Original Article

Risk of Dengue Incidence in Children and Adolescents in Zulia, Venezuela, using a Negative Binomial Generalized Linear Mixed Model

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Abstract

Introduction: Dengue is the most important arboviral disease. Its incidence has increased 30-fold over the last 50 years, causing global concerns. Studies have showed children to be the most vulnerable.

Methods: Observational study using dengue cases from Zulia state, Venezuela, modelling through a Negative Binomial Generalized Linear Mixed Model (GLMM) accounting for heterogeneity in the variance via a hierarchical Bayesian framework, was done. We assessed risk factors such as age and sex. The Bayesian framework enabled the estimation of Relative Risk (RR) and a Binomial regression was run using the WinBUGS software.

Results: During 2002-2008, there were 49,330 cases of dengue in Zulia state, Venezuela. Most of them (18.71%) in 2007. The model revealed that children aged from 5 to 14 y-old had 1.59-higher risk (95%CI 1.41-1.79) compared with those aged from 0-4 y-old. Those aged 25-44 years old and ≥45, have significantly less RR than the baseline category, RR 0.5228 (95%CI 0.46-0.59) and 0.3069 (95%CI 0.27-0.34).

Conclusions: The findings confirmed that groups most at risk were children aged 5 to 14 years. Modelling and predicting dengue epidemiology are still a need in multiple countries, especially those at risk of newer epidemics, as is the case of Zulia and Venezuela.

Key words: Dengue; Mathematical Models; Epidemiology; Venezuela.

Introduction

Dengue fever is a vector borne disease, in which the virus is transmitted by the bite of a female mosquito belonging to the *Aedes aegypti* species. The first important epidemic of severe dengue in the Americas was reported in Cuba in 1981 and the second affected Venezuela during 1989 and 1990 [1,2]. According to some authors, Venezuela reported the highest number of cases of severe dengue [3]. This fact demonstrates that Venezuela is a country at serious risk regarding the spread of dengue fever. Zulia state is located on the northwestern part of Venezuela, which has been considered by some experts as an endemic region for the past 15 years [4,1] (Figure 1). The aim of this study is to develop a Negative Binomial GLMM via a Hierarchical Bayesian framework for epidemiological data of dengue cases in Zulia state, Venezuela to estimate the Relative Risks (RR) of the disease in the entire Zulia state by comparing exposure groups of gender and age from 2002 to 2008.

The epidemiological data was comprised by hospital admissions of dengue cases provided by the Ministry of Health in Zulia state, Venezuela. Daily reported cases were monthly compiled in the entire state of Zulia and this data was stratified by groups of age and gender. Annual population size was also provided by the Ministry of Health covering from 2002 to 2008. The annual estimation based on the first month for each year was interpolated to fill the monthly gaps for the missing information.

Figure 1. Zulia state and its municipalities, Venezuela.

The main purpose of this study was the comparison between groups. However, when new extra variation occurs at different levels of the analysis, an extension of the Generalized Linear Model (GLM) into a Generalized Linear Mixed Model (GLMM) [5] is suggested. As a result, the new structure of GLMM comprises a fixed term and an extra random effect to account for the variance [6].

In this context the development of a Negative Binomial GLMM for count data on dengue cases in the whole of Zulia was conducted driven by a comprehensive exploratory analysis previously conducted [7-9].

Methods

Zulia state is located on the north west part of Venezuela, between 8.20º to 11.79º North latitude and 70.73º to 73.37º West longitude. It is divided into 21 municipalities, over an area of 50,230 square kilometers surrounding the Lake of Maracaibo, the largest lake in Latin America covering 12,870 square kilometers. According to the National Institute of Statistics, the estimated population in Zulia during 2008 was 3,752,898 habitants. A visual representation of the political map of Zulia with municipalities boundaries is displayed in Figure 1.

Some investigations state that dengue fever expands rapidly in urban areas due to disproportionate increase of human population [8,9]. In this respect, Table 1, shows the population size and cases at municipality level annually aggregated in Zulia state, during 2002-2008.

Significantly, the data was arranged in many different ways throughout the exploratory analysis. At the first instance a study was based on epidemiological records of hospital admissions weekly aggregated from January 2002 to December 2008. The reason of such approach was because the data was initially provided at this scale by the local agency of the Ministry of Health in Venezuela. In addition, annual population size was lineally interpolated to fill weekly and monthly gaps for the missing data.

Table 1. Estimated population and observed cases of dengue fever in Zulia state, Venezuela. Annually aggregated per municipality, 2002-2008.

