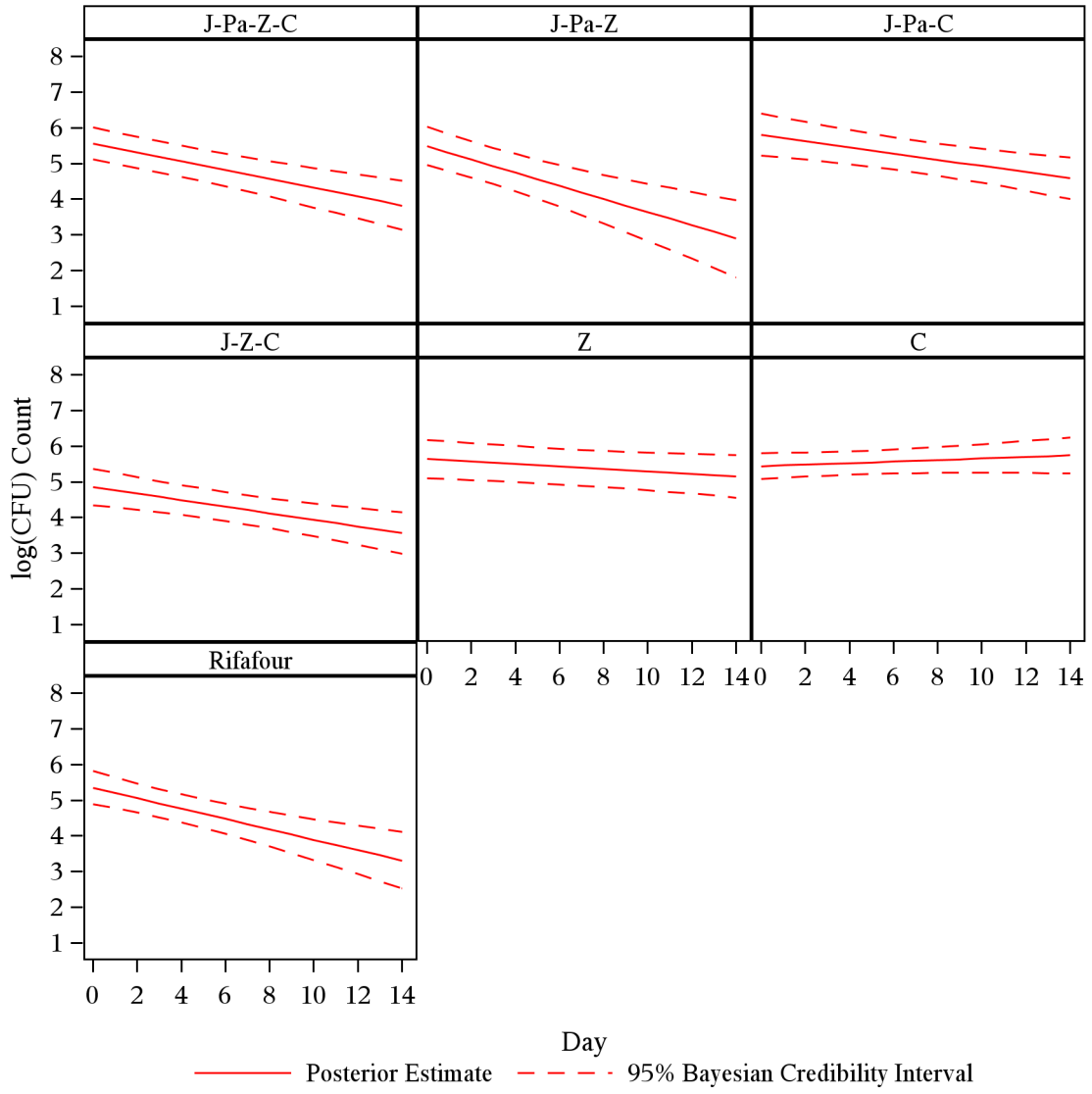
Model 2.1: **Residuals: Normal**
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.18: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J-Pa-Z-C (N=14)	14	5.558	[5.110; 6.009]
	J-Pa-Z (N=14)	12	5.480	[4.950; 6.025]
	J-Pa-C (N=15)	15	5.806	[5.218; 6.399]
	J-Z-C (N=14)	14	4.860	[4.345; 5.370]
	Z (N=15)	15	5.646	[5.102; 6.175]
	C (N=15)	14	5.438	[5.072; 5.805]
	Rifafour (N=15)	15	5.351	[4.893; 5.816]
$\boldsymbol{\lambda_j}$	J-Pa-Z-C (N=14)	14	0.124	[0.077; 0.172]
	J-Pa-Z (N=14)	12	0.184	[0.103; 0.266]
	J-Pa-C (N=15)	15	0.087	[0.033; 0.142]
	J-Z-C (N=14)	14	0.092	[0.040; 0.146]
	Z (N=15)	15	0.035	[-0.002; 0.073]
	C (N=15)	14	−0.022	[-0.061; 0.017]
	Rifafour (N=15)	15	0.146	[0.079; 0.213]

Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.17: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



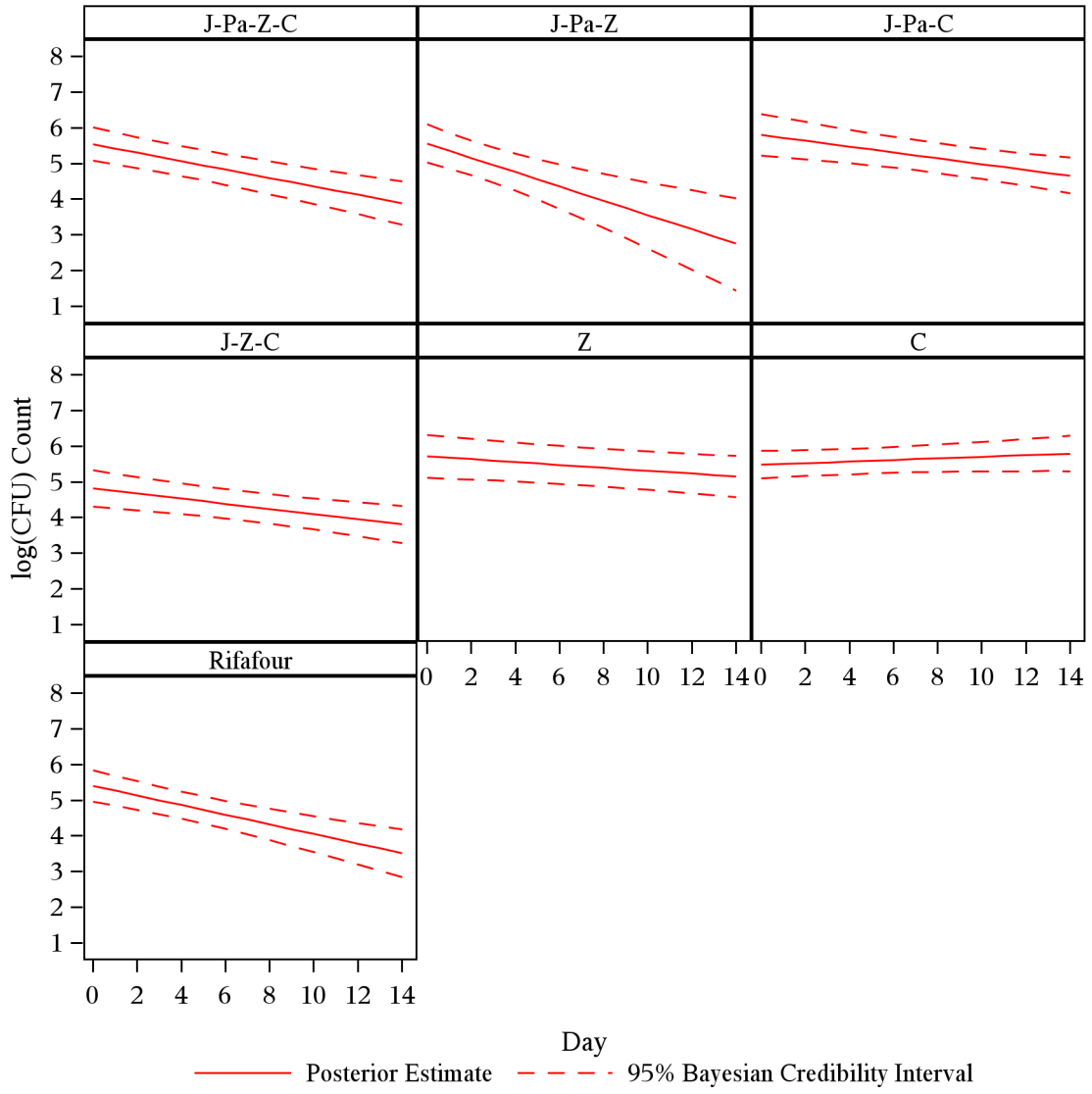
Model 2.2: Residuals: Student t
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.19: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J-Pa-Z-C (N=14)	14	5.538	[5.074; 6.006]
	J-Pa-Z (N=14)	12	5.555	[5.019; 6.093]
	J-Pa-C (N=15)	15	5.802	[5.219; 6.385]
	J-Z-C (N=14)	14	4.814	[4.299; 5.326]
	Z (N=15)	15	5.718	[5.113; 6.316]
	C (N=15)	14	5.480	[5.096; 5.866]
	Rifafour (N=15)	15	5.401	[4.964; 5.844]
$\boldsymbol{\lambda_j}$	J-Pa-Z-C (N=14)	14	0.118	[0.073; 0.163]
	J-Pa-Z (N=14)	12	0.200	[0.099; 0.305]
	J-Pa-C (N=15)	15	0.082	[0.034; 0.131]
	J-Z-C (N=14)	14	0.071	[0.025; 0.119]
	Z (N=15)	15	0.041	[0.004; 0.076]
	C (N=15)	14	−0.022	[-0.057; 0.013]
	Rifafour (N=15)	15	0.135	[0.080; 0.190]

Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.18: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



E.3.2.2 Conventional Bilinear Regression Model

Model 3.1: Residuals: Normal
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.20: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J-Pa-Z-C (N=14)	14	0.116	[0.048; 0.184]	−0.037	[-0.145; 0.071]
	J-Pa-Z (N=14)	12	0.173	[0.076; 0.272]	0.020	[-0.110; 0.151]
	J-Pa-C (N=15)	15	0.081	[0.017; 0.147]	−0.071	[-0.180; 0.037]
	J-Z-C (N=14)	14	0.105	[0.027; 0.187]	−0.048	[-0.164; 0.068]
	Z (N=15)	15	0.037	[-0.016; 0.089]	−0.115	[-0.217; -0.016]
	C (N=15)	14	–0.022	[-0.077; 0.034]	−0.174	[-0.277; -0.073]
	Rifafour (N=15)	15	0.153	[0.067; 0.240]		
$\mathbf{EBA_j(0-2)}$	J-Pa-Z-C (N=14)	14	0.168	[0.048; 0.291]	0.035	[-0.153; 0.224]
	J-Pa-Z (N=14)	12	0.208	[0.024; 0.388]	0.074	[-0.155; 0.304]
	J-Pa-C (N=15)	15	0.072	[-0.037; 0.180]	−0.061	[-0.240; 0.118]
	J-Z-C (N=14)	14	0.125	[-0.012; 0.263]	−0.009	[-0.206; 0.187]
	Z (N=15)	15	0.104	[-0.018; 0.250]	−0.030	[-0.220; 0.173]
	C (N=15)	14	0.012	[-0.091; 0.113]	−0.122	[-0.298; 0.052]
	Rifafour (N=15)	15	0.134	[-0.009; 0.278]		
$\mathbf{EBA_j(2-14)}$	J-Pa-Z-C (N=14)	14	0.107	[0.028; 0.176]	−0.049	[-0.176; 0.072]
	J-Pa-Z (N=14)	12	0.167	[0.058; 0.270]	0.011	[-0.138; 0.156]
	J-Pa-C (N=15)	15	0.083	[0.017; 0.151]	−0.073	[-0.196; 0.051]
	J-Z-C (N=14)	14	0.101	[0.011; 0.191]	−0.054	[-0.192; 0.077]
	Z (N=15)	15	0.026	[-0.042; 0.090]	−0.130	[-0.253; -0.011]
	C (N=15)	14	–0.027	[-0.090; 0.029]	−0.183	[-0.302; -0.067]
	Rifafour (N=15)	15	0.156	[0.054; 0.261]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table E.21: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\alpha_j}$	J-Pa-Z-C (N=14)	14	5.662	[5.154; 6.168]
	J-Pa-Z (N=14)	12	5.548	[4.821; 6.266]
	J-Pa-C (N=15)	15	5.765	[5.145; 6.383]
	J-Z-C (N=14)	14	4.932	[4.398; 5.467]
	Z (N=15)	15	5.747	[5.161; 6.340]
	C (N=15)	14	5.529	[5.096; 5.963]
	Rifafour (N=15)	15	5.323	[4.726; 5.907]
$\boldsymbol{\beta_{1j}}$	J-Pa-Z-C (N=14)	14	0.118	[0.063; 0.174]
	J-Pa-Z (N=14)	12	0.174	[0.088; 0.259]
	J-Pa-C (N=15)	15	0.082	[0.019; 0.145]
	J-Z-C (N=14)	14	0.106	[0.036; 0.181]
	Z (N=15)	15	0.061	[0.005; 0.126]
	C (N=15)	14	−0.024	[-0.072; 0.024]
	Rifafour (N=15)	15	0.149	[0.076; 0.223]
$\boldsymbol{\lambda_{1j}}$	J-Pa-Z-C (N=14)	14	0.168	[0.048; 0.291]
	J-Pa-Z (N=14)	12	0.208	[0.024; 0.388]
	J-Pa-C (N=15)	15	0.072	[-0.037; 0.180]
	J-Z-C (N=14)	14	0.125	[-0.012; 0.263]
	Z (N=15)	15	0.104	[-0.018; 0.250]
	C (N=15)	14	0.012	[-0.091; 0.113]
	Rifafour (N=15)	15	0.134	[-0.009; 0.278]
$\boldsymbol{\beta_{2j}}$	J-Pa-Z-C (N=14)	14	−0.051	[-0.148; 0.048]
	J-Pa-Z (N=14)	12	−0.034	[-0.181; 0.112]
	J-Pa-C (N=15)	15	0.010	[-0.098; 0.114]
	J-Z-C (N=14)	14	−0.019	[-0.149; 0.113]
	Z (N=15)	15	−0.043	[-0.139; 0.045]
	C (N=15)	14	−0.036	[-0.121; 0.050]
	Rifafour (N=15)	15	0.015	[-0.100; 0.130]

