ROBUST FIT OF BAYESIAN MIXED EFFECTS REGRESSION MODELS WITH APPLICATION TO COLONY FORMING UNIT COUNT IN TUBERCULOSIS RESEARCH

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ABSTRACT

Early bactericidal activity of tuberculosis drugs is conventionally assessed using statistical regression modeling of colony forming unit (CFU) counts over time. Typically, most CFU counts deviate little from the regression curve, but gross outliers due to erroneous sputum sampling are occasionally present and can markedly influence estimates of the rate of change in CFU count, which is the parameter of interest. A recently introduced Bayesian nonlinear mixed effects (NLME) regression model was adapted to offer a robust approach that accommodates both outliers and potential skewness in the data. At its most general, the proposed regression model fits the skew Student t distribution to residuals and random coefficients. Deviance information criterion statistics and compound Laplace-Metropolis marginal likelihoods (CLMMLs) were used to discriminate between alternative Bayesian NLME regression models. We present a relatively easy method to calculate the marginal likelihoods required to determine CLMMLs, by adapting methods available in currently available statistical software. The robust methodology proposed in this paper was applied to data from six clinical trials. The results provide strong evidence that the distribution of CFU count is often heavy tailed and negatively skewed (suggesting the presence of outliers). Therefore, we recommend that robust regression models, such as those proposed here, should be fitted to CFU count.

1 Robust Regression Models in Tuberculosis Research

1.1 Robust Regression Modeling

Conventional regression models, such as ordinary least squares models, do not accommodate heavy tails or skewness in the distribution of the data. Models which are not "robust" to deviations from certain assumptions may yield biased or misleading results, and such bias may go unnoticed. Robust models are designed to avoid the restrictions of conventional modeling techniques when certain assumptions do not necessarily hold.[1] A regression model should give statistically sound and unbiased results even when there are deviations from the usual assumptions, such as the assumption of normality of residuals, or absence of gross outliers.

Individual data points are generally considered outlying observations ("outliers") if they do not follow the pattern (or trend) of the majority of the remainder of the data, or if they are considered to be "extreme" in some sense. Outliers in the data may cause bias in the estimates of parameters of interest, or may inflate Type I and Type II error rates.[2] In the field of biopharmaceutical research, for example, outliers may adversely affect the interpretation of treatment group comparisons. Regardless of how an outlying observation is defined, a robust regression model should maintain the validity of inferences made, and the influence of outliers on statistical inferences should be small.

In the past, there has been great interest in robust regression techniques (for example, see earlier work by Tukey[3] and Huber[4], respectively based on contaminated distributions and M-estimation). However, use of these older methods has been limited due to their complex and computationally intensive implementation.[5] More recently, robust models based on heavy tailed and asymmetrical distributions, in a Bayesian framework, have been suggested (see Gelman *et al.*[6] and Sahu *et al.*[7]). One important advantage of Bayesian inference is that it does not rely on asymptotic approximations, as classical inference methods often do for complex

models.[8] Bayesian methods are therefore attractive for inference in complex models such as robust nonlinear mixed effects (NLME) regression modeling.[9–11]

1.2 Early Bactericidal Activity of Tuberculosis Drugs

In the clinical development of anti-tuberculosis (TB) drugs the assessment of their bactericidal activity is of interest.[12] The rate of decline in colony forming unit (CFU) count over specified time intervals is an important surrogate marker for the conventional Phase III efficacy endpoint of TB trials, namely the proportion of relapse-free patients after two years of follow-up following 6 months of treatment.[12] In early Phase II (Phase IIa) trials, the early bactericidal activity (EBA) of an anti-TB drug can be characterized by the rate of change (decline), during the first two weeks of treatment, in CFU count collected from sputum samples of TB patients.[13] The rate of decline in CFU count is typically assessed using statistical regression modeling of CFU count over time.[14]

1.3 Need for Robust Regression Models in Tuberculosis Research

Measuring CFU count requires assays of multiple sputum plates per sputum sample, dilution of samples, waiting periods for culture growth, and labor intensive counting procedures for CFUs.[15] Furthermore, sputum samples are prone to contamination.[16] Due to such factors, gross outliers in CFU count are occasionally observed. These outliers can markedly influence estimates of the rate of change in CFU count, which is the parameter of interest. In addition, individual profiles may include zero CFU counts which do not follow the remainder data pattern over time. Such implausible zero CFU counts can cause the CFU versus time profiles to be highly erratic.[17]

Finally, some treatment regimens occasionally exhibit remarkable decline in CFU count over time in a subset of patients (Diacon *et al.*[13]; Pa-Z-M regimen) so that the distribution of the patient-specific slopes (which characterize the rate of decline in CFU count) may be heavy

tailed.

EBA trials usually include only a small number of patients per treatment group (say 15 patients; Diacon *et al.*[13]). Outliers in such small datasets can have a great impact on the statistical validity of the associated findings.[18]

Gillespie *et al.*[17] has suggested that, when fitting regression models to CFU counts, it is important to exclude implausible data points which do not adhere to the expected longitudinal biologic pattern. Gillespie *et al.*[17] and Gillespie *et al.*[19,20] applied an iterative approach for exclusion of outliers in CFU count. However, it is difficult or impossible to specify objective decision rules for identification and exclusion of outliers, so that it seems attractive to accommodate outliers using robust regression techniques, rather than to exclude specific data points from the analysis.