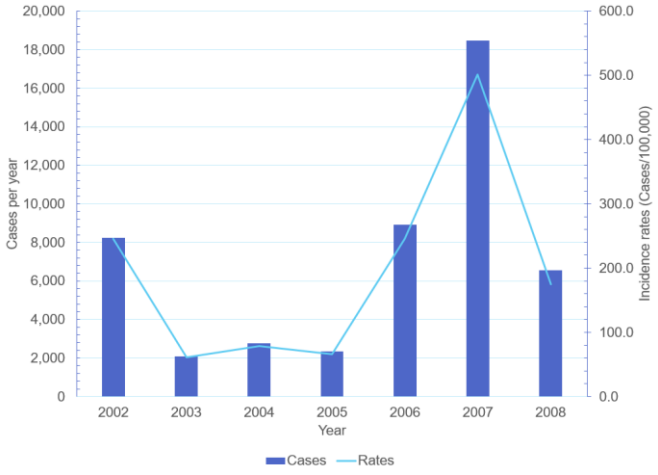
	Cases								Rates (cases/100,000 pop.)							
Municipality	2002	2003	2004	2005	2006	2007	2008	2002-2008	2002	2003	2004	2005	2006	2007	2008	2002-2008
Maracaibo	3,442	574	774	705	3,366	7,006	2,656	18,523	257.4	42.2	56.0	50.2	235.8	483.1	180.4	1,318.5
Cabimas	106	62	160	49	108	2,088	351	2,924	42.8	24.5	62.1	18.6	40.3	764.6	126.2	1,112.6
Lagunillas	324	56	319	162	286	445	88	1,680	169.5	28.5	158.4	78.4	135.0	204.8	39.5	812.5
Colon	332	291	245	313	319	552	434	2,486	273.3	233.7	192.1	239.6	238.4	403.0	309.7	1,901.6
Catatumbo	83	93	34	16	123	197	133	679	235.4	258.7	92.8	42.9	323.7	509.1	337.7	1,819.5
Urdaneta	405	33	82	52	600	143	85	1,400	593.4	47.4	115.6	71.9	814.1	190.5	111.2	1,935.3
San Francisco	824	189	368	379	1,707	2,470	695	6,632	214.4	48.5	93.0	94.4	419.1	598.0	166.0	1,651.6
Mara	430	189	136	144	139	1,055	374	2,467	234.7	99.9	69.7	71.5	66.9	492.7	169.5	1,223.6
Miranda	450	240	77	92	172	635	154	1,820	518.7	272.0	85.9	100.9	185.7	674.9	161.2	1,996.6
Rosario	299	72	23	21	286	319	124	1,144	404.4	96.2	30.4	27.4	368.9	406.9	156.5	1,493.1
Baralt	231	15	14	42	26	214	51	593	281.6	17.9	16.4	48.4	29.4	237.9	55.7	683.3
Sucre	93	28	40	52	61	223	211	708	165.3	48.8	68.4	87.2	100.5	360.5	335.0	1,187.7
Fco. Pulgar	89	47	55	6	14	67	34	312	254.4	129.2	145.5	15.3	34.3	158.1	77.3	792.2
Machiques	286	70	17	17	116	301	350	1,157	252.1	60.3	14.3	14.0	93.5	237.4	270.3	953.0
Simon Bolivar	130	17	96	53	74	145	45	560	325.1	41.7	231.4	125.5	172.1	331.3	101.1	1,325.4
Padilla	96	20	63	75	39	159	64	516	903.5	184.7	571.2	667.7	341.0	1,366.0	540.4	4,593.6
J.E.Lossada	238	41	16	16	647	781	265	2,004	251.6	42.3	16.1	15.8	623.1	735.3	244.0	1,973.7
J.M.Semprum	82	24	79	6	194	150	94	629	284.4	80.5	256.6	18.9	590.6	442.3	268.6	1,974.4
Sta. Rita	126	14	134	99	363	1,070	199	2,005	262.0	28.7	270.9	197.4	714.1	2,077.2	381.4	3,998.5
V.Rodriquez	50	3	8	13	200	183	111	568	95.0	5.6	14.5	23.1	348.3	312.0	185.4	1,010.2
Paez	127	11	11	20	63	260	31	523	198.9	17.0	16.7	30.0	93.4	380.2	44.8	785.6
Total	8,243	2,089	2,751	2,332	8,903	18,463	6,549	49,330	245.8	61.1	78.9	65.7	246.0	500.9	174.5	1,388.5

*Cumulated rate.