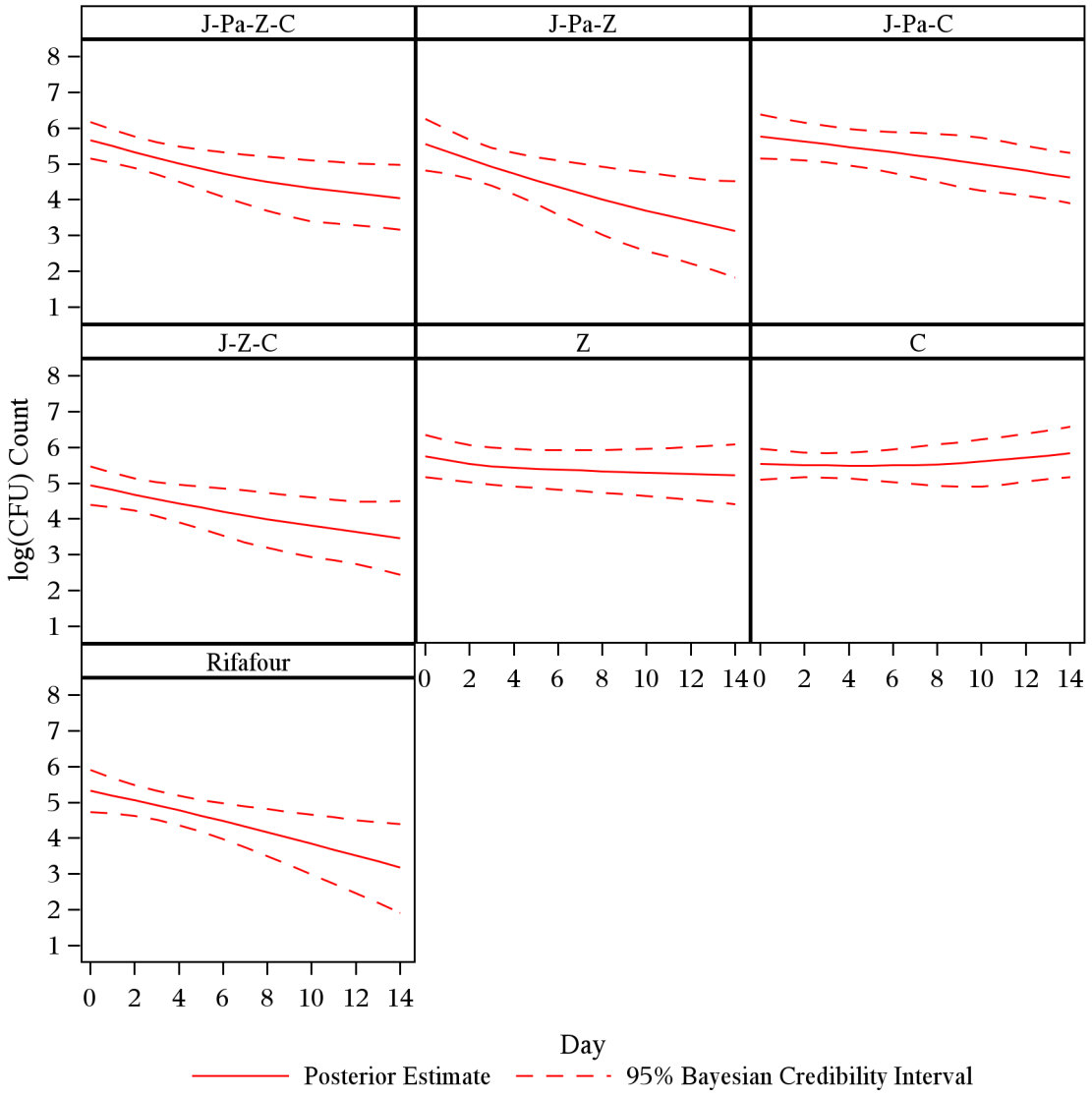
Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Table E.21: Posterior Estimates and Corresponding 95% BCIs for Mean Regression Model Parameters

Parameter	Treatment Group	n	Posterior Estimate	95% BCI
$\boldsymbol{\beta_{2fj}}$	J-Pa-Z-C (N=14)	14	−0.051	[-0.406; 0.304]
	J-Pa-Z (N=14)	12	−0.034	[-0.531; 0.462]
	J-Pa-C (N=15)	15	0.010	[-0.355; 0.378]
	J-Z-C (N=14)	14	−0.016	[-0.488; 0.468]
	Z (N=15)	15	−0.043	[-0.340; 0.249]
	C (N=15)	14	−0.036	[-0.317; 0.245]
	Rifafour (N=15)	15	0.014	[-0.401; 0.422]
$\boldsymbol{\lambda_{2j}}$	J-Pa-Z-C (N=14)	14	0.067	[-0.038; 0.169]
	J-Pa-Z (N=14)	12	0.140	[-0.017; 0.296]
	J-Pa-C (N=15)	15	0.092	[-0.047; 0.224]
	J-Z-C (N=14)	14	0.086	[-0.074; 0.255]
	Z (N=15)	15	0.017	[-0.062; 0.095]
	C (N=15)	14	−0.060	[-0.156; 0.033]
	Rifafour (N=15)	15	0.164	[0.036; 0.296]
$\boldsymbol{\kappa_j}$	J-Pa-Z-C (N=14)	14	6.753	[2.291; 10.780]
	J-Pa-Z (N=14)	12	6.624	[2.277; 10.750]
	J-Pa-C (N=15)	15	8.734	[3.414; 10.930]
	J-Z-C (N=14)	14	7.140	[2.709; 10.760]
	Z (N=15)	15	3.714	[2.027; 9.694]
	C (N=15)	14	7.181	[2.376; 10.830]
	Rifafour (N=15)	15	4.289	[2.062; 9.891]

Note: BCI: Bayesian credibility interval. N = Total number of patients. N = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.19: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



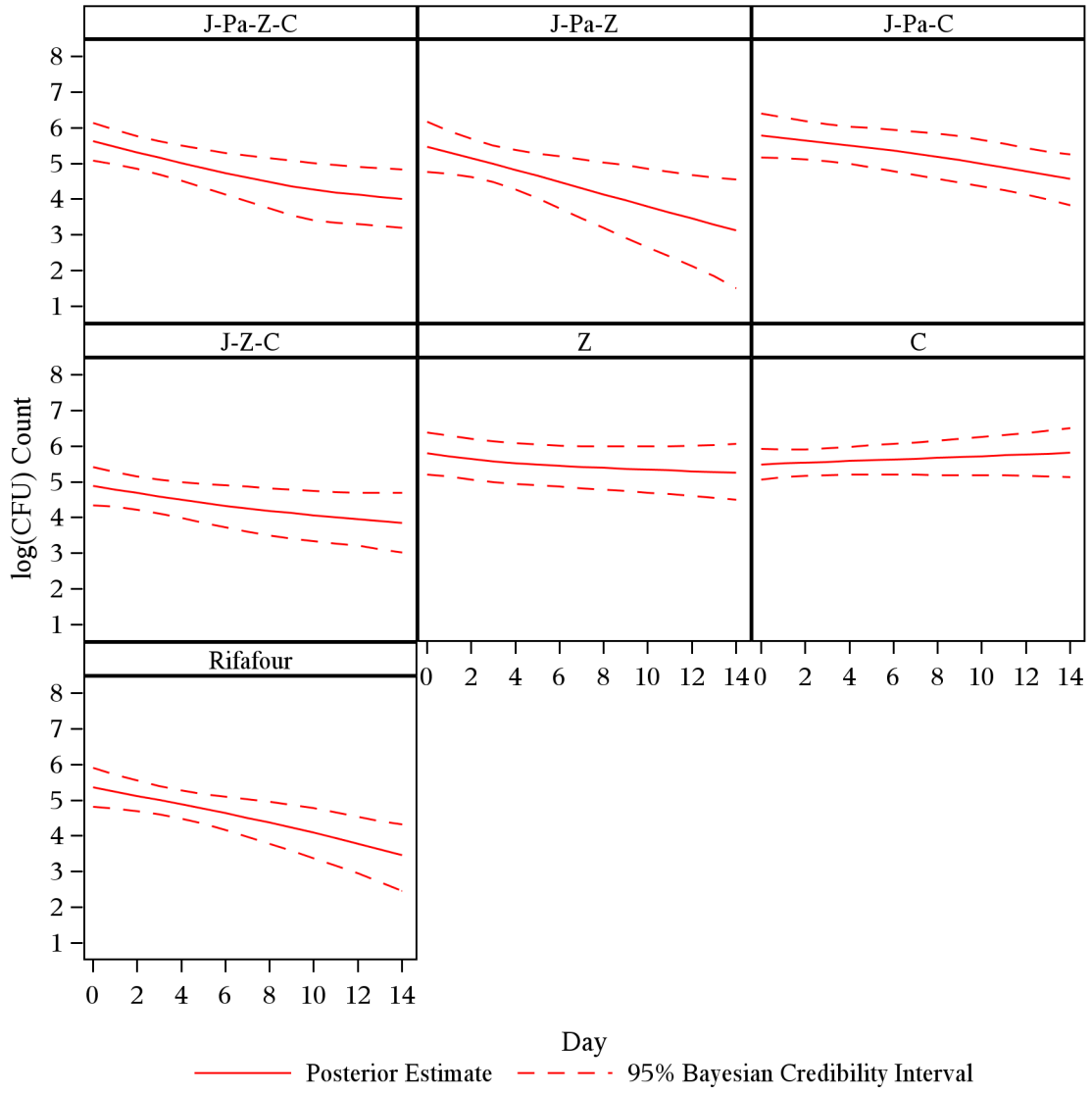
Model 3.2: Residuals: Student t
Random Coefficients: Normal
Covariance Matrix: "Default" Wishart

