APPENDICES

A generalized Bayesian nonlinear mixed effects regression model for zero inflated longitudinal count data in tuberculosis trials

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Appendix A: Exponential family of distributions

Table 1: Exponential family of distributions of zero inflated generalized NLME regression model for CFU count over time

Distribution	π_{ij}	$\boldsymbol{\tau_{jk}}$	$\boldsymbol{\eta}\left(f\left(\boldsymbol{\phi_{ij}},\boldsymbol{\theta_j},t_{ijk},o_{ijk}\right),\boldsymbol{\tau_{jk}}\right)$	$h\left(y_{ijk},\boldsymbol{\tau_{jk}}\right)$	$\boldsymbol{T}\left(y_{ijk}\right)$	$A\left(f\left(\boldsymbol{\phi_{ij}},\boldsymbol{\theta_j},t_{ijk},o_{ijk}\right),\boldsymbol{\tau_{jk}}\right)$
Poisson	0		$\log\left(\lambda_{ijk}\right)$	$\frac{1}{y_{ijk}!}$	y_{ijk}	λ_{ijk}
ZIP	π_{ij}		$\log\left(\lambda_{ijk}\right)$	$\frac{1}{y_{ijk}!}$	y_{ijk}	λ_{ijk}
NEGBIN	0	ρ_{jk}	$\log\left(\frac{\lambda_{ijk}}{\lambda_{ijk}+\rho_{jk}}\right)$	$\binom{y_{ijk}+\rho_{jk}-1}{y_{ijk}}$	y_{ijk}	$-\rho_{jk}\log\left(\frac{\rho_{jk}}{\lambda_{ijk}+\rho_{jk}}\right)$
ZINB	π_{ij}	ρ_{jk}	$\log\left(\frac{\lambda_{ijk}}{\lambda_{ijk}+\rho_{jk}}\right)$	$\binom{y_{ijk}+\rho_{jk}-1}{y_{ijk}}$	y_{ijk}	$-\rho_{jk}\log\left(\frac{\rho_{jk}}{\lambda_{ijk}+\rho_{jk}}\right)$
Lognormal	0	σ^2_{jk}	$\begin{bmatrix}\frac{\log\left(\lambda_{ijk}\right)}{\sigma^2_{jk}}\\ -\frac{1}{2\sigma^2_{jk}}\end{bmatrix}$	$\frac{1}{\sqrt{2\pi}y_{ijk}}$	$\begin{bmatrix}\log\left(y_{ijk}\right)\\ \left[\log\left(y_{ijk}\right)\right]^2\end{bmatrix}$	$\frac{\log\left(\lambda_{ijk}\right)^2}{2\sigma^2_{jk}}+\log\left(\sigma_{jk}\right)$

CFU: Colony forming unit. NEGBIN: Negative binomial. NLME: Nonlinear mixed effects. ZINB: Zero inflated negative binomial. ZIP: Zero inflated Poisson. $\lambda_{ijk} = f\left(\boldsymbol{\phi_{ij}},\boldsymbol{\theta_j},t_{ijk},o_{ijk}\right) = \exp\left(\alpha_{ij}-\beta_{1ij}t_{ijk}-\beta_{2ij}\gamma_j\log\left[\frac{e^{\frac{t_{ijk}-\kappa_j}{\gamma_j}}+e^{-\frac{t_{ijk}-\kappa_j}{\gamma_j}}}{e^{\frac{\kappa_j}{\gamma_j}}+e^{-\frac{\kappa_j}{\gamma_j}}}\right]-o_{ijk}\right)$. $\boldsymbol{\phi_{ij}} = \left(\alpha_{ij},\beta_{1ij},\beta_{2ij}\right)'$. $\boldsymbol{\theta_j} = \left(\kappa_j,\gamma_j\right)'$. $o_{ijk} = \log\left(c_{ijk}10^{d_{ijk}}/n_{ijk}\right)$. n_{ijk}, c_{ijk} & d_{ijk} are respectively n, “factor” and “dilution” as per Equation (2).