As indicated above, a subset of CFU counts might be reported as zero or "no count" values. Genuine zero CFU 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 CFU counts. Thus, genuine zero CFU counts will typically occur towards the end of a CFU versus time profile. However, CFU counts of zero should be confirmed to be "genuine", that is, they must be distinguished from missing values or from contaminated or otherwise invalid data. Genuine zero CFU counts are valid data and must be included in the analysis. The database, however, does not always indicate whether a zero CFU count is genuine, contaminated, missing or invalid. One approach is to include zero CFU counts in the analysis whilst limiting the potential outlier problem by using a robust regression method.

Various authors (Hafner *et al.*[21], Davies *et al.*[14], Davies *et al.*[22], Rustomjee *et al.*[23], Sloan *et al.*[24]) have used repeated measures linear, and mixed effects bi-exponential or multi-exponential regression models for log(CFU) count, assuming normal distributions for both the residuals, random effects and random coefficients in these models. Such mixed effects regression models can lead to improved precision of estimates of random effects relative to

their fixed effects counterparts, yield appropriate fixed effects estimates and standard errors, and may reduce the bias caused by missing data.[14]

Burger and Schall[25] proposed a class of biphasic Bayesian NLME regression models for log(CFU) count which is more flexible than bi-exponential regression models. The Bayesian implementation of the biphasic regression model was based on vague prior distributions and specified normal distributions for residuals and random coefficients. This Bayesian NLME regression model has been applied to EBA datasets of recently published clinical trials.[12,26,27]

In the present paper the conventional normal regression model of Burger and Schall[25] is adapted to offer a robust approach that accommodates outliers and potential skewness. In particular this regression model specifies the skew Student t distribution for residuals and random coefficients. The empirical performance of the proposed methodology is investigated in a wide range of datasets.

2 OUTLINE OF THE PRESENT PAPER

Section 3 provides an overview of the conventional normal NLME regression model fitted by Burger and Schall[25], and proposes an extension of the regression model to increase its robustness to outliers and skewness. This section also introduces deviance information criterion (DIC) statistics and compound Laplace-Metropolis marginal likelihoods (CLMMLs) to discriminate between alternative Bayesian mixed effects regression models. The calculation of CLMMLs, because of the required multidimensional integrals, is known to be challenging and cumbersome. An approach is introduced through which marginal likelihoods can be calculated relatively easily by adapting methods available in SAS® and the R project. Section 4 provides applications of the methodologies introduced in Section 3 using CFU count datasets of recently published clinical trials. Section 5 presents a simulation study to compare the performance of the various regression models. Section 6 provides a discussion of the results and

key findings of this study.

3 BAYESIAN MIXED EFFECTS REGRESSION MODELS

3.1 Nonlinear Mixed Effects Regression Model

The Bayesian NLME regression model proposed by Burger and Schall[25] is as follows:

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

where $\log(y_{ijk})$ is the log(CFU) count for patient $i = 1,\ldots,N_j$ in treatment group $j = 1,\ldots,J$ at timepoint $k = 1,\ldots,T_{ij}$, and $t_{ijk} \geq 0$ & ε_{ijk} are the corresponding measurement times and residuals.

Note that, in the context of this model, zero counts are specified as censored observations.[23] CFU counts discussed in this paper are calculated as $\text{CFU} = (\text{CFU}_1 + \text{CFU}_2)/2 \times 20 \times 10^{\text{dilution}}$, where CFU_1 and CFU_2 are the counts from two replicate culture plates, and the factor $20 \times 10^{\text{dilution}}$ compensates for the dilution used in the counting process. The smallest possible count above zero is 1 for one of the two plates, and zero for the other plate, and therefore the smallest value of $\log_{10}(\text{CFU})$ from a non-zero count is 1 (if dilution = 0). Thus, on the logarithmic scale to the base of 10, a zero count is specified as a left-censored value of 1.

The model includes the following random coefficients: Intercepts (α_{ij}); two slopes characterizing the rate of change over time (β_{1ij} and β_{2ij}); node (or inflection point) at which transition from one slope to another occurs (κ_{ij}); "smoothness" parameter governing the "speed" of transition (γ_{ij}).

The terms α_{ij}, β_{1ij}, β_{2ij}, κ_{ij} and γ_{ij} are the sums of fixed effects and associated random

coefficients, namely:

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

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

The regression model has been fitted using OpenBUGS.[28] Posterior samples were monitored using iteration and autocorrelation plots, and Brooks-Gelman-Rubin statistics of parallel chains.[25,29,30]

3.2 Specification of Residuals and Random Coefficients

Table 3.1 provides a summary of the various specifications of the Bayesian mixed effects regression model in Equation (1) which will be fitted to log(CFU) count.

Table 3.1: Model Specifications for Bayesian Mixed Effects Regression Models

		Distributions	
Regression Model	**No.**	**Residuals**	**Random Coefficients**
$R_N C_N$	1	Normal	Normal
$R_T C_N$	2	Student t	Normal
$R_{ST} C_N$	3	Skew Student t	Normal
$R_{ST} C_T$	4	Skew Student t	Student t

Regression model $R_{ST}C_T$ is the most general regression model considered and has the largest flexibility (with respect to robustness) for both the residuals and random coefficients of the regression model in Equation (1). Since the normal distribution can be considered a Student t distribution with infinite degrees of freedom, the four models in Table 3.1 are nested.

The corresponding distributions specified for residuals and random coefficients are discussed below in detail.

Regression Model 1 ($R_N C_N$): Residuals: Normal
Random Coefficients: Normal

The conventional model by Burger and Schall[25] incorporated the assumption that the residuals follow *i.i.d.* normal distributions, i.e.:

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

where 0 and $\sigma^2_{\varepsilon_j}$ are the mean and residual variances, respectively, of the corresponding normal distribution.