Table E.22: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
	Treatment		Posterior		Posterior	
Parameter	Group	n	Estimate	95% BCI	Estimate	95% BCI
$\mathbf{EBA_j(0-14)}$	J-Pa-Z-C (N=14)	14	0.115	[0.054; 0.178]	−0.021	[-0.117; 0.071]
	J-Pa-Z (N=14)	12	0.168	[0.066; 0.282]	0.032	[-0.093; 0.165]
	J-Pa-C (N=15)	15	0.087	[0.024; 0.151]	−0.050	[-0.145; 0.043]
	J-Z-C (N=14)	14	0.074	[0.006; 0.140]	−0.063	[-0.162; 0.035]
	Z (N=15)	15	0.038	[-0.012; 0.087]	−0.098	[-0.188; -0.014]
	C (N=15)	14	–0.023	[-0.070; 0.023]	−0.160	[-0.247; -0.078]
	Rifafour (N=15)	15	0.136	[0.068; 0.211]		
$\mathbf{EBA_j(0-2)}$	J-Pa-Z-C (N=14)	14	0.153	[0.049; 0.263]	0.033	[-0.114; 0.182]
	J-Pa-Z (N=14)	12	0.161	[-0.017; 0.335]	0.041	[-0.164; 0.243]
	J-Pa-C (N=15)	15	0.068	[-0.043; 0.177]	−0.052	[-0.202; 0.099]
	J-Z-C (N=14)	14	0.099	[-0.023; 0.224]	−0.020	[-0.177; 0.141]
	Z (N=15)	15	0.079	[-0.010; 0.174]	−0.040	[-0.177; 0.099]
	C (N=15)	14	–0.025	[-0.126; 0.071]	−0.145	[-0.290; -0.002]
	Rifafour (N=15)	15	0.119	[0.014; 0.223]		
$\mathbf{EBA_j(2-14)}$	J-Pa-Z-C (N=14)	14	0.109	[0.042; 0.172]	−0.030	[-0.133; 0.064]
	J-Pa-Z (N=14)	12	0.169	[0.056; 0.301]	0.030	[-0.108; 0.177]
	J-Pa-C (N=15)	15	0.090	[0.025; 0.159]	−0.049	[-0.150; 0.050]
	J-Z-C (N=14)	14	0.070	[-0.008; 0.143]	−0.070	[-0.178; 0.034]
	Z (N=15)	15	0.031	[-0.030; 0.089]	−0.108	[-0.207; -0.017]
	C (N=15)	14	–0.023	[-0.077; 0.030]	−0.162	[-0.258; -0.075]
	Rifafour (N=15)	15	0.139	[0.069; 0.220]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.20: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



E.4 Other Datasets

E.4.1 CL001 Trial

Figure E.21 shows nested plots of the observed log(CFU) counts by treatment group.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.23 for Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.22 by study day and treatment group for Model 1.1.

Table E.23: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
Parameter	**Treatment Group**	**n**	**Posterior Estimate**	**95% BCI**	**Posterior Estimate**	**95% BCI**
$\text{EBA}_j(0-14)$	TMC207 100 mg (N=15)	15	0.046	[-0.006; 0.100]	−0.028	[-0.160; 0.120]
	TMC207 200 mg (N=15)	15	0.062	[0.012; 0.115]	−0.012	[-0.144; 0.137]
	TMC207 300 mg (N=15)	15	0.079	[0.012; 0.150]	0.005	[-0.135; 0.159]
	TMC207 400 mg (N=15)	15	0.104	[0.045; 0.164]	0.029	[-0.106; 0.179]
	Rifafour (N=8)	8	0.074	[-0.065; 0.196]		
$\text{EBA}_j(0-2)$	TMC207 100 mg (N=15)	15	0.033	[-0.057; 0.129]	−0.218	[-0.447; -0.006]
	TMC207 200 mg (N=15)	15	0.006	[-0.094; 0.085]	−0.245	[-0.475; -0.039]
	TMC207 300 mg (N=15)	15	0.037	[-0.070; 0.143]	−0.214	[-0.449; 0.002]
	TMC207 400 mg (N=15)	15	0.089	[-0.002; 0.178]	−0.161	[-0.391; 0.045]
	Rifafour (N=8)	8	0.251	[0.064; 0.463]		
$\text{EBA}_j(2-14)$	TMC207 100 mg (N=15)	15	0.049	[-0.012; 0.111]	0.004	[-0.149; 0.180]
	TMC207 200 mg (N=15)	15	0.072	[0.018; 0.132]	0.027	[-0.125; 0.204]
	TMC207 300 mg (N=15)	15	0.086	[0.012; 0.170]	0.041	[-0.118; 0.227]
	TMC207 400 mg (N=15)	15	0.106	[0.043; 0.173]	0.061	[-0.094; 0.239]
	Rifafour (N=8)	8	0.045	[-0.124; 0.185]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$ are shown in Figure E.23, Figure E.24 and Figure E.25 by treatment group and model. Similar to

Figure E.21: Observed log(CFU) Counts Over Time

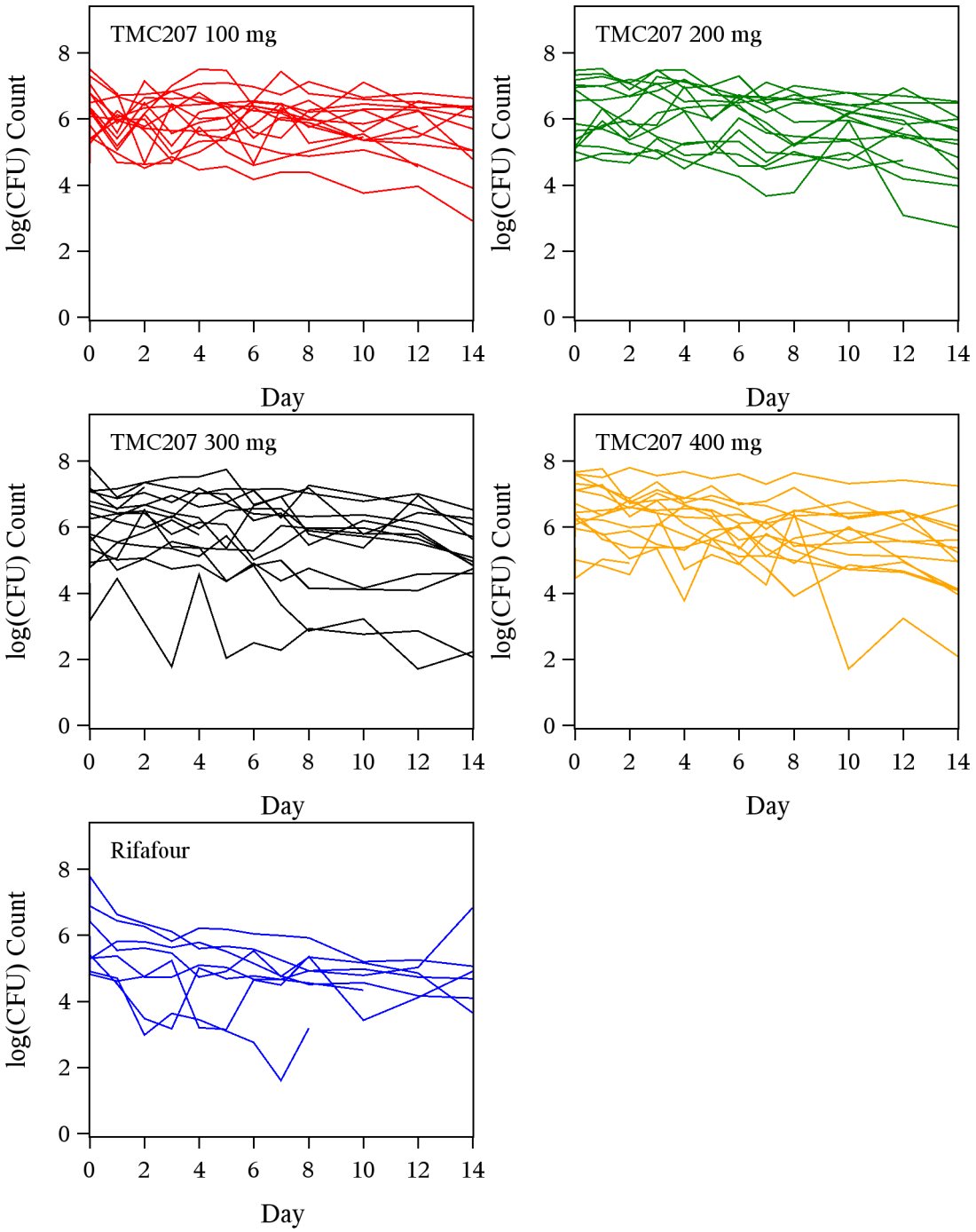
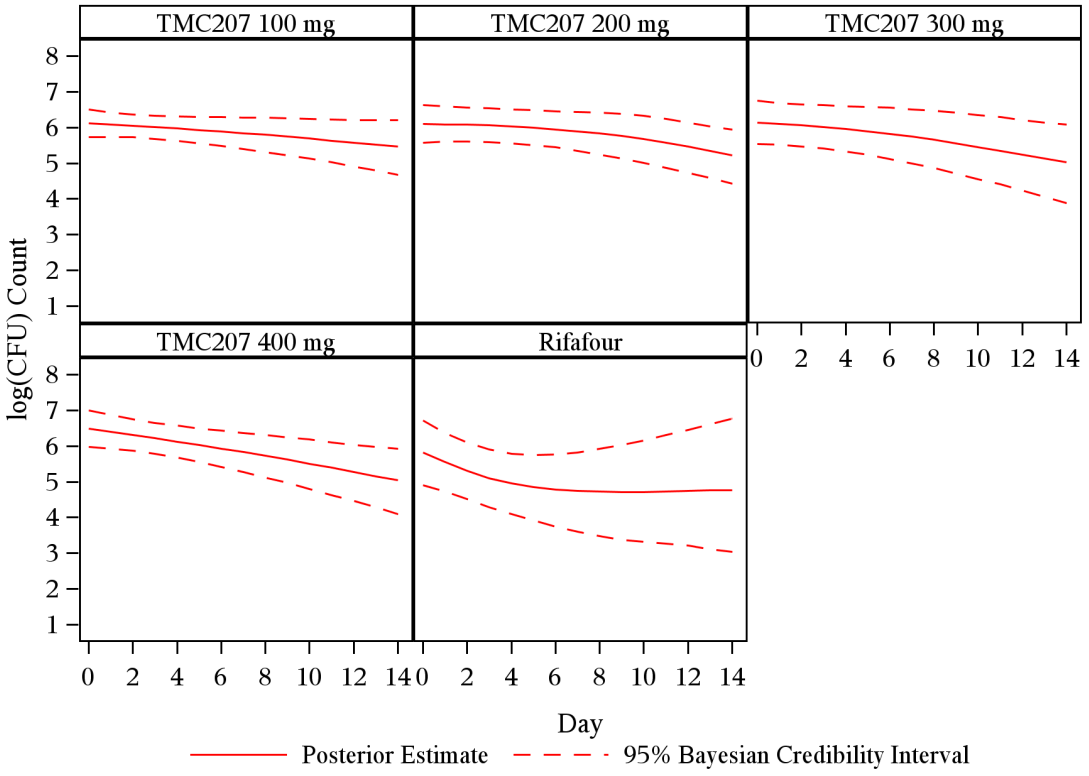


Figure E.22: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



the NC001 trial, the linear models (Model 2.1 and Model 2.2) occasionally yield results substantially different to those of other models.

Model comparison statistics for the various Bayesian NLME regression models fitted are provided in Table E.24.

The DIC favors conventional bilinear regression models over differential hyperbolic tangent regression models, followed by linear regression models.

Bayes factors (marginal likelihoods) favor linear regression models, followed by differential hyperbolic tangent and conventional bilinear regression models.

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

The Bayes factors indicate that building skewness into the distributions of residuals does not improve model fitting.

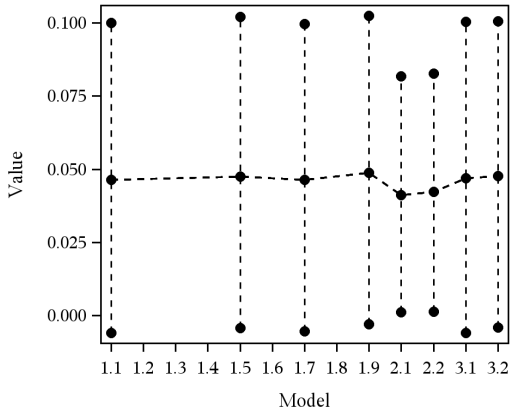
The ICPOs suggest the models fit the data reasonably well.

