

M.C.M. Wong<sup>1\*</sup>, K.F. Lam<sup>2</sup>,  
and E.C.M. Lo<sup>1</sup>

<sup>1</sup>Dental Public Health, Faculty of Dentistry, and <sup>2</sup>Department of Statistics and Actuarial Science, The University of Hong Kong, 34 Hospital Road, Hong Kong SAR, China; \*corresponding author, mcmwong@hkucc.hku.hk

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## ABSTRACT

The recording of multiple interval-censored failure times is common in dental research. Modeling multilevel data has been a difficult task. This paper aims to use the Bayesian approach to analyze a set of multilevel clustered interval-censored data from a clinical study to investigate the effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting active dentin caries in Chinese pre-school children. The time to arrest dentin caries on a surface was measured. A three-level random-effects Weibull regression model was used. Analysis was performed with WinBUGS. Results revealed a strong positive correlation (0.596) among the caries lesions' arrest times on different surfaces from the same child. The software WinBUGS made the above complicated estimation simple. In conclusion, the annual application of silver diamine fluoride on caries lesions, and caries removal before the application, were found to shorten the arrest time.

**KEY WORDS:** Bayesian approach, biostatistics, multilevel modeling, WinBUGS, survival data.

# Bayesian Analysis of Clustered Interval-censored Data

## INTRODUCTION

Survival analysis encompasses a variety of statistical techniques for analyzing failure time data. When independent exact failure times are recorded with right-censored failure times (*e.g.*, unobserved failure times due to subject drop-outs), various parametric, semi-parametric, and non-parametric methods are available in standard statistical software packages to estimate the survival curves and to investigate the effects of the covariates on survival (Allison, 1995; Venables and Ripley, 1999; Fleming and Lin, 2002; SPSS Inc., 2002). However, in practice, subjects are usually not monitored continuously but are examined periodically at pre-scheduled time points, *e.g.*, every 6 mos. When a failure is observed, the event actually occurred between the current and the previous examination times (interval-censored data). Few methods are available to analyze interval-censored failure time data (Lindsey and Ryan, 1998). A common approach to handling interval-censored data is to assign a particular value to the failure time (*e.g.*, midpoint of the time interval) and then proceed as if the data are being collected on a continuous scale. However, this can lead to biased and misleading results (Prentice and Gloeckler, 1978).

Recording multiple failure times from the same subject is a common practice in dental research. It is obvious that data from the same subject are not independent. Thus, when one is analyzing clustered failure time data, it is important to estimate the intra-cluster association. 'Multilevel modeling' (Gilthorpe *et al.*, 2000b; Leyland and Goldstein, 2001) or 'hierarchical linear modeling' (Bryk and Raudenbush, 1992) is a class of statistical techniques developed to take into account the intra-cluster dependence in the analysis of clustered data. Analysis of clustered multilevel interval-censored data using the 'frequentist' approach for parameter estimation requires tailor-made computer programs. It would be desirable for dental researchers if the clustered multilevel interval-censored data could be analyzed by some software.

Bayesian analysis by the Monte Carlo Markov Chain (MCMC) has been a popular tool for analyzing complex data recently, and it has made its way into the medical and dental arena due to advances in computational and modeling techniques. Basically, Bayesian analysis generates conclusions based on the synthesis of new information from a study (the observed data) and previous knowledge or external evidence from independent sources (priors). By specifying a probability model for the observed data,  $D$ , given a set of unknown parameters,  $\theta$  (unknown quantities that are of interest), and assuming that  $\theta$  is random with a prior distribution  $\pi(\theta)$  derived from external evidence, one can make a Bayesian inference concerning  $\theta$  via the posterior distribution  $\pi(\theta|D)$  (revised distribution of  $\theta$  based on the observed data and priors), according to Bayes' theorem (Bayes, 1763). [For an introduction to Bayesian analysis in dental research, refer to Gilthorpe and co-workers (2000a) and Petrie and co-workers (2003).] Both point and credible interval estimates could be obtained from the posterior distribution. The fundamental difference between the classic 'frequentist' confidence

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interval and the Bayesian credible interval is that, for a long series of 95% confidence intervals, 95% of them should contain the true  $\theta$ , whereas there is a 95% probability that the true  $\theta$  lies in a 95% credible interval based on a specific prior distribution (Spiegelhalter *et al.*, 2004).