The random coefficients μ_{ij} were assumed to follow tri-variate normal distributions, and truncated normal distributions were specified for κ_{ij} and γ_{ij}. $\Omega_{\mu j}$, $\sigma^2_{\kappa_j}$ and $\sigma^2_{\gamma_j}$ are respectively the covariance matrices of μ_{ij}, and scale parameters of κ_{ij} and γ_{ij}. Detail on the specification of associated random effects and prior distributions is provided in the relevant paper.

This regression model contains no robust properties since both residuals and random coefficients are assumed to follow conventional normal distributions which do not accommodate outliers of any nature.

Regression Model 2 ($\mathbf{R_T C_N}$): <u>Residuals:</u> Student t
<u>Random Coefficients</u>: Normal

The conventional model (Model 1) can incorporate the assumption that the residuals follow *i.i.d.* Student t distributions, i.e.:

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

where 0, $\sigma^2_{\varepsilon j}$ and v_j are the mean, scale parameters and degrees of freedom, respectively, of the corresponding Student t distribution. The degrees of freedom v_j are assigned uniform prior distributions, namely $v_j \sim U(2, 100)$.

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

Regression Model 3 ($R_{ST}C_N$): Residuals: Skew Student t

Random Coefficients: Normal

The conventional model (Model 1) can incorporate the assumption that the residuals follow *i.i.d.* skew Student t distributions, i.e.:

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

where 0, $\sigma^2_{\varepsilon j}$, δ_j and v_j are the mean, scale and skewness parameters, and degrees of freedom, respectively, of the corresponding skew Student t distribution. The skewness parameters are assigned normal prior distributions, namely $\delta_j \sim N(0,10^4)$.

A slightly revised reparameterization of the density function of $\varepsilon_{ijk}|\sigma^2_{\varepsilon_j},\delta_j,v_j$ by Sahu *et al.*[7] can be written as:

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

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

The Student t distribution is a special case of the skew Student t distribution when $\delta_j=0$.

The skew Student t distribution is negatively skewed for $\delta_j < 0$, and positively skewed for $\delta_j > 0$. In this regard, the skew Student t distribution is more flexible than the conventional Student t distribution.

The skew Student t distribution can be hierarchically specified by normal, truncated normal and gamma distributions as follows[7]:

$$\varepsilon_{ijk}|\sigma^2_{\varepsilon_j}, \delta_j, v_j, \xi_{1ijk}, \xi_{2ijk} \sim N\left(\left[\xi_{1ijk} - \left(\frac{v_j}{\pi}\right)^{\frac{1}{2}} \frac{\Gamma\left(\frac{v_j-1}{2}\right)}{\Gamma\left(\frac{v_j}{2}\right)}\right] \cdot \delta_j, \frac{\sigma^2_{\varepsilon_j}}{\xi_{2ijk}}\right)$$

$$\xi_{1ijk}|\xi_{2ijk} \sim TN\left(0, \frac{1}{\xi_{2ijk}}\right) I(0,\infty)$$

$$\xi_{2ijk} \sim G\left(\frac{v_j}{2}, \frac{v_j}{2}\right)$$

Based on law of total probability, the set of nuisance parameters (ξ_{1ijk} and ξ_{2ijk}) integrated out results in the skew Student t distribution:

$$P\left(\varepsilon_{ijk}|, \sigma^2_{\varepsilon_j}, \delta_j, v_j\right) =$$
$$\int P\left(\varepsilon_{ijk}|, \sigma^2_{\varepsilon_j}, \delta_j, v_j, \xi_{1ijk}, \xi_{2ijk}\right) \cdot P\left(\xi_{1ijk}|\xi_{2ijk}\right) P\left(\xi_{2ijk}\right) \mathrm{d}\left(\xi_{1ijk}, \xi_{2ijk}\right)$$

Section A of the supplementary material provides OpenBUGS example code for the implementation of regression model $\mathrm{R_{ST}C_N}$ for a typical 14-day EBA study.

Regression Model 4 ($\mathbf{R_{ST}C_T}$): <u>Residuals:</u> Skew Student t
<u>Random Coefficients</u>: Student t

Model 3 can incorporate the assumption that the vectors of random intercepts and slopes follow *i.i.d.* tri-variate Student t distributions, i.e.:

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

where μ_j are the vectors of mean intercepts and slopes, and $\Omega_{\mu j}$ and w_j are scale matrices and degrees of freedom, respectively, of the corresponding tri-variate Student t distribution. The degrees of freedom w_j are assigned uniform prior distributions, namely $w_j \sim U(2, 100)$.

The tri-variate Student t distribution can accommodate heavily tailed intercepts and slopes (depending on the 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.

3.3 Model Comparison

DIC statistics and CLMMLs will be used to discriminate among the regression models in Table 3.1.

3.3.1 Deviance Information Criterion

Although DIC statistics can be obtained directly from OpenBUGS,[31] it should be noted that, for regression models $R_{ST}C_N$ and $R_{ST}C_T$, the likelihood of the normal distribution (specified in OpenBUGS) is conditional on a set of nuisance parameters. The DIC statistics obtained from OpenBUGS for these regression models are therefore not appropriate and should not be reported. The probability and cumulative density functions of the skew Student t distribution should thus be specified explicitly.