Table E.24: Comparison of Bayesian NLME Regression Models

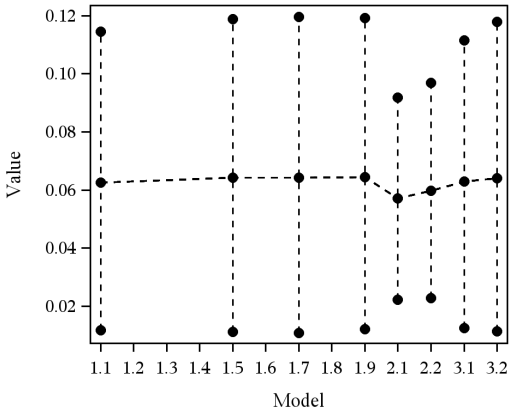
		DIC					% ICPO $< x$		
Regression Function	**Model**	$\overline{\mathbf{D}(\boldsymbol{\theta}_m, M)}$	$\mathbf{D}(\bar{\boldsymbol{\theta}}_m, M)$	p_m	**DIC**(M)	$\ln(\hat{f}(\boldsymbol{y}\|M))$	$x = 40$	$x = 70$	$x = 100$
Differential	Model 1.1	1038.00	899.20	139.30	1178.00^{6}	-1004.94^{6}	98.18	98.79	99.15
hyperbolic	Model 1.5	932.90	785.50	147.50	1080.00^{3}	-979.61^{4}	98.18	98.91	99.15
tangent	Model 1.7	933.10	786.20	146.90	1080.00^{2}	-978.01^{3}	98.30	98.91	99.15
	Model 1.9	NR	NR	NR	NR	-1012.23^{7}	NR	NR	NR
Linear	Model 2.1	1106.00	979.40	127.00	1233.00^{7}	-888.00^{2}	98.30	98.79	99.15
	Model 2.2	1010.00	882.70	127.60	1138.00^{4}	-863.05^{1}	98.06	99.03	99.03
Conventional	Model 3.1	1031.00	895.10	135.60	1166.00^{5}	-1028.61^{8}	98.30	98.79	99.03
bilinear	Model 3.2	925.40	780.50	144.90	1070.00^{1}	-1001.43^{5}	98.06	98.91	99.15

Note: CPO: Conditional posterior ordinate; ICPO: Reciprocal of CPO; DIC: Deviance information criterion; NLME: Nonlinear mixed effects; NR: Not reported. See Table 3.1 for the specifications of each Bayesian mixed effects regression model. Superscripts indicate the ranking of model comparison statistics from least favored to most favored.

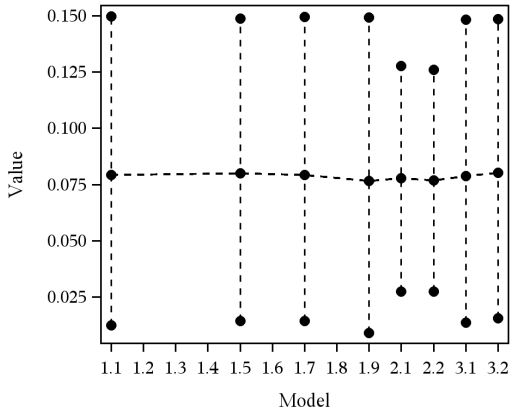
Figure E.23: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-14)$ by Treatment Group and Model



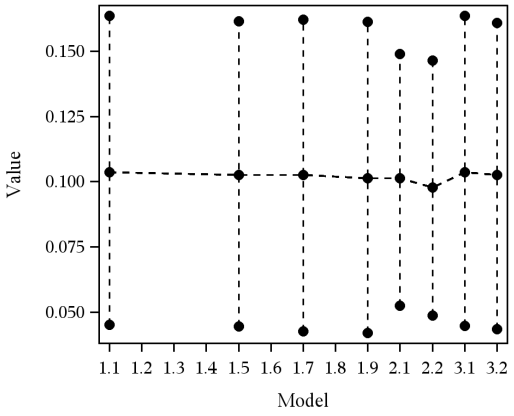
(a) TMC207 100 mg



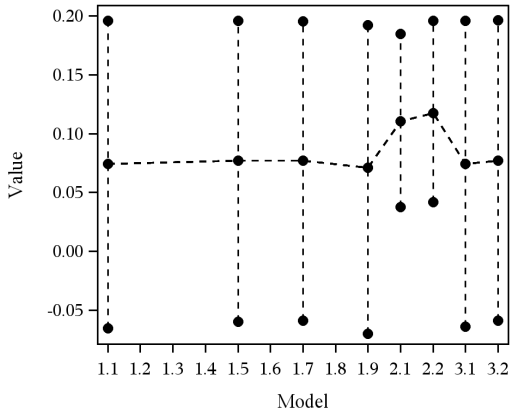
(b) TMC207 200 mg



(c) TMC207 300 mg

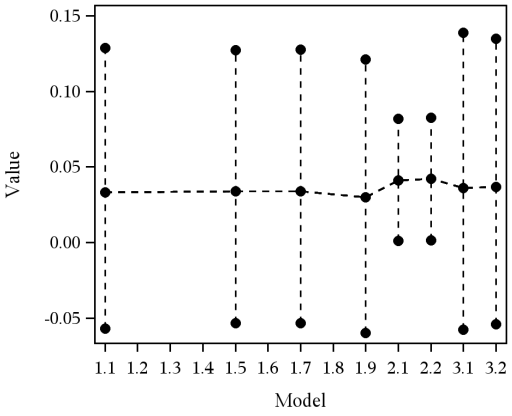


(d) TMC207 400 mg

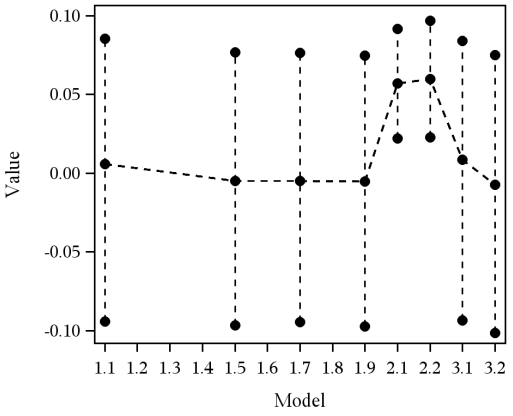


(e) Rifafour

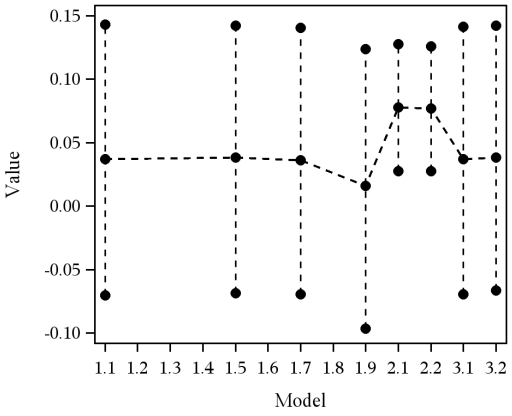
Figure E.24: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-2)$ by Treatment Group and Model



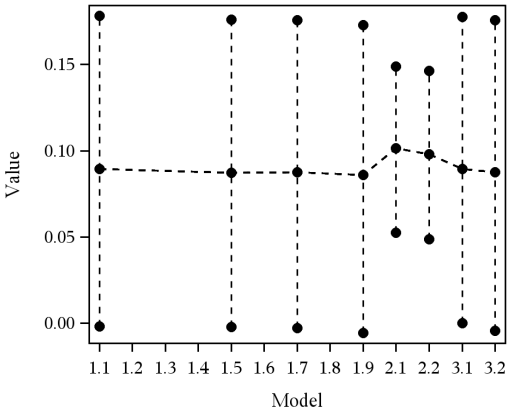
(a) TMC207 100 mg



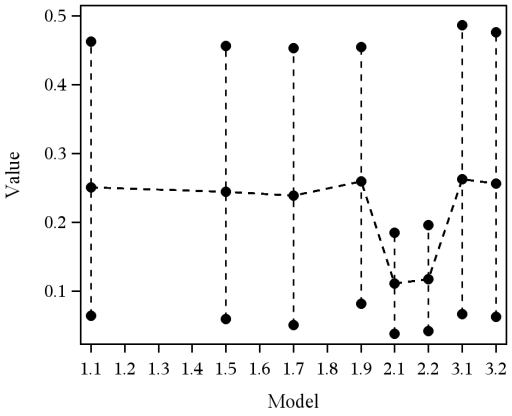
(b) TMC207 200 mg



(c) TMC207 300 mg

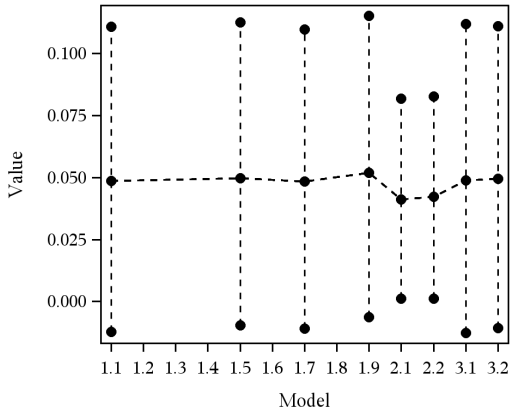


(d) TMC207 400 mg

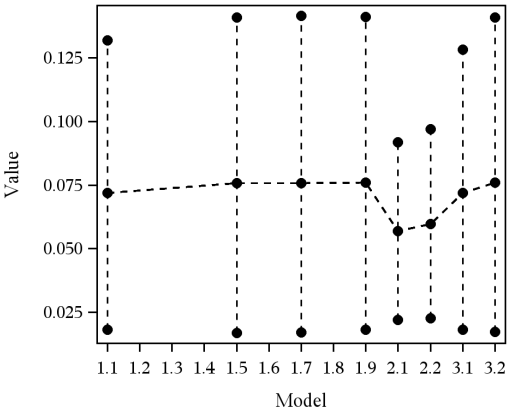


(e) Rifafour

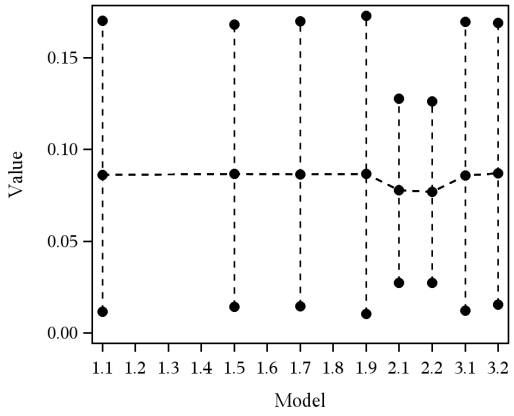
Figure E.25: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(2-14)$ by Treatment Group and Model