This paper aims to use the Bayesian approach to analyze a set of multilevel clustered interval-censored data from a clinical study to investigate the effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting active dentin caries in Chinese pre-school children.

## MATERIALS & METHODS

### Dataset

The data were from a prospective controlled clinical trial investigating the effectiveness of silver diamine fluoride (SDF) and sodium fluoride varnish (NaF) in arresting active dentin caries in Chinese pre-school children (Lo *et al.*, 2001; Chu *et al.*, 2002). Approval from the Ethics Committee of the Faculty of Dentistry, University of Hong Kong, was obtained prior to the implementation of the study. Children with written parental consent attending eight kindergartens participated in the study. At the baseline, one trained dentist examined the kindergarten children's upper incisors and canines. After the examination, children with dentin caries in at least 1 of their primary anterior teeth were sequentially allocated to one of five groups. For children in the first group, soft dentin in the caries lesions was removed by means of hand instruments. The cavities were then painted with a 38% SDF solution every 12 mos. Children in the second group had SDF applied to the caries lesions every 12 mos without prior removal of the carious tissue. For children in the third group, soft dentin in the caries lesions was removed, and then a 5% NaF varnish was applied to the caries lesions every 3 mos. Children in the fourth group had NaF applied every 3 mos without prior removal of caries. Water was painted onto the carious teeth in the last group of children.

Follow-up examinations were carried out every 6 mos after baseline by the same examiner, who did not know the subjects' group assignments. Caries was diagnosed at cavitation level and explored with a sharp sickle-shaped probe at the center of the cavity. A tooth surface could be recorded as sound, caries-active, caries-arrested, filled, or missing.

### Statistical Analysis

The analysis was performed at the tooth surface level. For each child, 24 tooth surfaces (4 from each of the 6 anterior teeth) were clinically examined, and those surfaces with dentin caries at the baseline examination were included in this analysis. We carried out multilevel modeling to compare the effectiveness of SDF and NaF with or without caries removal in arresting dentin caries, by taking into account the possible dependence due to the clustering effect of the kindergartens and the subject. The time to arrest of caries on a surface, namely,  $T$ , was used as the outcome measure of effectiveness. Thus, the shorter the arrest time, the more effective was the agent to arrest dentin caries. Since the children were examined every 6 mos, the arrest time was grouped into (0,6), (6,12), (12,18), (18,24), and (24,30) mos. For carious tooth surfaces that were not arrested at the time of exfoliation, subject drop-out, or at the end of the study, the arrest time was assigned as 0+, 6+, 12+, 18+, 24+, or 30+ mos. The arrest times of the five groups (1 = SDF+caries removal, 2 =

SDF, 3 = NaF+caries removal, 4 = NaF, 5 = Control) were compared, and location of residence (1 = urban *vs.* 0 = rural) and gender (1 = boy *vs.* 0 = girl) were also included in the model as covariates.

Since the arrest times were not totally independent, 2 additive random effects were included in the model, to account for the clustering effects of the carious tooth surfaces in the same child's mouth, and of children attending the same kindergarten, namely,  $B_j$  ( $j = 1, 2, \dots, 367$ ) and  $C_k$  ( $k = 1, 2, \dots, 8$ ), respectively. The random effects  $B_j$  and  $C_k$  were assumed to follow the  $N(0, \sigma_{\text{child}}^2)$  and  $N(0, \sigma_{\text{school}}^2)$  distributions, respectively. Finally, conditional on the random effects, the arrest times  $T_{ijk}$  ( $i = 1, 2, \dots, n_{ijk}$ ) are independent and assumed to follow a Weibull distribution with survivor  $P(T_{ijk} > t | B_j, C_k)$  and hazard  $\lambda_{ijk}(t)$  functions