3.3.2 Compound Laplace-Metropolis Marginal Likelihood

For calculation of CLMMLs, the methodology proposed by Lewis and Raftery[32] suggests the Laplace method to approximate the required integrals (the marginalization of random effects for each patient in the trial). However, the use of Laplace's method for multidimensional integrals can be challenging. In order for asymptotic Laplace approximations to be reliable, an ad-

equate amount of observations associated with each patient's likelihood should be available.[33] In the current application the latter requirement is problematic since individual profiles with a significant amount of missing data do usually occur in EBA trials.

An approach to address the aforementioned concerns associated with Laplace approximated integrals is described here in detail. The approach provides a generalized methodology for the regression models in Table 3.1 and is reasonably easy to implement with SAS® and the R project.

For regression model $R_N C_N$, the associated CLMML can be calculated by marginalizing the random effects for each patient using the multidimensional numerical integration library "R2Cuba" of the R project.[34] This integration package uses numerical techniques which do not rely on asymptotic theory, and is particularly appropriate for high dimensional integration. The marginal likelihood of patient i in treatment group j is expressed as follows:

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

Here, $\hat{\mu_j}$, $\hat{\kappa}_j$, $\hat{\gamma}_j$, $\hat{\Omega}_{\mu j}$, $\hat{\sigma}^2_{\kappa_j}$, $\hat{\sigma}^2_{\gamma_j}$ and $\hat{\sigma}^2_{\varepsilon j}$ are respectively the mean of the posterior distribution of μ_j, κ_j, γ_j, $\Omega_{\mu j}$, $\sigma^2_{\kappa_j}$, $\sigma^2_{\gamma_j}$ and $\sigma^2_{\varepsilon j}$, y_{ij} denote $T_{ij}\times 1$ vectors containing $\left(\log[y_{ij1}],\ldots,\log[y_{ijT_{ij}}]\right)'$, and

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

Let $|R_{\left(\mu_j,\kappa_j,\gamma_j,\sigma^2_{\varepsilon j},j=1,\ldots,J\right)}|$ and $s_{\left(\mu_j,\kappa_j,\gamma_j,\sigma^2_{\varepsilon j},j=1,\ldots,J\right)}$ respectively denote the determinant of the correlation matrix and the sum of the logarithm of the standard deviations of the posterior distributions of μ_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 CLMML for regression model $R_N C_N$ can be written as:

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

The following libraries of the R project are used for the specification of the relevant density and cumulative distribution functions in Equation (2):

- The normal and Student t distribution included in library "sn" (skewness parameters equal to 0).[35]
- The multivariate normal distribution included in library "mnormt".[36]
- The truncated normal distribution included in library "truncnorm".[37]
- The Wishart distribution included in library "mixAK".[38]

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

The parameterization of the skew Student t distribution included in library "sn" differs to that used for regression model $R_{ST}C_T$.[7] These counterparts should therefore be specified explicitly.

Section B of the supplementary material provides SAS® and R example code for the calculation of the CLMML of regression model $R_N C_N$.

4 APPLICATION

The robust methodology proposed here was applied to a wide range of datasets, namely from the following six clinical trials: CL001[39], CL007[40], CL010[41], NC001[13], NC002 (EBA substudy)[12] and NC003[26]. Thus our database consists of six datasets, containing data for 68, 65, 67, 85, 45 and 99 patients, respectively (429 patients in total).

Section 4.1 presents the results of a preliminary investigation of the observed CFU count from clinical trials listed above, and results from regression models fitted jointly to the data of all patients (per trial) are discussed in Section 4.2.

4.1 Preliminary Investigation

Figure C.1 through C.6 in the supplementary material show the observed log(CFU) count over time for each study by treatment group. A visual inspection of the log(CFU) versus time profiles suggests the following:

- Data within individual profiles: Outliers and skewness in CFU count seem to be present in some trials. In addition, the zero CFU counts (or left-censored log(CFU) counts) may cause heavy tails and skewness in the distribution of the residuals and random coefficients. For further illustration purposes, Figure D.1 in the supplementary material depicts the reciprocal of conditional posterior ordinates (ICPOs),[42] based on regression model $R_N C_N$, for each observed data point of the NC003 trial. A significant amount of ICPOs are estimated to be larger than 100, and therefore give indication that extreme outliers are present in the data.

- Differences between individual profiles: Outliers in the rates of decrease of CFU count over time seem to be present in some trials. In particular, the Pa-Z-M treatment group of the NC001 trial contains two profiles with a substantial amount of zero CFU counts toward the end of the observation period. These two profiles (versus the remainder) em-

pirically show very high EBA over the 14-day treatment period. For further illustration purposes, box and whisker plots for posterior estimates of by-patient $\text{EBA}_{\text{CFU}_j}(0-14)$, based on regression model $\text{R}_\text{N}\text{C}_\text{N}$, are shown in Figure E.1 (supplementary material) by treatment group of the NC001 trial.

Given these observations, the full set of regression models was fitted to each dataset for assessment of model robustness.

4.2 Regression Fits

For regression model $\text{R}_\text{ST}\text{C}_\text{T}$, 2 700 000 iterations were simulated. Among those 2 700 000 iterations, the initial 200 000 iterations were discarded (burn-in). The thinning factor was set to 200 to reduce autocorrelation.

Plots of observed log(CFU) count together with fits of regression models $\text{R}_\text{N}\text{C}_\text{N}$ and $\text{R}_\text{ST}\text{C}_\text{T}$ are included in Figure 4.1a and Figure 4.1b for two specific patients in the NC003 trial. These profiles contain a CFU count at Day 11 (Figure 4.1a) and a zero (left-censored) CFU count at Day 13 (Figure 4.1b) which respectively appear to be potentially contaminated and biologically highly implausible. Figure 4.1a and Figure 4.1b clearly illustrate that the regression model with heavy tailed and skew distributions ($\text{R}_\text{ST}\text{C}_\text{T}$) is associated with more robust fits relative to the normal distribution ($\text{R}_\text{N}\text{C}_\text{N}$).