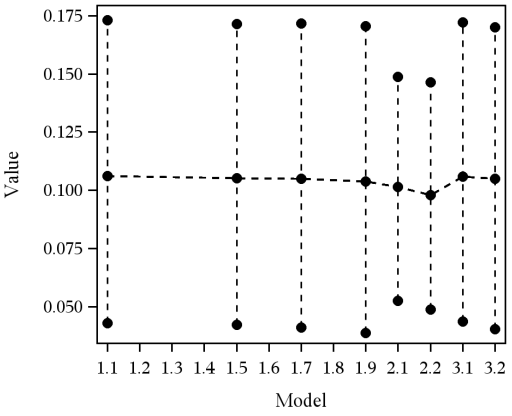
(a) TMC207 100 mg



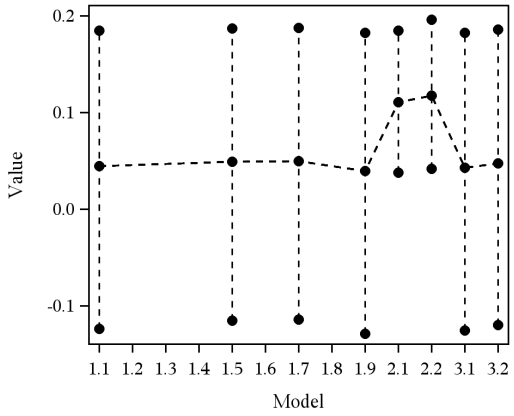
(b) TMC207 200 mg



(c) TMC207 300 mg



(d) TMC207 400 mg

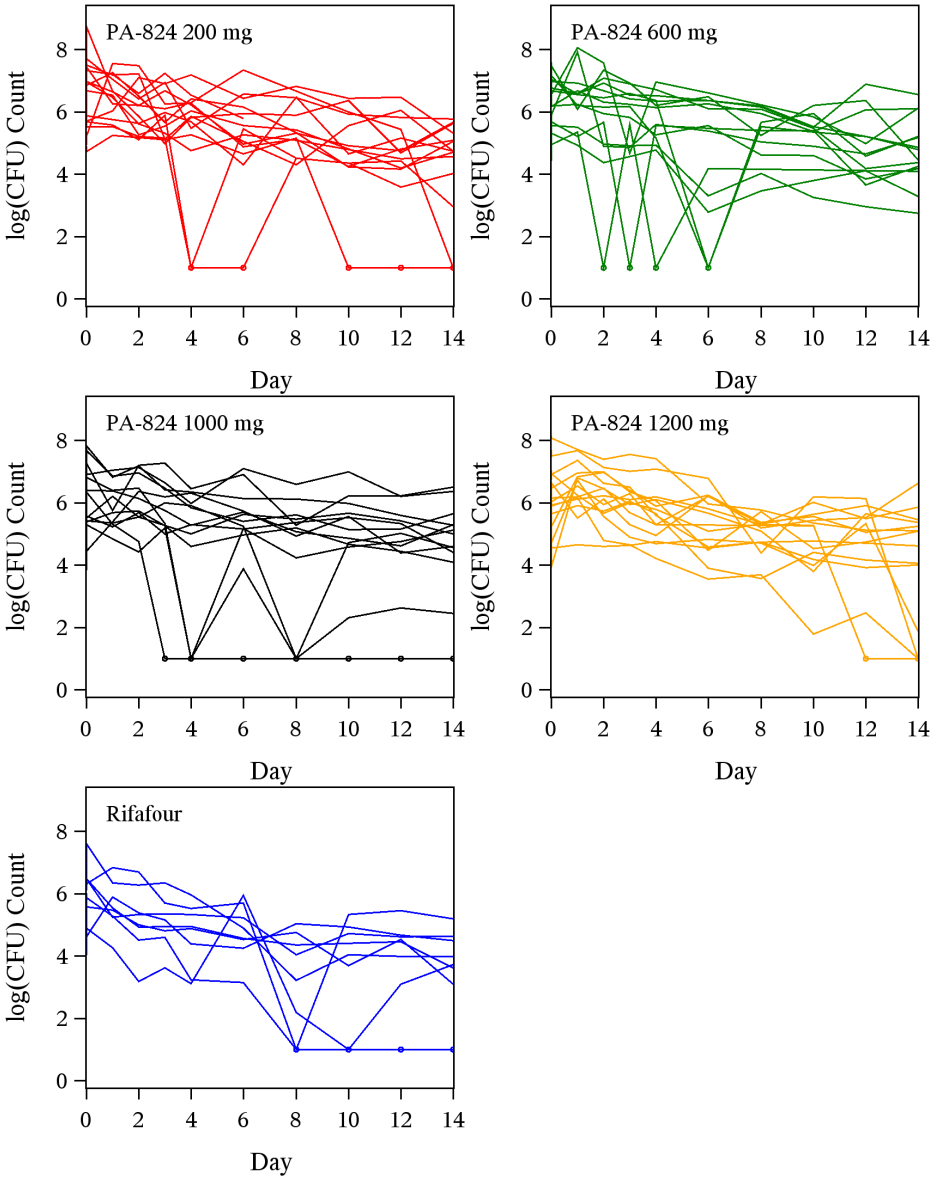


(e) Rifafour

E.4.2 CL007 Trial

Figure E.26 shows nested plots of the observed log(CFU) counts by treatment group. The log(CFU) versus time profiles seem erratic for some patients.

Figure E.26: Observed log(CFU) Counts Over Time



Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.25 for Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.27 by study day and treatment group for Model 1.1.

Table E.25: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
Parameter	**Treatment Group**	**n**	**Posterior Estimate**	**95% BCI**	**Posterior Estimate**	**95% BCI**
$\text{EBA}_j(0-14)$	PA-824 200 mg (N=15)	15	0.157	[0.051; 0.272]	0.003	[-0.207; 0.228]
	PA-824 600 mg (N=15)	14	0.106	[-0.001; 0.204]	−0.048	[-0.253; 0.174]
	PA-824 1000 mg (N=16)	13	0.113	[-0.054; 0.292]	−0.041	[-0.284; 0.217]
	PA-824 1200 mg (N=15)	15	0.168	[0.071; 0.274]	0.014	[-0.191; 0.237]
	Rifafour (N=8)	8	0.154	[-0.046; 0.335]		
$\text{EBA}_j(0-2)$	PA-824 200 mg (N=15)	15	0.169	[-0.021; 0.363]	−0.112	[-0.465; 0.245]
	PA-824 600 mg (N=15)	14	0.227	[0.046; 0.418]	−0.054	[-0.404; 0.300]
	PA-824 1000 mg (N=16)	13	0.277	[-0.030; 0.592]	−0.004	[-0.423; 0.426]
	PA-824 1200 mg (N=15)	15	0.149	[0.024; 0.276]	−0.132	[-0.453; 0.191]
	Rifafour (N=8)	8	0.281	[-0.020; 0.580]		
$\text{EBA}_j(2-14)$	PA-824 200 mg (N=15)	15	0.155	[0.024; 0.293]	0.022	[-0.215; 0.292]
	PA-824 600 mg (N=15)	14	0.085	[-0.045; 0.195]	−0.047	[-0.278; 0.219]
	PA-824 1000 mg (N=16)	13	0.086	[-0.114; 0.263]	−0.047	[-0.328; 0.244]
	PA-824 1200 mg (N=15)	15	0.171	[0.067; 0.288]	0.038	[-0.186; 0.304]
	Rifafour (N=8)	8	0.133	[-0.107; 0.331]		

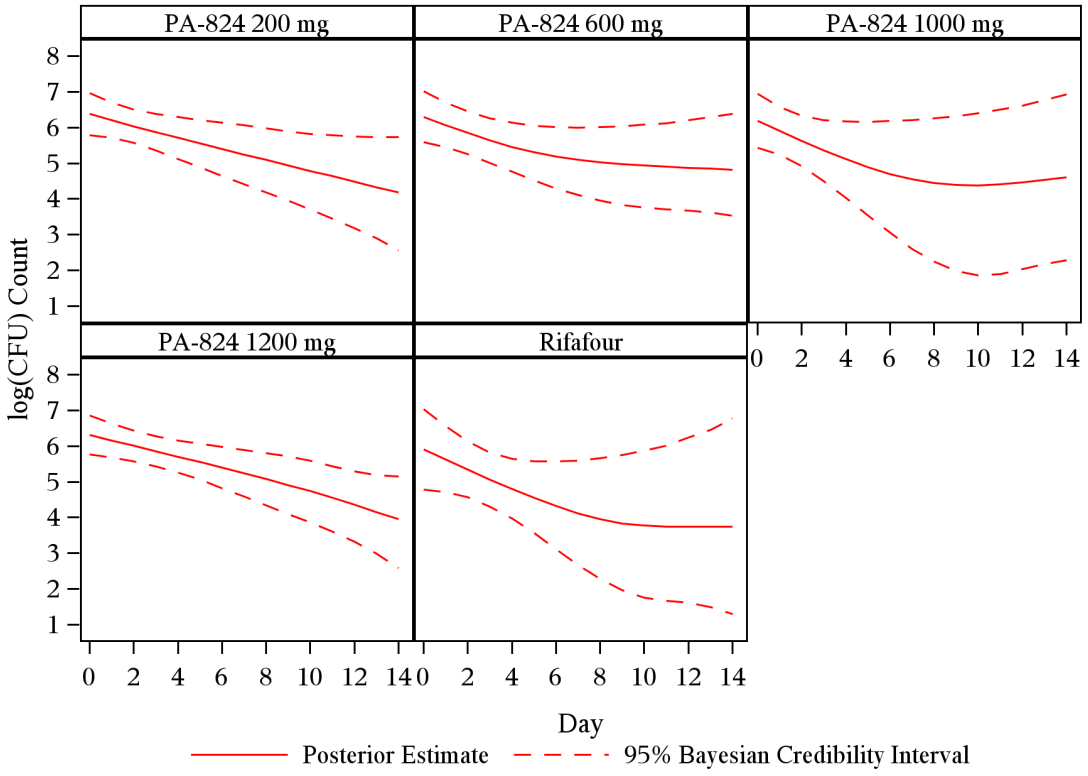
Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$ are shown in Figure E.28, Figure E.29 and Figure E.30 by treatment group and model. Similar to the NC001 trial, the linear models (Model 2.1 and Model 2.2) occasionally yield results substantially different to those of other models. Similar to the NC003 trial, the posterior estimates for $\text{EBA}_j(t_1 - t_2)$ of the models with normally distributed residuals are higher or lower than those of the Student t distributed residuals due to the presence of outliers.

Model comparison statistics for the various Bayesian NLME regression models fitted are provided in Table E.26.

The DIC favors conventional bilinear regression models over differential hyperbolic tangent regression models, followed by linear regression models.

Figure E.27: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



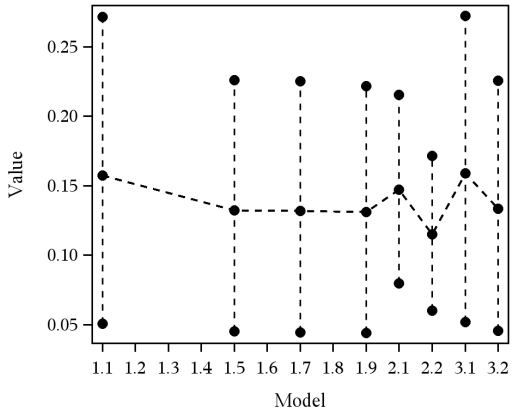
Bayes factors (marginal likelihoods) favor linear regression models, followed by differential hyperbolic tangent and conventional bilinear regression models.

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

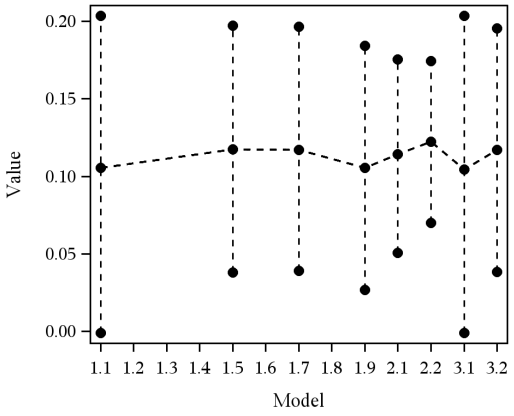
The Bayes factors indicate that building skewness into the distributions of residuals does not improve model fitting.

The ICPOs suggest the models fit the data reasonably well.

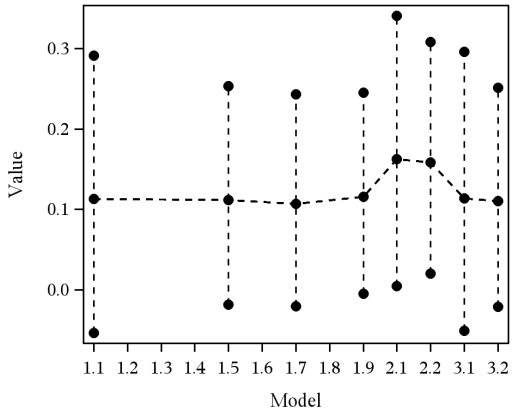
Figure E.28: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-14)$ by Treatment Group and Model



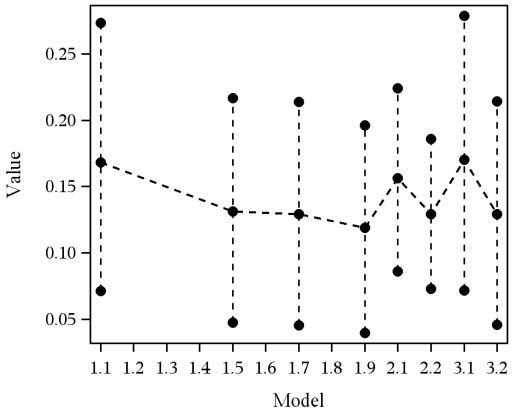
(a) PA-824 200 mg



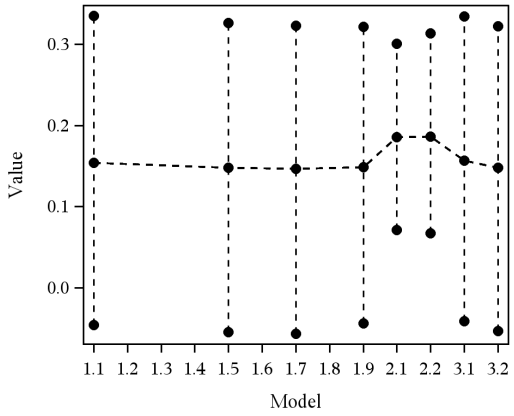
(b) PA-824 600 mg



(c) PA-824 1000 mg

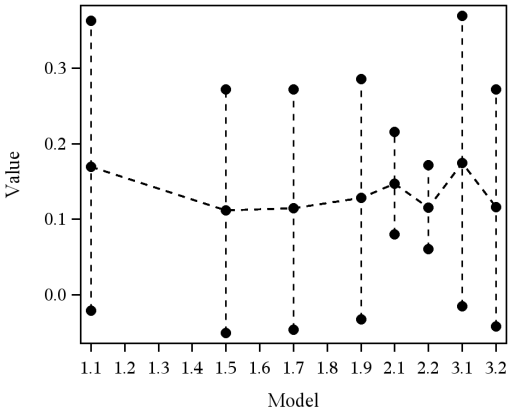


(d) PA-824 1200 mg

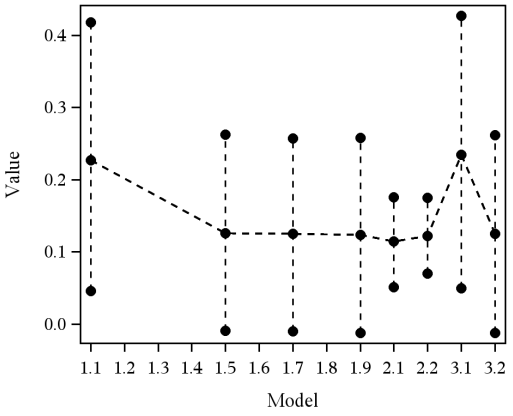


(e) Rifafour

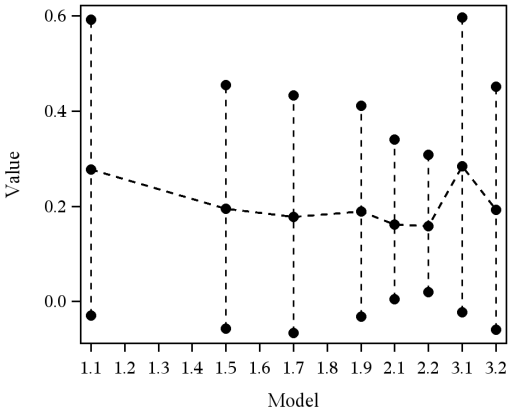
Figure E.29: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-2)$ by Treatment Group and Model