$$P(T_{ijk} > t | B_j, C_k) = \exp(-\mu_{ijk} t^r)$$

and

$$\lambda_{ijk}(t) = \mu_{ijk} r t^{r-1},$$

respectively, where

$$\mu_{ijk} = \exp(\beta_0 + \beta_1 X_{1ijk} + \dots + \beta_p X_{pijk} + B_j + C_k),$$

and  $X$  are the observed covariates, such as group allocation. In this study, all the covariates  $X$  are coded as 1 or 0, indicating the presence or absence of a certain characteristic or treatment. Typically, a positive regression coefficient  $\beta$  corresponds to a higher risk of the failure being observed among those with the associated characteristic, relative to those without. Alternatively, it is natural to report a more intuitive measure, namely, the relative risks [RR =  $\exp(\beta)$ , RR > 1 indicates a higher risk of failure]. In this study, a positive  $\beta$  or RR > 1 corresponds to a higher chance of arrest of active dentin caries and thus expects a shorter arrest time.

The shape parameter  $r$  characterizes the shape of the distribution ( $r > 1$  for increasing failure rate;  $r < 1$  for decreasing failure rate; and  $r = 1$  for constant failure rate). With the above model, the intra-cluster correlation between the logarithmic arrest times from the same child and from children attending the same kindergarten can be estimated by  $[\sigma_{\text{school}}^2 + \sigma_{\text{child}}^2] / [\sigma_{\text{school}}^2 + \sigma_{\text{child}}^2 + \pi^2/6]$  and  $\sigma_{\text{school}}^2 / [\sigma_{\text{school}}^2 + \sigma_{\text{child}}^2 + \pi^2/6]$ , respectively (Lindeboom and Van Den Berg, 1994).

With the arrest time  $T_{ijk}$  being interval-censored in the interval  $(t_1, t_2)$ , conditioned on the random effects  $B_j$  and  $C_k$ , the contribution to the likelihood can be expressed as

$$P(t_1 < T_{ijk} < t_2 | B_j, C_k) = \exp(-\mu_{ijk} t_1^r) - \exp(-\mu_{ijk} t_2^r).$$

'Unconditioning' the random effects is very often an intractable task in the interval-censored set-up, particularly in multilevel modeling (with more than one random effect). Hence, the Bayesian approach with MCMC algorithms was adopted, and the analysis was carried out with the software WinBUGS, version 1.3, in which Gibbs' sampler was used for the generation of samples (Spiegelhalter *et al.*, 1999). A three-level model was considered, with tooth surfaces as level 1, children as level 2, and kindergartens as level 3. In the estimation of the parameters, the first 5000 simulations were treated as burn-ins and discarded, while the estimation was based on the next 10,000 simulations. Non-informative priors were adopted in this analysis, since we did not want to impose any prior beliefs on the effects of the

treatments. A graphed presentation of the model used in the analysis and the model statements used for the programming are shown in the Appendix for technical reference (readers could skip this without loss of continuity).

**RESULTS**

A total of 375 children, 209 boys (56%) and 166 girls (44%), with a mean age of 4.1 yrs (SD = 0.9) was included in the study. The mean dmfs of the children was 4.7, and the mean number of active-caries surfaces was 4.0 (Table 1).

In the analysis, 1483 surfaces with dentin caries from 367 children were included. Results from 10,000 simulations, generated from the posterior distributions of the parameter estimates (Table 2), concluded that the correlation between the arrest times of children from the same school was negligible [ $\sigma^2_{\text{school}} = 0.025$ ; 95% credible interval = (0.001, 0.151), Table 2]. However, the clustering effect among the arrest times from the same child was very strong [ $\sigma^2_{\text{child}} = 2.394$ ; 95% credible interval = (1.822, 3.066), Table 2], and the estimated intra-cluster correlation coefficient among the arrest times of different caries surfaces from the same child was 0.596. In the following discussions, the effects are considered statistically insignificant if the 95% credible intervals for  $\beta$  include 0 or, equivalently,

the 95% credible interval for RR includes 1, and *vice versa*. Effects of location of residence and gender on the arrest times were statistically insignificant (Note 1 in Table 2). The two agents (SDF and NaF) with caries removal and SDF without caries removal significantly shortened the arrest time of the dentin caries compared with the controls (Note 2 in Table 2). When soft caries was removed prior to the application of the test agents, the arrest times could further be significantly shortened (Note 3 in Table 2). When the two agents were compared, SDF had shorter arrest times than NaF, both with and without prior caries removal (Note 4 in Table 2). As an