Figure 4.2a (429 patients) and Figure 4.2b (32 treatment groups) respectively present the posterior estimates of by-patient and mean $\text{EBA}_{\text{CFU}_j}(0-14)$ for regression models $\text{R}_\text{N}\text{C}_\text{N}$ and $\text{R}_\text{ST}\text{C}_\text{T}$ by trial and treatment group. As indicated by Davies *et al.*[14] and Burger and Schall[25], EBA estimates calculated from mixed effects regression models are generally shrunken towards their corresponding mean estimates. However, despite this "shrinkage effect", extreme outliers in CFU count can still have a significant impact on the estimation of and inferences on EBA. In view of the fits presented in Figure 4.1a and Figure 4.1b, regression model $\text{R}_\text{ST}\text{C}_\text{T}$ in Figure 4.2a and Figure 4.2b, compared to regression model $\text{R}_\text{N}\text{C}_\text{N}$, clearly provides a larger

shrinkage effect with respect to EBA. That is, regression model $R_{ST}C_T$ yields smaller EBA estimates than regression model R_NC_N. The EBA estimates of the skew Student t regression model therefore appear to be more robust to outliers than those of the conventional normal regression model.

Figure 4.3a and Figure 4.3b respectively present the posterior estimates of v_j and δ_j for regression model $R_{ST}C_T$ by trial and treatment group. The estimates for the degrees of freedom and skewness parameters provide evidence that the CFU counts are heavy tailed and slightly skewed: Figure 4.3a shows that the estimates of degrees of freedom are below 10 in 16 out of 32 cases [heavy tailed], and Figure 4.3b that the estimate of the skewness parameter is below 0 in 28 out of 32 cases [skewed to the left]). All estimates for the degrees of freedom of the vectors of random intercepts are above 30 (data not shown) which suggests that their distributions are not heavy tailed (that is, for all practical purposes follow normal distributions). As a case in point, the Pa-Z-M regimen of the NC001 trial (see Section 4.1) includes two patients with zero CFU counts observed towards the end of the data profiles. As a result, the EBA estimates for these patients are substantially larger than the overall mean. In this regard the regression model $R_{ST}C_T$ provides a slightly smaller, but significant, $\text{EBA}_{\text{CFU}_j}(0-14)$ estimate (for Pa-Z-M of the NC001 trial) than regression model R_NC_N.

Model comparison statistics for the various Bayesian mixed effects regression models fitted are provided in Table 4.1. The results presented in Table 4.1 suggest the following:

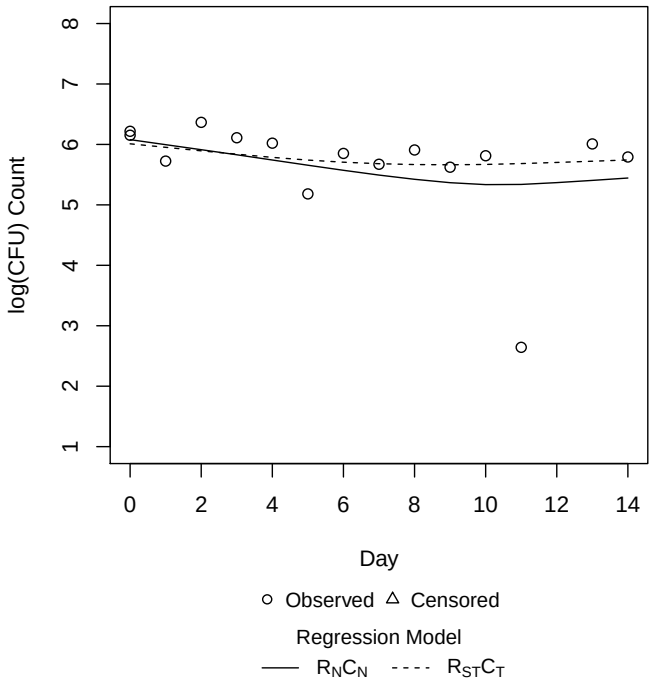
- Both model comparison statistics, namely DICs and CLMMLs, select models with Student t distributed residuals (R_TC_N) over the normal distribution (R_NC_N) in all cases.

- The DIC statistics select the skew Student t distribution ($R_{ST}C_N$ and $R_{ST}C_T$) for the residuals over the standard (symmetric) Student t distribution (R_TC_N), whereas the CLMMLs generally select the standard Student t distribution (R_TC_N).