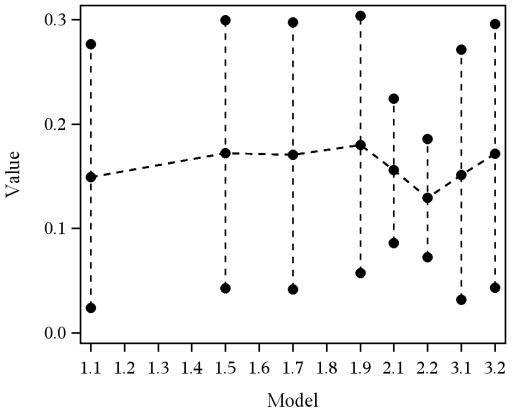
(a) PA-824 200 mg



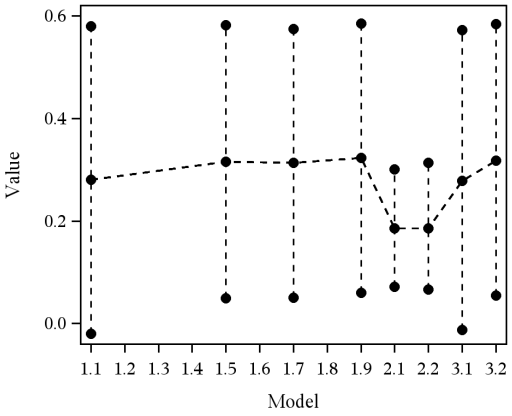
(b) PA-824 600 mg



(c) PA-824 1000 mg

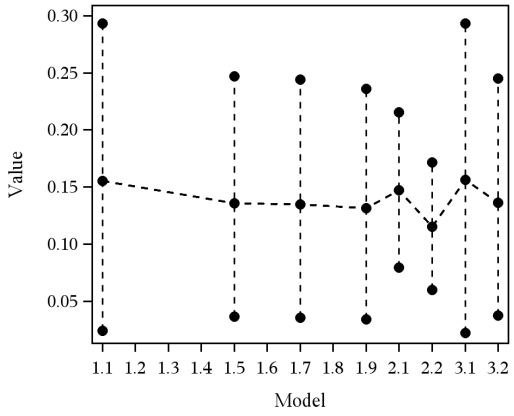


(d) PA-824 1200 mg

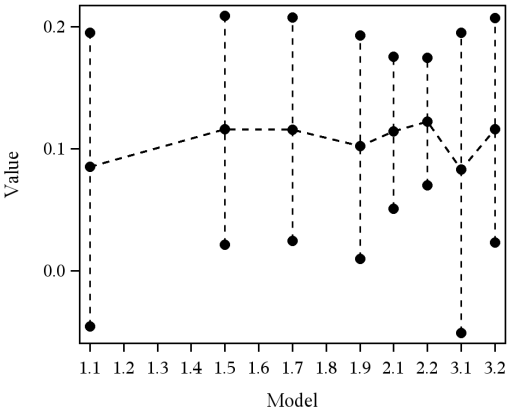


(e) Rifafour

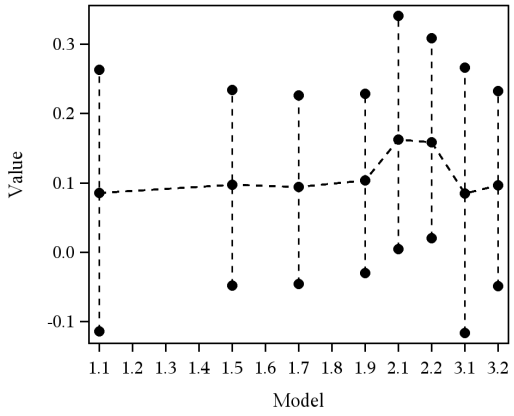
Figure E.30: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(2-14)$ by Treatment Group and Model



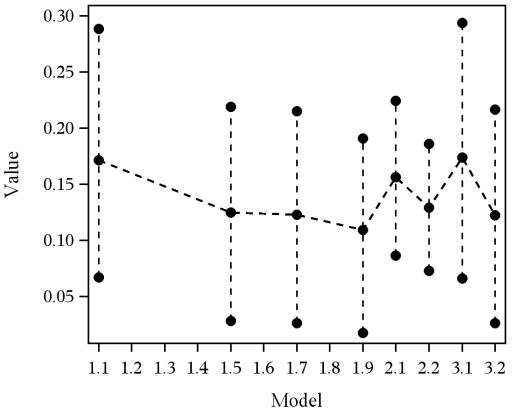
(a) PA-824 200 mg



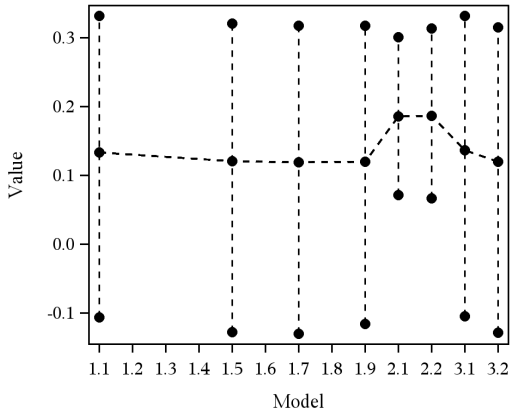
(b) PA-824 600 mg



(c) PA-824 1000 mg



(d) PA-824 1200 mg



(e) Rifafour

Table E.26: Comparison of Bayesian NLME Regression Models

		DIC					% ICPO $< x$		
Regression Function	**Model**	$\overline{D(\theta_m, M)}$	$D(\bar{\theta}_m, M)$	p_m	$DIC(M)$	$\ln(\hat{f}(y\|M))$	$x = 40$	$x = 70$	$x = 100$
Differential	Model 1.1	1635.00	1464.00	171.30	1807.00[6]	-1223.31[7]	96.56	96.56	96.99
hyperbolic	Model 1.5	1189.00	1028.00	161.10	1351.00[3]	-1102.62[2]	95.55	95.98	96.56
tangent	Model 1.7	1188.00	1026.00	162.00	1350.00[2]	-1110.70[3]	95.55	95.98	96.70
	Model 1.9	NR	NR	NR	NR	-1119.74[4]	NR	NR	NR
Linear	Model 2.1	1826.00	1710.00	116.80	1943.00[7]	-1167.19[6]	95.84	96.41	96.99
	Model 2.2	1346.00	1214.00	131.50	1477.00[4]	-1016.22[1]	94.69	95.55	95.98
Conventional	Model 3.1	1616.00	1442.00	174.40	1791.00[5]	-1311.55[8]	96.41	96.56	96.99
bilinear	Model 3.2	1186.00	1028.00	158.10	1345.00[1]	-1147.60[5]	95.55	95.98	96.56

Note: CPO: Conditional posterior ordinate; ICPO: Reciprocal of CPO; DIC: Deviance information criterion; NLME: Nonlinear mixed effects; NR: Not reported. See Table 3.1 for the specifications of each Bayesian mixed effects regression model. Superscripts indicate the ranking of model comparison statistics from least favored to most favored.

E.4.3 CL010 Trial

Figure E.31 shows nested plots of the observed log(CFU) counts by treatment group.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.27 for Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.32 by study day and treatment group for Model 1.1.