**Table 1.** Number of Study Children at Baseline and Their Mean Age, Caries Experience, and Number of Active-caries Tooth Surfaces in Their Upper Primary Anterior Teeth

Treatment Group	No. of Subjects (boy:girl)	No. of Drop-outs	Age (yrs) (SD <sup>a</sup> )	dmfs (SD <sup>a</sup> )	No. of Active-caries Surfaces (SD <sup>a</sup> )
SDF+caries removal	76 (43:33)	15	4.0 (0.9)	4.8 (2.5)	4.1 (2.3)
SDF	77 (41:36)	15	4.3 (0.9)	5.1 (3.3)	4.3 (2.7)
NaF+caries removal	76 (40:36)	14	4.1 (0.9)	4.7 (3.7)	3.9 (2.7)
NaF	73 (44:29)	12	4.1 (0.9)	4.5 (3.3)	3.8 (2.5)
Control	73 (41:32)	11	4.1 (0.9)	4.3 (2.8)	3.7 (2.5)
All groups	375 (209:166)	67	4.1 (0.9)	4.7 (3.1)	4.0 (2.5)
P-values <sup>b</sup>	0.890	0.935	0.208	0.587	0.663

<sup>a</sup> SD = standard deviation.

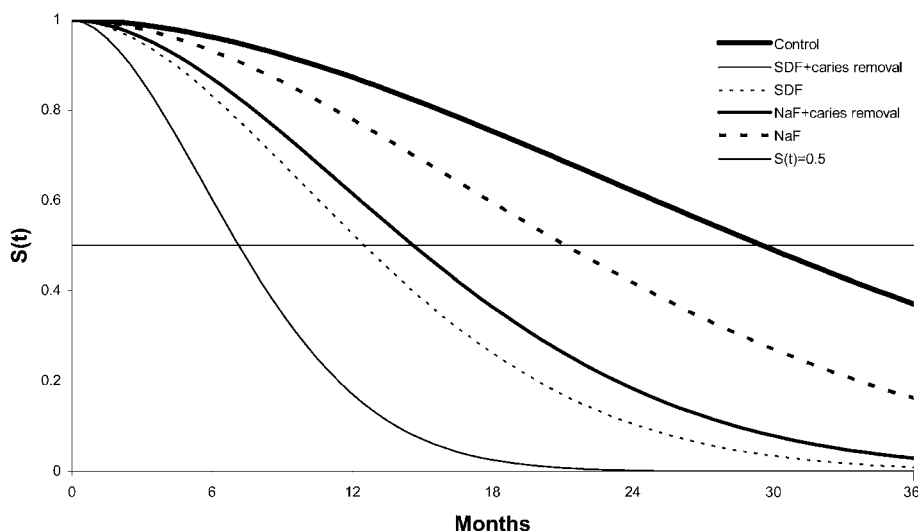
<sup>b</sup> P-values for independent chi-squared tests or independent ANOVA tests, whichever were appropriate.