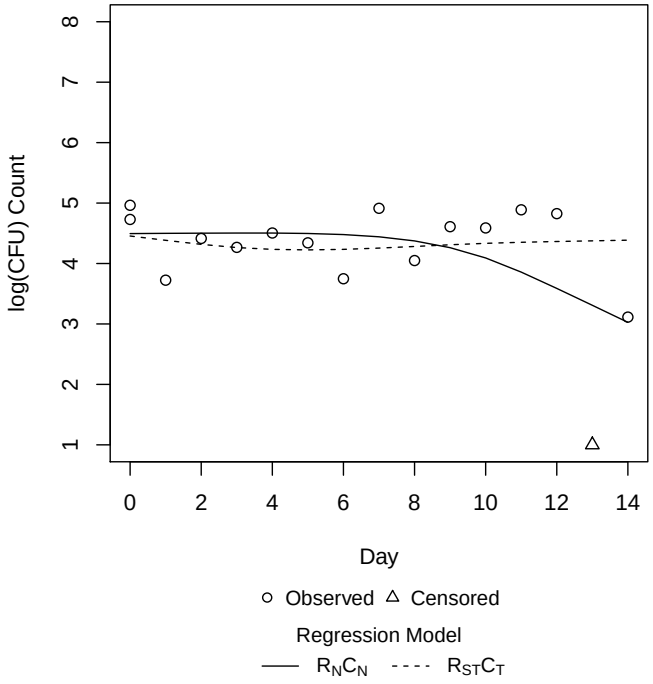
- Overall, the CLMMLs select the normal distribution for random intercepts and slopes

Figure 4.1: Observed and Fitted log(CFU) Versus Time Profiles: R_NC_N and $R_{ST}C_T$

(a) Potentially Contaminated

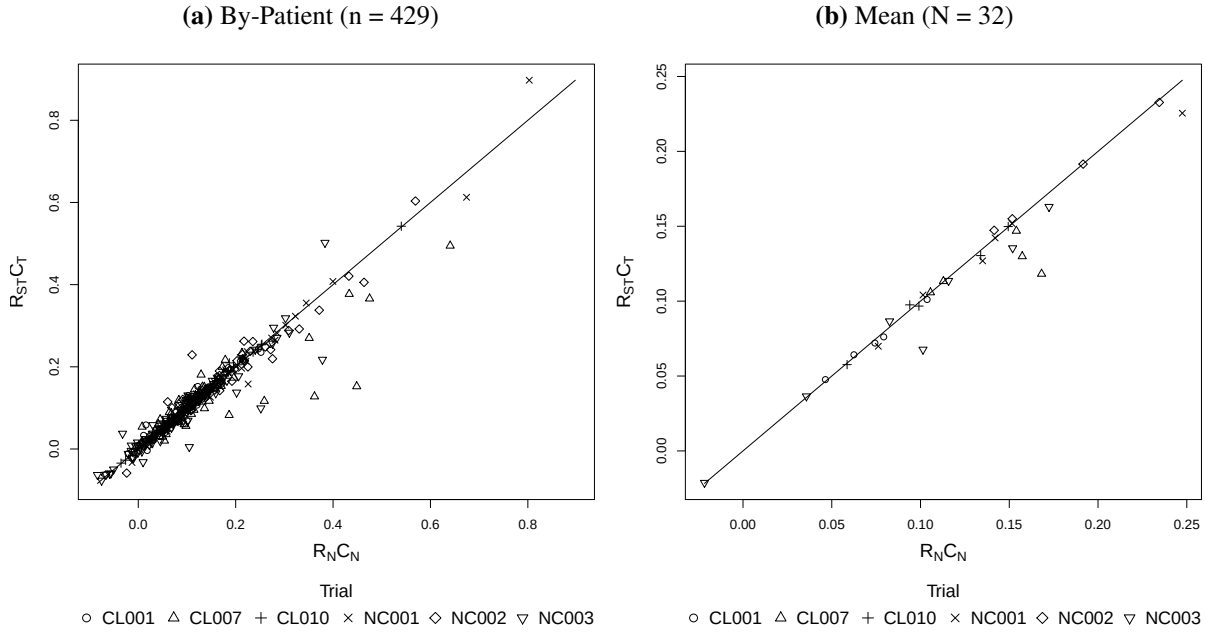


(b) Biologically Highly Implausible



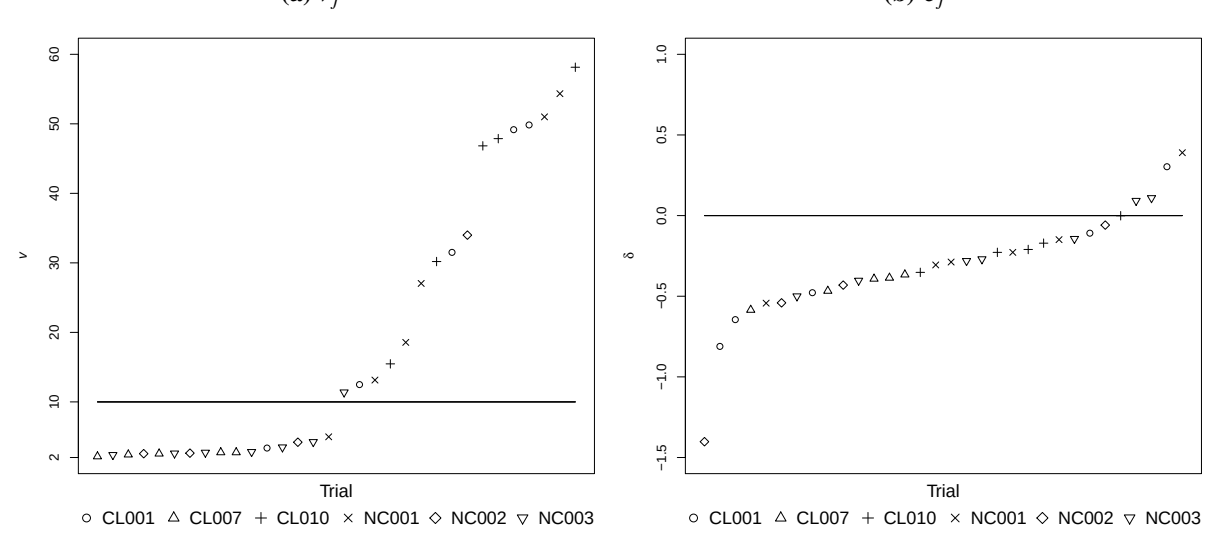
Note: R_NC_N: Residuals and random coefficients assumed to follow normal distributions. $R_{ST}C_T$: Residuals and random coefficients respectively assumed to follow skew Student t and tri-variate Student t distributions. CFU: Colony forming unit. Censored: Zero CFU counts, on the logarithmic scale to the base of 10, specified as left-censored values of 1.