Appendix B: Specification of random effects and prior distributions

In Equation (5), the random coefficients $\boldsymbol{\phi_{ij}} = \boldsymbol{\mu_{ij}}$ are assumed to follow tri-variate normal distributions as follows:

$$\boldsymbol{\mu_{ij}} \sim \text{Normal}\left(\boldsymbol{\mu_j}, \Omega_{\boldsymbol{\mu}j}\right) \tag{1}$$

where $\Psi_j = \Omega_{\boldsymbol{\mu}j}$ are the covariance matrices of $\boldsymbol{\phi_{ij}} = \boldsymbol{\mu_{ij}}$.

Multivariate normal and Wishart prior distributions are specified, respectively, for $\boldsymbol{\mu_j}$ and $\Omega_{\boldsymbol{\mu}j}^{-1}$, namely:

$$\boldsymbol{\mu_j} \sim \text{Normal}(\mathbf{0}, 10^4 \times I_3) \tag{2}$$

$$\Omega_{\boldsymbol{\mu}j}^{-1} \sim \text{Wishart}(3, 3 \times R_j) \tag{3}$$

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

The parameters κ_j and γ_j are assumed to follow uniform prior distributions, namely:

$$\kappa_j \sim \text{Uniform}(L_\kappa, U_\kappa) \tag{4}$$

$$\gamma_j \sim \text{Uniform}(L_\gamma, U_\gamma) \tag{5}$$

where L_κ, U_κ, L_γ and U_γ are the pre-specified lower and upper bounds for parameters κ_j and γ_j, respectively.

For the choice of R_j, we fitted the model as a generalized linear mixed effects regression model under the assumption that the node and smoothness parameters (κ_j and γ_j) are fixed at $(U_\kappa + L_\kappa)/2$ and $(U_\gamma + L_\gamma)/2$, respectively. We calculated the “frequentist" estimates for $\Omega_{\boldsymbol{\mu}j}$ via maximum likelihood estimation using the SAS® procedure PROC GLIMMIX, to serve as R_j.

The dispersion parameters ρ_{jk}, scale parameters σ_{jk}^{-2}, and zero inflation probabilities π_{jk} are assumed to follow vague gamma and beta prior distributions, namely:

$$\rho_{jk} \sim \text{Gamma}\,(0.1, 0.1) \tag{6}$$

$$\sigma_{jk}^{-2} \sim \text{Gamma}\,(0.0001, 0.0001) \tag{7}$$

$$\pi_{jk} \sim \text{Beta}\,(0.1, 0.1) \tag{8}$$

The prior distributions for the ZIGP regression model are presented in Section 1 of the online appendix of this paper.

The ZIP distribution can alternatively be specified as a mixture of Poisson and Bernoulli distributions as follows:

$$y_{ijk} \sim \text{Poisson}\,(\lambda_{ijk}\,[1 - u_{ijk}]) \tag{9}$$

$$u_{ijk} \sim \text{Bernoulli}\,(\pi_{jk}) \tag{10}$$

Similarly, the ZINB distribution can alternatively be specified as a mixture of NEGBIN and Bernoulli distributions as follows:

$$y_{ijk} \sim \text{NEGBIN}\,(\lambda_{ijk}\,[1 - u_{ijk}]\,, \rho_{jk}) \tag{11}$$

$$u_{ijk} \sim \text{Bernoulli}\,(\pi_{jk}) \tag{12}$$

From the law of total probability, the distributions marginalized over u_{ijk} result in the ZIP and ZINB distributions.

Appendix C: Laplace-Metropolis approximation of Bayes factors

The Laplace-Metropolis approximation of $\log(f\left[\boldsymbol{y}|M\right])$ (that is, CLMML) under Model M can be written as[15,23,24] (see Table 1 and Appendix Table 1):