**Table 2.** Parameter Estimates with WinBUGS—Results from 10,000 Simulations after 5000 Burn-ins

	Estimates <sup>a</sup>			
	Mean (SE <sup>b</sup> )	95% Credible Interval	Relative Risk	95% Credible Interval
Treatment groups				
Control	-6.478 (0.348)	(-7.182, -5.840)		
<i>Contrast relative to control</i>				
<sup>2</sup> SDF+caries removal vs. Control	2.561 (0.318)	( 1.932, 3.202)	12.949	(6.903, 24.582)
<sup>2</sup> SDF vs. Control	1.554 (0.313)	( 0.944, 2.173)	4.730	(2.570, 8.785)
<sup>2</sup> NaF+caries removal vs. Control	1.270 (0.320)	( 0.663, 1.923)	3.561	(1.941, 6.841)
<sup>2</sup> NaF vs. Control	0.606 (0.320)	(-0.009, 1.250)	1.833	(0.991, 3.490)
<i>Contrast for other pairwise comparisons</i>				
<sup>4</sup> SDF+caries removal vs. NaF+caries removal	1.291 (0.294)	( 0.674, 1.842)	3.636	(1.962, 6.309)
<sup>4</sup> SDF vs. NaF	0.948 (0.292)	( 0.388, 1.528)	2.581	(1.474, 4.609)
<sup>3</sup> SDF+caries removal vs. SDF	1.007 (0.292)	( 0.453, 1.578)	2.737	(1.573, 4.845)
<sup>3</sup> NaF+caries removal vs. NaF	0.664 (0.303)	( 0.059, 1.253)	1.943	(1.061, 3.501)
<sup>1</sup> Gender (boys vs. girls)	0.092 (0.183)	(-0.269, 0.439)	1.096	(0.764, 1.551)
<sup>1</sup> Location (urban vs. rural)	0.238 (0.240)	(-0.248, 0.711)	1.269	(0.780, 2.036)
$\sigma^2_{\text{school}}$	0.025 (0.054)	( 0.001, 0.151)		
$\sigma^2_{\text{child}}$	2.394 (0.320)	( 1.822, 3.066)		
r	1.805 (0.068)	( 1.682, 1.955)		

<sup>a</sup> A positive estimate or relative risk > 1 corresponds to a higher chance of arrest of active dentin caries and then a shorter arrest time.

<sup>b</sup> SE = standard errors of the estimates drawn from the posterior distributions.



**Figure.** Survival curves of the arrest times of caries for a girl living in the rural area.

illustration, the survival curves of the arrest times of the five groups for a girl living in the rural area are shown in the Fig. The median times for a caries-active surface to become arrested when SDF was applied, with and without caries removal, were 7.0 and 12.5 mos, respectively. The median arrest times when NaF was applied, with and without caries removal, were 14.5 and 21.0 mos, respectively, while that in the controls was 30 mos (Fig.).

## DISCUSSION

When we compared the results obtained from the analysis performed at the tooth-surface level using a Bayesian approach in analyzing clustered interval-censored data in this paper with the analysis performed at the subject level, reported previously (Lo *et al.*, 2001; Chu *et al.*, 2002), we found, in both analyses, that SDF solution applied annually to active caries lesions was more effective in arresting caries than was NaF applied every 3 mos. However, with the analysis performed at the tooth-surface level, it was also found that having the soft caries removed could shorten the arrest time. Since the correlation among the arrest times of caries lesions in tooth surfaces from the same child was found to be very strong, any analysis ignoring this correlation would yield biased or invalid results. When survival analysis is performed at the tooth-surface level, it is possible to estimate the median time for a caries-active tooth surface to become arrested. This provides more information on the effectiveness of the agents.

Recently, in dental research, several approaches have been proposed for handling clustered survival data with exact failure times (Chuang *et al.*, 2002a,b; Gilthorpe *et al.*, 2002), or for handling clustered interval-censored data (Härkänen *et al.*, 2000, 2002; Hannigan *et al.*, 2001; Bogaerts *et al.*, 2002). Both the 'frequentist' and the Bayesian approaches have been used, different models (frailty *vs.* marginal) have been suggested, and different software packages (SAS, S-plus) have been recommended. To our knowledge, this is the first study in dental research to use the software package WinBUGS for analyzing multilevel (clustered) interval-censored data, and to report the correlations among the failure

times. Multilevel modeling in terms of multivariate frailty can also be applied if the data structure is much more complicated—for instance, multi-stage clustering or nested design in a randomized controlled trial.