Figure 4.2: Posterior Estimates of By-Patient and Mean $\text{EBA}_{\text{CFU}_j}(0-14)$: $\text{R}_\text{N}\text{C}_\text{N}$ and $\text{R}_\text{ST}\text{C}_\text{T}$



Note: N = Number of treatment groups. n = Number of patients. $\text{R}_\text{N}\text{C}_\text{N}$: Residuals and random coefficients assumed to follow normal distributions. $\text{R}_\text{ST}\text{C}_\text{T}$: Residuals and random coefficients respectively assumed to follow skew Student t and tri-variate Student t distributions. CFU: Colony forming unit. $\text{EBA}_{\text{CFU}}(t_1 - t_2)$: Daily rate of change in log(CFU) count from Day t_1 to Day t_2 of treatment group j.

Figure 4.3: Posterior Estimates of v_j and δ_j: $\text{R}_\text{ST}\text{C}_\text{T}$



Note: $\text{R}_\text{ST}\text{C}_\text{T}$: Residuals and random coefficients respectively assumed to follow skew Student t and tri-variate Student t distributions. v_j: Degrees of freedom of the skew Student t distribution assumed for the residuals of treatment group j. δ_j: Skewness parameter of the skew Student t distribution assumed for the residuals of treatment group j.

($R_{ST}C_N$) over the Student t distribution ($R_{ST}C_T$), whereas the DICs have no preference (DIC differences are negligible).

Table 4.1: Comparison of Bayesian NLME Regression Models Using DICs and CLMMLs

Trial	**Model Comparison Statistic**	$\mathbf{R_NC_N}$	$\mathbf{R_TC_N}$	$\mathbf{R_{ST}C_N}$	$\mathbf{R_{ST}C_T}$
CL001	DIC	$1178^{\{4\}}$	$1080^{\{3\}}$	$1013^{\{2\}}$	$1012^{\{1\}}$
	CLMML	$-1004^{\{2\}}$	$-979^{\{1\}}$	$-1012^{\{4\}}$	$-1009^{\{3\}}$
CL007	DIC	$1807^{\{4\}}$	$1351^{\{3\}}$	$1232^{\{1\}}$	$1233^{\{2\}}$
	CLMML	$-1223^{\{4\}}$	$-1102^{\{1\}}$	$-1119^{\{2\}}$	$-1143^{\{3\}}$
CL010	DIC	$821^{\{4\}}$	$760^{\{3\}}$	$743^{\{1\}}$	$745^{\{2\}}$
	CLMML	$-861^{\{2\}}$	$-849^{\{1\}}$	$-906^{\{4\}}$	$-901^{\{3\}}$
NC001	DIC	$1635^{\{4\}}$	$1526^{\{3\}}$	$1487^{\{1\}}$	$1488^{\{2\}}$
	CLMML	$-1382^{\{2\}}$	$-1365^{\{1\}}$	$-1396^{\{3\}}$	$-1407^{\{4\}}$
NC002	DIC	$1002^{\{4\}}$	$764^{\{3\}}$	$708^{\{2\}}$	$707^{\{1\}}$
	CLMML	$-749^{\{3\}}$	$-692^{\{1\}}$	$-741^{\{2\}}$	$-757^{\{4\}}$
NC003	DIC	NE	$2318^{\{3\}}$	$2287^{\{1,2\}}$	$2287^{\{1,2\}}$
	CLMML	$-2087^{\{4\}}$	$-1855^{\{1\}}$	$-1880^{\{2\}}$	$-1918^{\{3\}}$

Note: DIC: Deviance Information Criterion. CFU: Colony forming unit. CLMML: Compound Laplace-Metropolis marginal likelihood on the logarithmic scale. NE: Not estimable. NLME: Nonlinear mixed effects. Superscripts indicate the ranking of model comparison statistics from most favored to least favored.

5 SIMULATION STUDY

In this section we report the results of a simulation study to assess the performance of the proposed regression models. Datasets were simulated from the $R_{ST}C_T$ regression model where model parameters were chosen to mimic log(CFU) count versus time profiles of the Pa-Z-M and Rifafour treatment groups in the NC001 trial (see Diacon *et al.*[13]).

The slope parameters for the two treatments were chosen as $\beta_{11} = 0.32$, $\beta_{21} = -0.22$, $\beta_{12} = 0.22$ and $\beta_{22} = -0.25$, while the following parameter values were chosen for both treatments ($j = 1,2$): $\alpha_j = 7$, $\kappa_j = 5$, $\gamma_j = 1$, $\delta_j = -0.5$, $v = 2$, $w_j = 25$, $\sigma^2_{\varepsilon_j} = 0.15$ and

$$\Omega_{\mu j} = \begin{bmatrix} 0.30 & 0.01 & -0.01 \\ 0.01 & 0.02 & -0.0001 \\ -0.01 & -0.0001 & 0.0005 \end{bmatrix}.$$

In summary, the aforementioned parameter values mimic profiles that contain heavy tailed residuals but are only slightly skewed to the left. The EBA for Pa-Z-M and Rifafour are respectively $\text{EBA}_{\text{CFU}_1}(0-14) = 0.25714$ and $\text{EBA}_{\text{CFU}_2}(0-14) = 0.14857$.