$$\log(f\left[\boldsymbol{y}|M\right]) = \frac{1}{2}\log\left(2\pi\right)pJ + \frac{1}{2}\log\left|R_{\left(\boldsymbol{\phi_j},\boldsymbol{\theta_j},\boldsymbol{\tau_{jk}},\pi_{jk},j=1,\ldots,J\right)}\right| + s_{\left(\boldsymbol{\phi_j},\boldsymbol{\theta_j},\boldsymbol{\tau_{jk}},\pi_{jk},j=1,\ldots,J\right)} + \sum_{j=1}^{J}\sum_{i=1}^{N_j}\left(\log\left[P\left(\boldsymbol{y_{ij}}|\hat{\boldsymbol{\phi}}_{\boldsymbol{j}},\hat{\Psi}_j,\hat{\boldsymbol{\theta}}_{\boldsymbol{j}},\hat{\boldsymbol{\tau}}_{\boldsymbol{jk}},\hat{\pi}_{jk}\right)\right]\right) + \sum_{j=1}^{J}\left(\log\left[P\left(\hat{\boldsymbol{\phi}}_{\boldsymbol{j}},\hat{\Psi}_j,\hat{\boldsymbol{\theta}}_{\boldsymbol{j}},\hat{\boldsymbol{\tau}}_{\boldsymbol{jk}},\hat{\pi}_{jk}\right)\right]\right) \quad (13)$$

where p is the number of parameters among $\boldsymbol{\phi_j}$, Ψ_j, $\boldsymbol{\theta_j}$, $\boldsymbol{\tau_{jk}}$ & π_{jk} of treatment group j, and $P\left(\boldsymbol{y_{ij}}|\hat{\boldsymbol{\phi}}_{\boldsymbol{j}},\hat{\Psi}_j,\hat{\boldsymbol{\theta}}_{\boldsymbol{j}},\hat{\boldsymbol{\tau}}_{\boldsymbol{jk}},\hat{\pi}_{jk}\right) = \int P\left(\boldsymbol{y_{ij}}|\boldsymbol{\phi_{ij}},\hat{\boldsymbol{\phi}}_{\boldsymbol{j}},\hat{\Psi}_j,\hat{\boldsymbol{\theta}}_{\boldsymbol{j}},\hat{\boldsymbol{\tau}}_{\boldsymbol{jk}},\hat{\pi}_{jk}\right) \mathrm{d}\boldsymbol{\phi_{ij}}$ (see Equation (6)). Here, $\hat{\boldsymbol{\phi}}_{\boldsymbol{j}}$, $\hat{\Psi}_j$, $\hat{\boldsymbol{\theta}}_{\boldsymbol{j}}$, $\hat{\boldsymbol{\tau}}_{\boldsymbol{jk}}$ and $\hat{\pi}_{jk}$ are respectively the mean of the posterior distribution of $\boldsymbol{\phi_j}$, Ψ_j, $\boldsymbol{\theta_j}$, $\boldsymbol{\tau_{jk}}$ and π_{jk}. $\left|R_{\left(\boldsymbol{\phi_j},\boldsymbol{\theta_j},\boldsymbol{\tau_{jk}},\pi_{jk},j=1,\ldots,J\right)}\right|$ and $s_{\left(\boldsymbol{\phi_j},\boldsymbol{\theta_j},\boldsymbol{\tau_{jk}},\pi_{jk},j=1,\ldots,J\right)}$ respectively denote the determinant of the correlation matrix and the sum of the logarithm of the standard deviations of the posterior distributions of $\boldsymbol{\phi_j}$, $\boldsymbol{\theta_j}$, $\boldsymbol{\tau_{jk}}$ and π_{jk}.

The multidimensional integration library “R2Cuba” of the R project was used to approximate the Laplace integrals.[52]

Appendix D: Summary statistics

Table 2: Summary statistics of observed CFU count over time

Treatment	Day	n	Mean	SD	CV	Minimum	Median	Maximum	Zeros (%)
M-PA100-Z	Day 0	110	4022762	8592024	214	0	509500	55500000	1.8
	Day 3	54	5252617	36022027	686	0	62150	265000000	5.6
	Day 7	51	43318	91253	211	0	7800	570000	9.8
	Day 14	49	13708	26824	196	0	2350	121000	18.4
	Day 21	47	17594	71960	409	0	245	460000	34.0
	Day 28	42	1272	4744	373	0	0	28600	66.7
	Day 35	39	1890	7482	396	0	0	45000	74.4
	Day 42	36	468	2017	431	0	0	12000	72.2
	Day 49	34	190	840	441	0	0	4800	85.3
	Day 56	35	47	205	437	0	0	1200	85.7
M-PA200-Z	Day 0	107	4472336	9638695	216	0	380000	51333333	0.9
	Day 3	53	432749	1043900	241	0	48000	4700000	3.8
	Day 7	47	94440	211236	224	0	15900	1090000	6.4
	Day 14	47	32462	173048	533	0	1830	1190000	17.0
	Day 21	49	1718	5884	342	0	160	38000	34.7
	Day 28	40	3741	22128	592	0	0	140000	57.5
	Day 35	40	160	492	307	0	0	2200	77.5
	Day 42	37	19131	115050	601	0	0	700000	86.5
	Day 49	32	313	1768	565	0	0	10000	93.8
	Day 56	35	1830	10818	591	0	0	64000	94.3