The Bayesian approach rests on an essentially subjective interpretation of the observed data in the light of external evidence, judgment, and past experiences (*i.e.*, the informative priors) and then to derive the conclusion in a manner that fits naturally with the clinical decision-making process (Spiegelhalter *et al.*, 1994). It is well-known that turning informally expressed opinion into a mathematical prior distribution is perhaps the most difficult aspect of Bayesian analysis and therefore

should be introduced with caution (Spiegelhalter, 2001). In situations where informative priors are unavailable, or to provide a kind of 'objective' Bayesian analysis free from subjectivity, non-informative priors can be adopted, as in this study. Bayesian inference has several advantages over the 'frequentist' approaches, particularly in the flexibility of model-building for complex data. Moreover, for many models, 'frequentist' inference can be obtained as a special case of Bayesian inference with the use of non-informative priors (Ibrahim *et al.*, 2001). The Bayesian approach enables us to make exact inference based on the posterior distribution for any sample size, whereas the 'frequentist' approach relies heavily on the large sample approximation, and there is always the issue of whether the sample size is large enough for the approximation to be valid (Ibrahim *et al.*, 2001). There is a danger that the additional complexity of Bayesian methods could lead to improper data analysis if it is not used correctly. In addition, software for implementation of Bayesian methods is still limited in user-friendliness (Spiegelhalter *et al.*, 2004).

Bayesian inference Using Gibbs Sampling (BUGS or WinBUGS) is a piece of freely available computer software for the Bayesian analysis of complex statistical models using Markov chain Monte Carlo (MCMC) methods (Spiegelhalter *et al.*, 1999). It is reasonably easy to use and comes with a wide range of examples (Spiegelhalter *et al.*, 1996a,b). However, much technical statistical knowledge is required for it to be used correctly.

With the abovementioned advantages and the availability of the software WinBUGS, analysis of clustered multilevel interval-censored data is made possible and simple. In conclusion, the annual application of silver diamine fluoride to caries lesions, and caries removal before the application, were found to have shortened the arrest time.

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M.C.M. Wong<sup>1\*</sup>, K.F. Lam<sup>2</sup>,  
and E.C.M. Lo<sup>1</sup>

<sup>1</sup>Dental Public Health, Faculty of Dentistry, and  
<sup>2</sup>Department of Statistics and Actuarial Science, Faculty of  
Social Sciences, The University of Hong Kong, 34 Hospital  
Road, Hong Kong SAR, China; \*corresponding author,  
memwong@hkucc.hku.hk