Figure E.31: Observed log(CFU) Counts Over Time

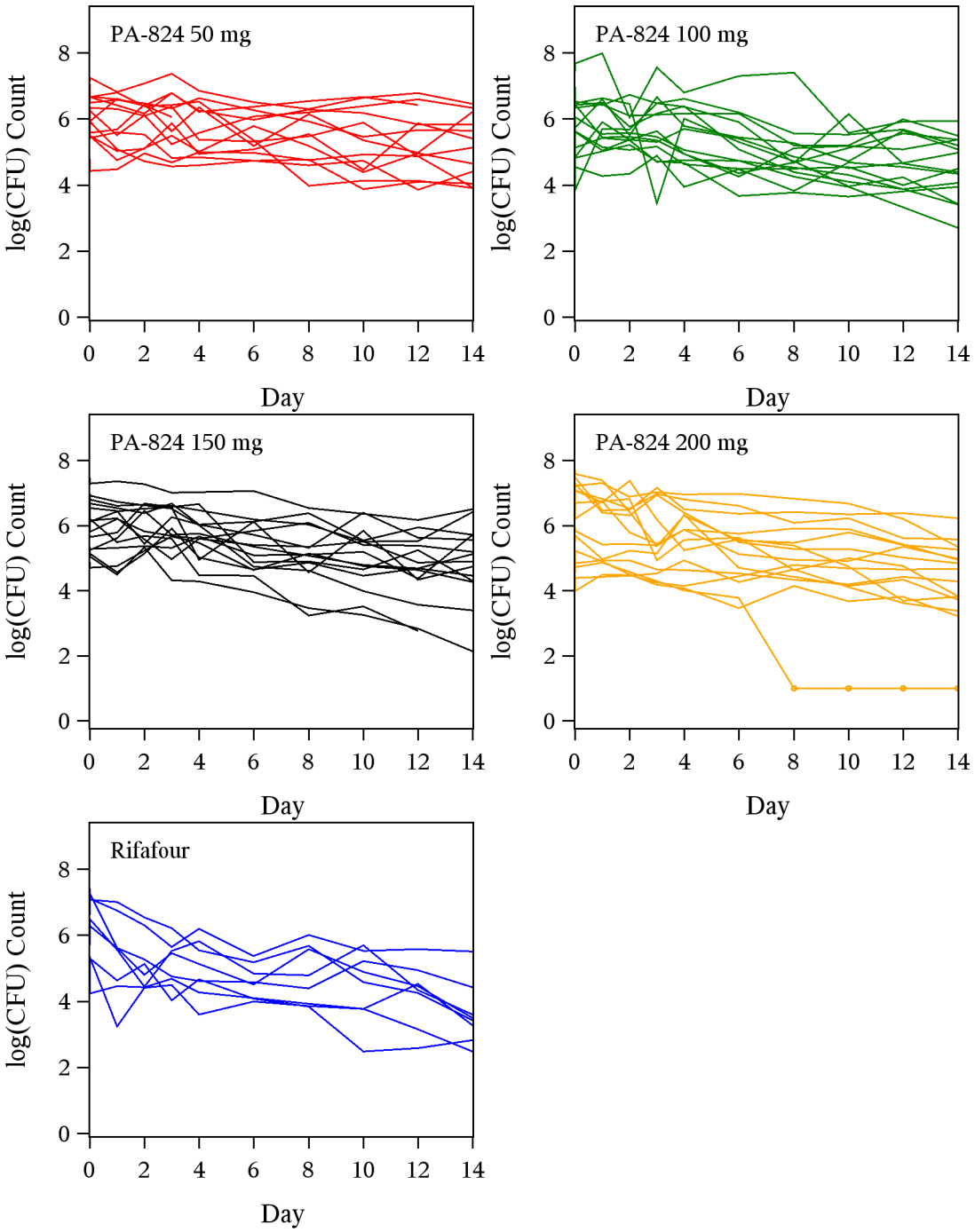


Table E.27: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
Parameter	**Treatment Group**	**n**	**Posterior Estimate**	**95% BCI**	**Posterior Estimate**	**95% BCI**
$\text{EBA}_j(0-14)$	PA-824 50 mg (N=15)	14	0.059	[0.003; 0.113]	−0.091	[-0.205; 0.026]
	PA-824 100 mg (N=15)	15	0.094	[0.037; 0.149]	−0.055	[-0.170; 0.061]
	PA-824 150 mg (N=15)	15	0.099	[0.040; 0.159]	−0.050	[-0.167; 0.069]
	PA-824 200 mg (N=16)	15	0.134	[0.044; 0.229]	−0.015	[-0.151; 0.122]
	Rifafour (N=8)	8	0.149	[0.047; 0.252]		
$\text{EBA}_j(0-2)$	PA-824 50 mg (N=15)	14	0.094	[0.007; 0.182]	−0.176	[-0.401; 0.037]
	PA-824 100 mg (N=15)	15	0.117	[0.009; 0.224]	−0.153	[-0.388; 0.069]
	PA-824 150 mg (N=15)	15	0.089	[-0.022; 0.193]	−0.180	[-0.411; 0.039]
	PA-824 200 mg (N=16)	15	0.124	[-0.018; 0.266]	−0.145	[-0.395; 0.097]
	Rifafour (N=8)	8	0.270	[0.076; 0.477]		
$\text{EBA}_j(2-14)$	PA-824 50 mg (N=15)	14	0.053	[-0.011; 0.111]	−0.077	[-0.211; 0.066]
	PA-824 100 mg (N=15)	15	0.090	[0.024; 0.153]	−0.039	[-0.176; 0.104]
	PA-824 150 mg (N=15)	15	0.101	[0.031; 0.172]	−0.029	[-0.168; 0.118]
	PA-824 200 mg (N=16)	15	0.136	[0.024; 0.252]	0.006	[-0.160; 0.176]
	Rifafour (N=8)	8	0.129	[0.000; 0.251]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$ are shown in Figure E.33, Figure E.34 and Figure E.35 by treatment group and model. Similar to the NC001 trial, the linear models (Model 2.1 and Model 2.2) occasionally yield results substantially different to those of other models.

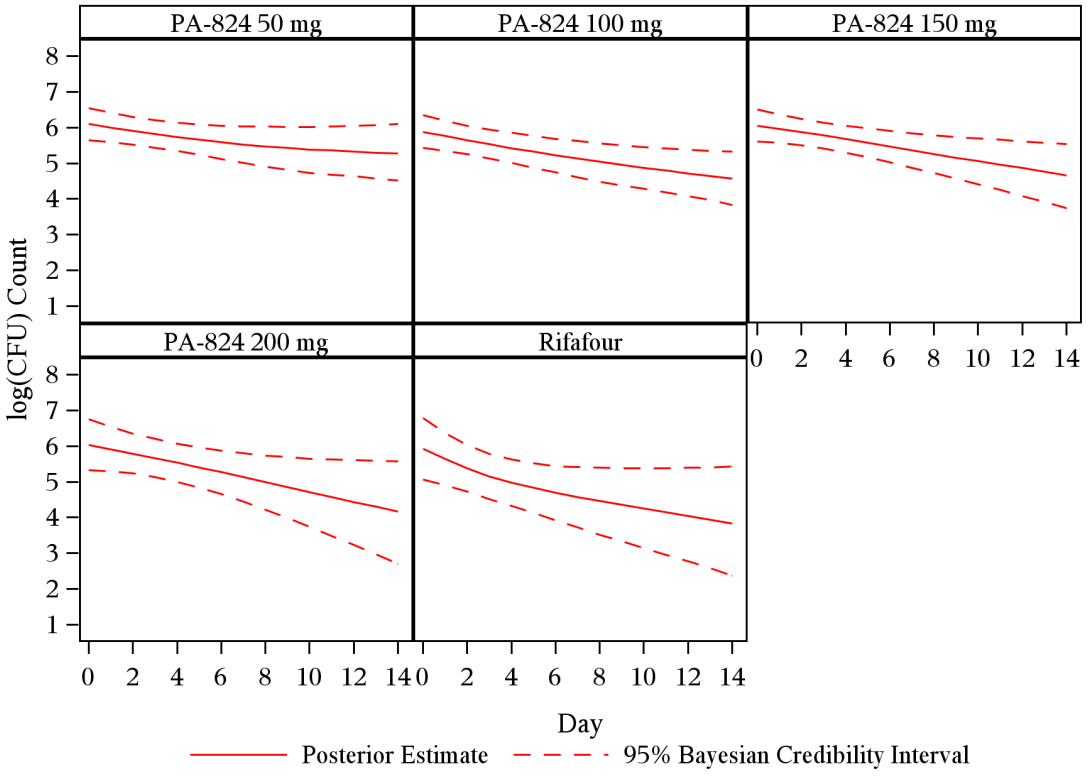
Model comparison statistics for the various Bayesian NLME regression models fitted are provided in Table E.28.

The DIC favors conventional bilinear regression models over differential hyperbolic tangent regression models, followed by linear regression models.

Bayes factors (marginal likelihoods) favor linear regression models, followed by differential hyperbolic tangent and conventional bilinear regression models.

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

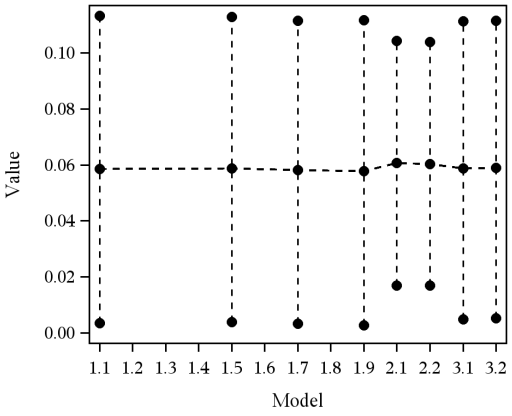
Figure E.32: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



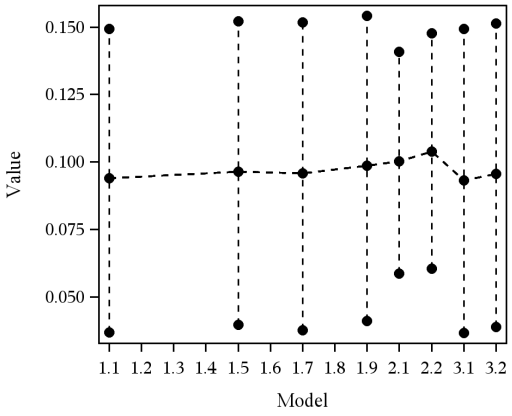
The Bayes factors indicate that building skewness into the distributions of residuals does not improve model fitting.

The ICPOs suggest the models fit the data reasonably well.

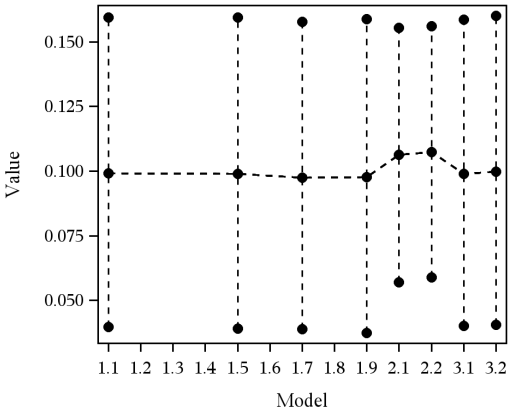
Figure E.33: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-14)$ by Treatment Group and Model



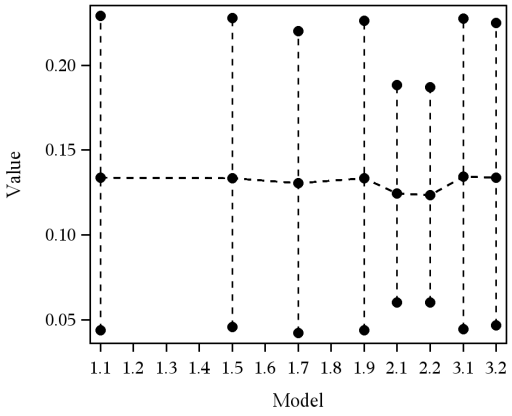
(a) PA-824 50 mg



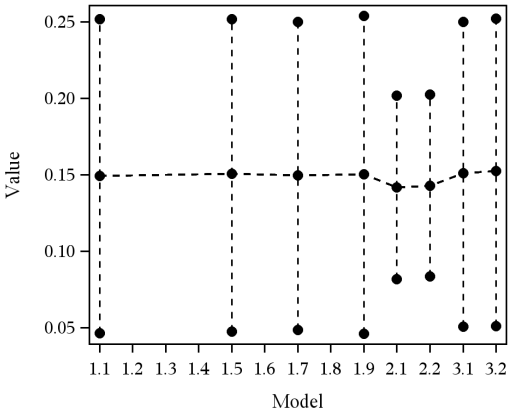
(b) PA-824 100 mg



(c) PA-824 150 mg

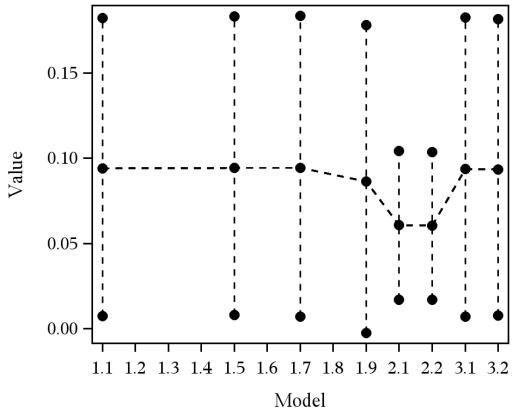


(d) PA-824 200 mg

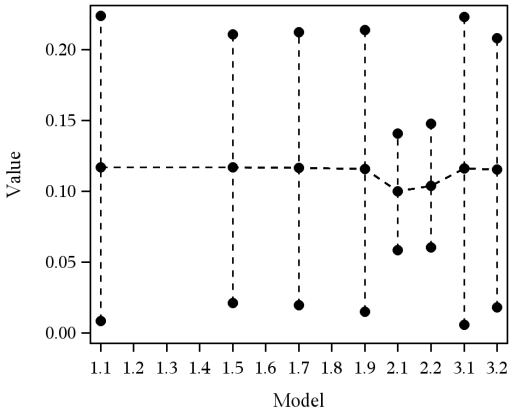


(e) Rifafour

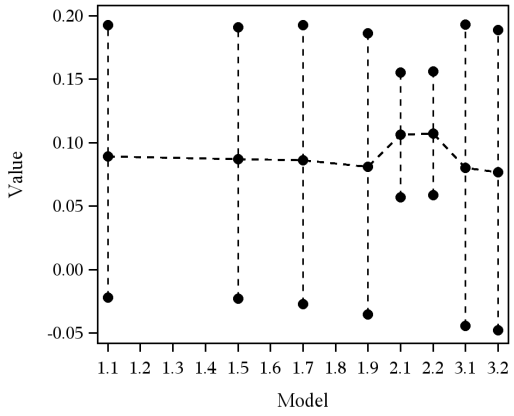
Figure E.34: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(0-2)$ by Treatment Group and Model