n = Number of CFU counts. CFU: Colony forming unit. CV: Coefficient of variation. SD: Standard deviation.

Table 2: Summary statistics of observed CFU count over time

Treatment	Day	n	Mean	SD	CV	Minimum	Median	Maximum	Zeros (%)
Rifafour	Day 0	104	3035046	7754022	255	50	330000	57000000	0.0
	Day 3	51	391262	816412	209	0	46150	4000000	7.8
	Day 7	47	90493	169618	187	0	29100	1000000	10.6
	Day 14	44	98332	387679	394	0	6088	2500000	15.9
	Day 21	42	51665	246875	478	0	845	1600000	23.8
	Day 28	37	1969	3556	181	0	370	15990	35.1
	Day 35	38	23117	128034	554	0	0	790000	55.3
	Day 42	37	5976	34337	575	0	0	209000	70.3
	Day 49	37	4087	17002	416	0	0	97000	73.0
	Day 56	32	20	78	383	0	0	410	87.5

n = Number of CFU counts. CFU: Colony forming unit. CV: Coefficient of variation. SD: Standard deviation.

Appendix E: Simulation results

Table 3: Accuracy & precision of BA $(0–56)$ estimates, and BCI coverage: ZINB & lognormal regression model

	Timepoint (days): π_{jk}					Regression model	
BA$_j$ $(0–56)$	0, 3, 7	14, 21	28, 35	42, 49, 56	Statistic	ZINB	Lognormal
0.1046	0	0	0	0	Bias	-0.0039	0.0113
					Absolute bias	0.0092	0.0147
					SE	0.0111	0.0145
					RMSE	0.0118	0.0183
					95% BCI coverage	94.6	90.7
0.1054	0	0.01	0.05	0.1	Bias	-0.0042	0.0175
					Absolute bias	0.0097	0.0190
					SE	0.0114	0.0147
					RMSE	0.0121	0.0228
					95% BCI coverage	94.3	82.3
0.1200	0	0	0	0	Bias	-0.0033	0.0147
					Absolute bias	0.0099	0.0171
					SE	0.0119	0.0149
					RMSE	0.0123	0.0209
					95% BCI coverage	95.4	86.4

BA$_j$ $(0–56)$: Daily rate of decline in $\log_{10}(\text{CFU})$ count from Day 0 to Day 56 of treatment group j. BCI: Bayesian credibility interval. CFU: Colony forming unit. RMSE: Root mean square error. SE: Standard error. ZINB: CFU counts of zero treated as observed data. Lognormal: CFU counts of zero treated as left censored observations.

Table 3: Accuracy & precision of BA $(0–56)$ estimates, and BCI coverage: ZINB & lognormal regression model

	Timepoint (days): π_{jk}					Regression model	
BA$_j$ $(0–56)$	0, 3, 7	14, 21	28, 35	42, 49, 56	Statistic	ZINB	Lognormal
0.1208	0	0.01	0.05	0.1	Bias	-0.0045	0.0215
					Absolute bias	0.0099	0.0225
					SE	0.0114	0.0153
					RMSE	0.0123	0.0264
					95% BCI coverage	95.9	75.0

BA$_j$ $(0–56)$: Daily rate of decline in $\log_{10}(\text{CFU})$ count from Day 0 to Day 56 of treatment group j. BCI: Bayesian credibility interval. CFU: Colony forming unit. RMSE: Root mean square error. SE: Standard error. ZINB: CFU counts of zero treated as observed data. Lognormal: CFU counts of zero treated as left censored observations.