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### APPENDIX

The following program statements were used to perform the survival analysis of clustered interval-censored data (these statements could be used in both WinBUGS and BUGS). (lower[i], upper[i]) was defined as the arrest time of tooth surface i, i = 1483. The interval-censored arrest times (lower[i], upper[i]) were read in the first loop (with N1 = 979 observations), and the right-censored arrest times (lower[i] only) were read in the second loop (with N-N1 = 504 observations). The arrest times t[i] were assumed to follow a Weibull distribution (dweib(r, mu[i])). The effects due to treatment (txgroup[i]), gender (gender[i]), and location of residence (location[i]) were estimated by beta.txgroup[j] (j = 1,2, 5 = M1), beta.gender, and beta.location, respectively. These parameters were assumed to follow normal distributions, with means 0 and variances 1000 (i.e., 0.001 = 1/1000, the non-informative priors). Two random effects, namely, b[child[i]] and c[school[i]], were added in the model to account for the dependence among the arrest times from the same child and between the arrest times of the children from the same school. Both random effects b[j] (j = 1,2, 367 = M2) and c[j] (j = 1,2, ,8 = M3) were assumed to follow normal distributions, with mean 0 and variances  $\sigma^2_{cluster}$  (= 1/tau.child) and  $\sigma^2_{school}$  (= 1/tau.school), respectively. Both tau.child and tau.school were assumed to have non-informative gamma prior distributions. Additional estimates were computed at the end of the program for comparison of differences between the treatment groups. The initial values of different parameters were set as follows: beta.gender = 0, beta.location = 0, beta.txgroup = c(0,0,0,0), r = 1, tau.child = 0.3, and tau.school = 0.3. A graphical presentation of the estimated survival models in the analysis of the arrest times of caries active lesions is shown after the program statements.

```

model
{
  for(i in 1 : N1) {
    t[i] ~ dweib(r, mu[i])(lower[i],upper[i])
    log(mu[i]) <- beta.txgroup[txgroup[i]] + beta.gender*gender[i] +
      beta.location*location[i] + b[child[i]] + c[school[i]]
  }

  for(i in N1+1 : N) {
    t[i] ~ dweib(r, mu[i])(lower[i],)
    log(mu[i]) <- beta.txgroup[txgroup[i]] + beta.gender*gender[i] +
      beta.location*location[i] + b[child[i]] + c[school[i]]
  }

  for(j in 1:M1) {
    beta.txgroup[j] ~ dnorm(0.0, 0.001)
  }
  beta.gender ~ dnorm(0.0, 0.001)
  beta.location ~ dnorm(0.0, 0.001)

  for(j in 1:M2) {
    b[j] ~ dnorm(0.0, tau.child)
  }
  for(j in 1:M3) {
    c[j] ~ dnorm(0.0, tau.school)
  }

  r ~ dgamma(1.0, 0.001)
  tau.child ~ dgamma(0.001, 0.001)
  tau.school ~ dgamma(0.001, 0.001)

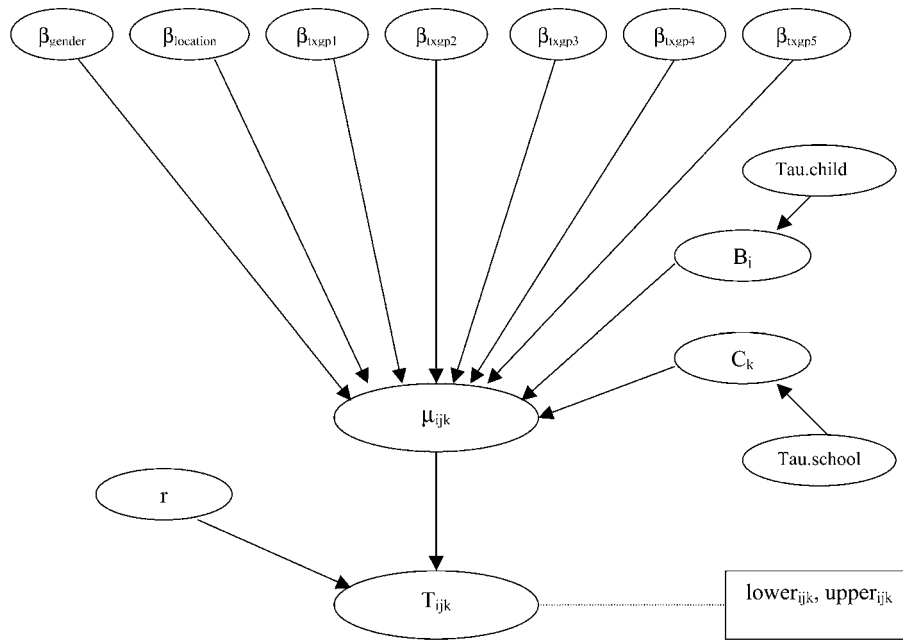
  sigma2.child <- 1/tau.child
  sigma2.school <- 1/tau.school
  alpha <- beta.txgroup[5]
  beta.1 <- beta.txgroup[1] - alpha
  beta.2 <- beta.txgroup[2] - alpha
  beta.3 <- beta.txgroup[3] - alpha
  beta.4 <- beta.txgroup[4] - alpha
  beta.12 <- beta.txgroup[1] - beta.txgroup[2]
  beta.13 <- beta.txgroup[1] - beta.txgroup[3]
  beta.24 <- beta.txgroup[2] - beta.txgroup[4]
  beta.34 <- beta.txgroup[3] - beta.txgroup[4]
}

```

The dataset was arranged in the following format:

list(N1 = 979, N = 1483, M1 = 5, M2 = 367, M3 = 8)

school[]	child[]	txgroup[]	gender[]	location[]	lower[]	upper[]
1	1	1	0	1	0	6
1	2	3	0	1	0	6
1	2	3	0	1	0	6
1	6	1	1	1	0	6
1	8	2	0	1	0	6
.....						
8	359	3	1	0	30	
8	359	3	1	0	30	
8	365	2	0	0	30	
8	367	5	1	0	30	
8	367	5	1	0	30	



Appendix Figure. Graphical presentation of Weibull regression model used in the analysis.