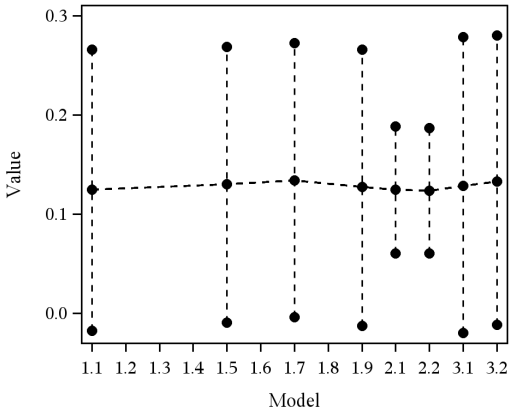
(a) PA-824 50 mg



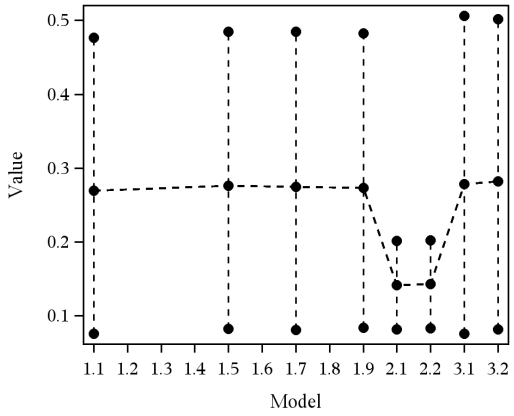
(b) PA-824 100 mg



(c) PA-824 150 mg

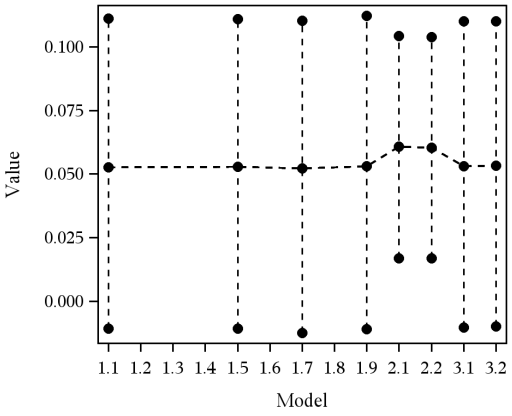


(d) PA-824 200 mg

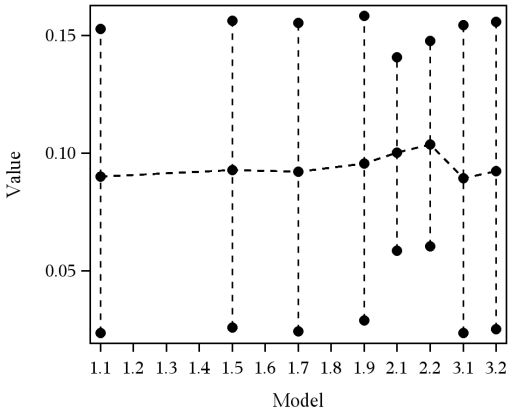


(e) Rifafour

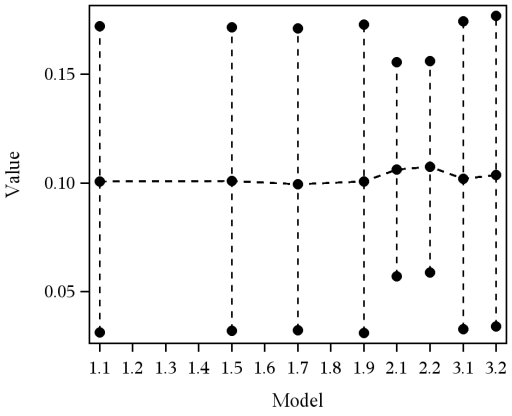
Figure E.35: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(2-14)$ by Treatment Group and Model



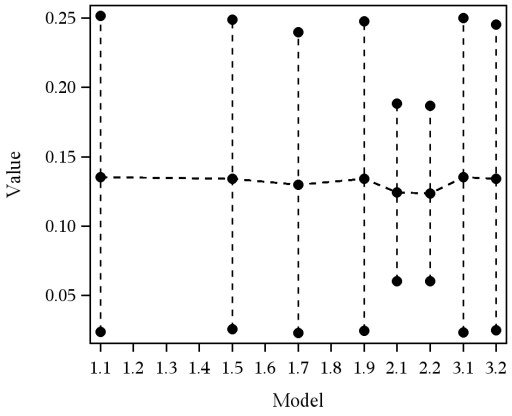
(a) PA-824 50 mg



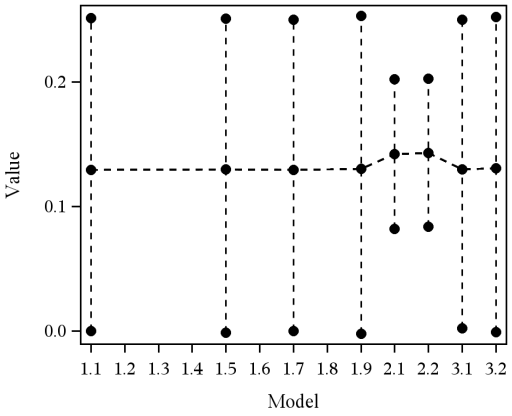
(b) PA-824 100 mg



(c) PA-824 150 mg



(d) PA-824 200 mg



(e) Rifafour

Table E.28: Comparison of Bayesian NLME Regression Models

		DIC					% ICPO $< x$		
Regression Function	**Model**	$\overline{D(\theta_m, M)}$	$D(\bar{\theta}_m, M)$	p_m	$DIC(M)$	$\ln(\hat{f}(y\|M))$	$x = 40$	$x = 70$	$x = 100$
Differential	Model 1.1	688.40	555.40	132.90	821.30^{5}	-861.51^{5}	98.47	98.75	99.03
hyperbolic	Model 1.5	630.90	501.90	128.90	759.80^{3}	-849.03^{4}	98.47	98.75	99.03
tangent	Model 1.7	630.50	501.40	129.10	759.70^{2}	-843.97^{3}	98.33	98.75	99.03
	Model 1.9	NR	NR	NR	NR	-888.61^{8}	NR	NR	NR
Linear	Model 2.1	808.60	677.70	130.90	939.40^{7}	-753.89^{2}	98.47	98.47	99.03
	Model 2.2	761.20	625.00	136.20	897.40^{6}	-741.84^{1}	98.19	98.75	99.17
Conventional	Model 3.1	681.90	547.50	134.40	816.30^{4}	-879.32^{7}	98.47	98.75	98.89
bilinear	Model 3.2	623.80	495.30	128.40	752.20^{1}	-867.88^{6}	98.47	98.75	99.03

Note: CPO: Conditional posterior ordinate; ICPO: Reciprocal of CPO; DIC: Deviance information criterion; NLME: Nonlinear mixed effects; NR: Not reported. See Table 3.1 for the specifications of each Bayesian mixed effects regression model. Superscripts indicate the ranking of model comparison statistics from least favored to most favored.

E.4.4 NC002 (EBA) Trial

Figure E.36 shows nested plots of the observed log(CFU) counts by treatment group. The log(CFU) versus time profiles seem erratic for some patients.

Posterior estimates and corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$, including pairwise comparisons versus Rifafour, are presented in Table E.29 for Model 1.1.

Posterior estimates and corresponding 95% BCIs for the mean log(CFU) versus time profiles are shown in Figure E.37 by study day and treatment group for Model 1.1.

Figure E.36: Observed log(CFU) Counts Over Time

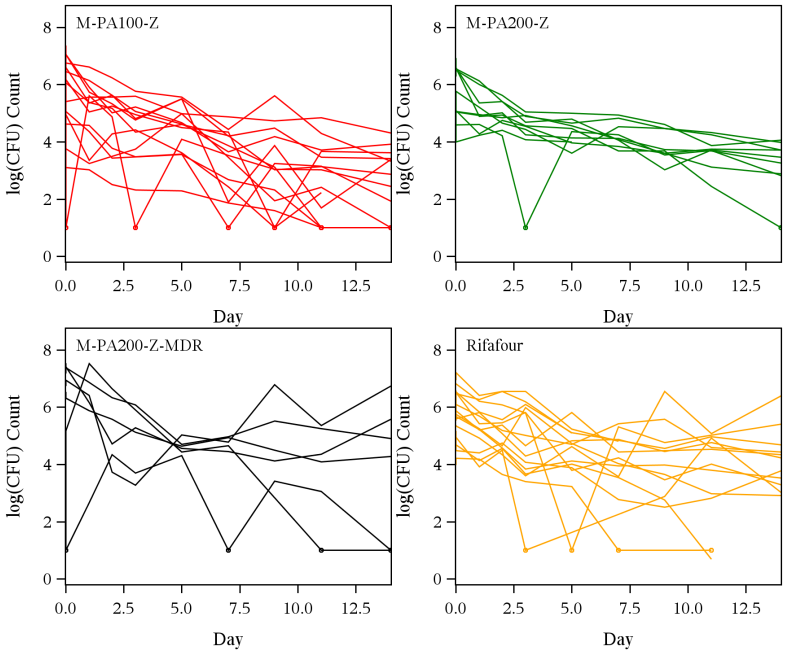
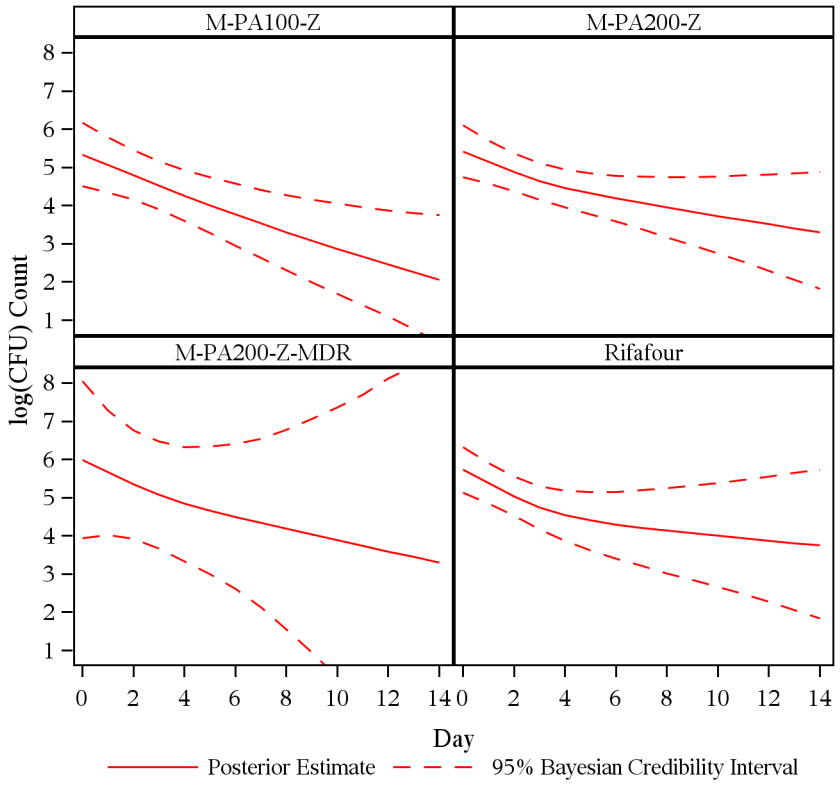


Table E.29: Posterior Estimates and Corresponding 95% BCIs for $\text{EBA}_j(t_1 - t_2)$

					Difference Versus Rifafour	
Parameter	**Treatment Group**	**n**	**Posterior Estimate**	**95% BCI**	**Posterior Estimate**	**95% BCI**
$\text{EBA}_j(0-14)$	M-PA100-Z (N=16)	14	0.235	[0.116; 0.351]	0.093	[-0.080; 0.267]
	M-PA200-Z (N=13)	10	0.152	[0.038; 0.261]	0.010	[-0.161; 0.180]
	M-PA200-Z-MDR (N=18)	6	0.192	[-0.168; 0.569]	0.050	[-0.333; 0.445]
	Rifafour (N=15)	15	0.142	[0.009; 0.269]		
$\text{EBA}_j(0-2)$	M-PA100-Z (N=16)	14	0.272	[0.083; 0.469]	−0.074	[-0.336; 0.183]
	M-PA200-Z (N=13)	10	0.275	[0.093; 0.476]	−0.071	[-0.327; 0.191]
	M-PA200-Z-MDR (N=18)	6	0.315	[-0.331; 0.958]	−0.031	[-0.698; 0.638]
	Rifafour (N=15)	15	0.346	[0.173; 0.525]		
$\text{EBA}_j(2-14)$	M-PA100-Z (N=16)	14	0.228	[0.088; 0.362]	0.121	[-0.088; 0.331]
	M-PA200-Z (N=13)	10	0.131	[-0.007; 0.259]	0.024	[-0.187; 0.230]
	M-PA200-Z-MDR (N=18)	6	0.171	[-0.294; 0.653]	0.064	[-0.434; 0.572]
	Rifafour (N=15)	15	0.107	[-0.058; 0.266]		

Note: BCI: Bayesian credibility interval; CFU: Colony forming unit; $\text{EBA}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2. N = Total number of patients. n = Number of patients in each category. Posterior estimate: Represents the mean of the associated posterior distribution.

Figure E.37: Posterior Estimates and Corresponding 95% BCIs for Mean log(CFU) Count Over Time



The DIC, marginal likelihood and ICPO < 40 for the model with normally distributed residuals are respectively 1002.00, -749.36 and 96.45%, and for the model with Student t distributed residuals are respectively 764.40, -692.70 and 95.74%.

Both the DIC and Bayes factors favor models with Student t distributed residuals over those with normally distributed residuals.

The ICPOs suggest the models fit the data reasonably well.