Accuracy and precision characteristics such as bias, standard error (SE), and root mean square error (RMSE) of the $\text{EBA}_{\text{CFU}_j}(0-14)$ estimates for the two treatment groups were calculated. The corresponding empirical coverage probability of the 95% Bayesian credibility intervals (BCIs) was also calculated.

The four candidate models (R_NC_N, R_TC_N, $R_{ST}C_N$ and $R_{ST}C_T$) were fitted to the simulated datasets (simulated from $R_{ST}C_T$). The simulation study was based on 5000 simulated datasets, each dataset consisting of 15 profiles per treatment. For simplicity, the regression models fitted κ_{ij} and γ_{ij} as fixed effects.

From Table 5.1, we observe that the bias of $\text{EBA}_{\text{CFU}_j}(0-14)$ estimates is close to zero for all models, probably due to the fact that the skewness in the data is negligible. The SE and RMSE suggest that the robust regression models (R_TC_N, $R_{ST}C_N$ and $R_{ST}C_T$) perform better relative to the conventional normal model (R_NC_N). The coverage probability of the 95% BCI

of the conventional normal model is somewhat higher than the nominal value (the 95% BCIs are conservative), whereas the robust regression models yield coverage probabilities that are quite close to the nominal value.

Table 5.1: Simulation Study of Bayesian NLME Regression Models: Accuracy and Precision of $\text{EBA}_{\text{CFU}_j}(0-14)$ Estimates, and Coverage of 95% BCIs

Treatment Group	Description	$\mathbf{R_N C_N}$	$\mathbf{R_T C_N}$	$\mathbf{R_{ST} C_N}$	$\mathbf{R_{ST} C_T}$
1	Bias	−0.0107	−0.0149	−0.0173	−0.0184
	SE	0.0496	0.0414	0.0414	0.0414
	RMSE	0.0508	0.0440	0.0449	0.0453
	95% BCI Coverage	96.7	95.5	94.5	94.8
2	Bias	−0.0091	−0.0150	−0.0159	−0.0161
	SE	0.0564	0.0416	0.0420	0.0407
	RMSE	0.0572	0.0442	0.0449	0.0438
	95% BCI Coverage	96.6	95.0	94.9	94.9

Note: BCI: Bayesian credibility interval. RMSE: Root mean square error. SE: Standard error.

6 DISCUSSION

Conventional regression models assume that the data follow normally distributed residuals which do not accommodate heavy tails or asymmetrical skewness in the distribution of the data. Robust regression models are designed to safeguard cases where the normality assumption does not necessarily hold. Robust NLME regression models using Bayesian approaches are relatively easy to implement, and are advantageous in the sense that they do not rely on asymptotic approximations as classical inference methods do for complex models.

In the clinical development of anti-TB drugs the assessment of their EBA of TB drugs is of interest. EBA is typically assessed using statistical regression modeling of CFU count over time. Outliers in CFU count due to erroneous sputum sampling can cause the data versus time profiles to be erratic, and accordingly yield potential heavy tails and skewness in the distribution of the residuals of model fits. Typically, most CFU counts deviate little from the regression curve, but gross outliers are occasionally present and can markedly influence estimates of the rate of change in CFU count which is the parameter of interest.

The conventional normal regression model of Burger and Schall[25] was adapted to offer a robust approach that accommodates outliers and potential skewness. In particular this regression model specified the skew Student t distribution for residuals, and the multivariate Student t distribution for random coefficients.

DIC statistics and CLMMLs were used to discriminate between alternative Bayesian mixed effects regression models. In this context, we presented a relatively easy method to calculate the marginal likelihoods required to determine CLMMLs, by adapting methods available in SAS® and the R project. It should be noted that the DIC statistic assesses model adequacy and prediction conditional on the random effects of the regression model (estimates on a by-patient basis), whereas the CLMML assesses the aforementioned on an overall (or marginal) basis.

Applying the proposed methodology to data from six clinical trials suggests that Bayesian NLME fits of data profiles containing outliers, based on the Student t distribution, are more plausible than fits based on the normal distribution. The degrees of freedom and skewness parameters of the fitted Student t distributions provide evidence that the distribution of CFU count is often heavy tailed and slightly skewed to the left (suggesting the presence of outliers).

Both model comparison statistics (DICs and CLMMLs) select models with Student t distributed residuals over the normal distribution. The DIC statistics indicate that building skewness into residuals improves model fit, whereas the CLMMLs do not. Thus the CLMMLs

generally do not suggest that the distribution of random intercepts and slopes is heavy tailed.

Even though the model comparison statistics do not provide consensus on which of the four candidate models is preferred, there is a clear indication that models which accommodate heavy tailed residuals are preferred (that is, the conventional normal model is not preferred in all cases). Furthermore, the simulation study suggested that the proposed robust regression models have good properties in terms of accuracy, precision and credibility interval coverage. For further clinical development of anti-TB drugs, it is essential that statistical conclusions based on data from EBA studies are appropriate (regardless of problems associated with CFU counting processes such as contamination). We recommend that robust regression models such as those proposed here should be fitted to verify findings or conclusions drawn from the analysis of CFU count.

7 DATA ACCESSIBILITY

The programming code supporting this paper has been included as part of the supplementary material.

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