As a result, epidemiological data from Zulia was initially aggregated per week covering the period from January 2002 to December 2008. Therefore, the incidence rates were also weekly estimates through the ratio between dengue cases and the corresponding population size.

Figure 2 shows the dengue incidence, cases and rates, in Zulia state from 2002 to 2008. A sharp severity of the disease was observed at the beginning and the end of 2007.

Figure 2. Evolution of cases and incidence rates of dengue in Zulia state, Venezuela, 2002-2008.



Both male and female categories were monthly aggregated during 84 months from 2002 to 2008, and broken down into five groups of age: 0 to 4 years old, 5

to 14 years old, 15 to 24 years old, 25 to 44 years old and 45 or more years old.

Researchers who have focused on risk factors of dengue fever in different parts of the world have found differences regarding the occurrence of the disease within groups of age, gender and ethnicity [10-13].

In the present study, dengue cases were grouped according to age groups and gender within the Zulia state, from 2002 to 2008. Unfortunately, a similar analysis could not be carried out at the municipality level owing to poor collection of dengue records aggregated at age group and sex by health authorities responsible for surveillance.

In this regard the dataset under analysis comprises dengue cases in Zulia state over the 364 weeks covering 2002 until 2008, broken down into five age groups, namely: 0 to 4 years, 5 to 14 years, 15 to 24 years, 25 to 44 years and over 45 years old.

The age group at risk of the disease are children between 5 and 14 years and the second and third most affected group were those in the 15 to 24 years and 0 to 4 years groups respectively. The statement that those in middle childhood are most at risk in Zulia state, confirms similar patterns observed in Thailand and Florida, in which the highest reported cases are within the population under 15 years old [12,13].

On the other hand, the incidence rates per 10,000 inhabitants grouped by gender in Zulia state was displayed in Figure 4. A similar pattern of the incidence rate was seen in both male and female groups. These findings are consistent with studies undertaken in some South American countries14 in which dengue cases amongst male and female groups did not show a significant variation.

The implementation of a Negative Binomial GLMM for count data accounting for heterogeneity on the variance [6,15] was conducted via a Hierarchical Bayesian approach by including a random term into the hierarchy [15]. The computational software for the Bayesian approach was implemented via the free package WinBUGS, specialized on Bayesian inference [16,17]. The application of a Hierarchical Bayesian approach provided the benefit of a full probability distribution for the parameters of interest by including the observed data as a likelihood function and prior distributions for unknown quantities.

By using a hierarchical structure, this approach easily handled the overdispersion [15, 18-22]. However, the Bayesian framework implemented in this study was based on non-informative or vague prior information in which the posterior distribution was expected to be dominated by the likelihood or observed data [23]. Hence, it was assumed two-stages levels within the hierarchy in the Bayesian Hierarchical Negative Binomial structure. In this study, the year 2002, age group between 0 to 5 and female category were treated as baseline references.

The extra Poisson variation in this analysis might be caused by spatial dependence amongst municipality units [24,25] or because of a temporal dependence [26] of the records. However, this statement cannot be justified due to the lack of available data at municipality level. As a result, the Bayesian framework was conducted by adapting a Negative Binomial formulation via a Poisson-Gamma distribution structure [27,28]. The specification was assumed to be a product of two parameters. Hence the parameterization turns out (Y_i) the reported cases of dengue fever during month i, with the mean μ_i and the dispersion parameter τ_i. The WinBUGS code derived from this study can be found in the Supplementary Material, and the specification of the model is defined as follows:

Likelihood

$$Y_i \sim Poisson(\tau_i \mu_i)$$

$$\log(\mu_i) = \log(pop_i) + \beta_0 + \beta_1 year + \beta_2 agegroup + eps_i$$

where:

$year \rightarrow 2002, 2003, 2004, 2005, 2006, 2007, 2008$

$agegroup \rightarrow 0\ to\ 4; 5\ to\ 14; 15\ to\ 25; 25\ to\ 44;$ 45 or more

Prior and hyper priors

The vague normal priors for the β's parameters were defined as:

$$\beta \sim Normal(0, 1.0 \times 10^{-6})$$

and the dispersion parameter defined as:

$$\tau_i \sim \Gamma(\alpha, \alpha)$$

$$\alpha = \exp(\log \alpha)$$

$$\log \alpha \sim Normal(0, 1.0 \times 10^{-6})$$

Results

During 2002-2008, there were 49,330 cases of dengue in Zulia state, Venezuela. Most of cases (18.71%) occurred in 2007 (18,463) (Table 1) (Figure 2) with a median of 6,549 cases per year (IQR 2,542-8,573). After running a Negative Binomial Hierarchical Bayesian

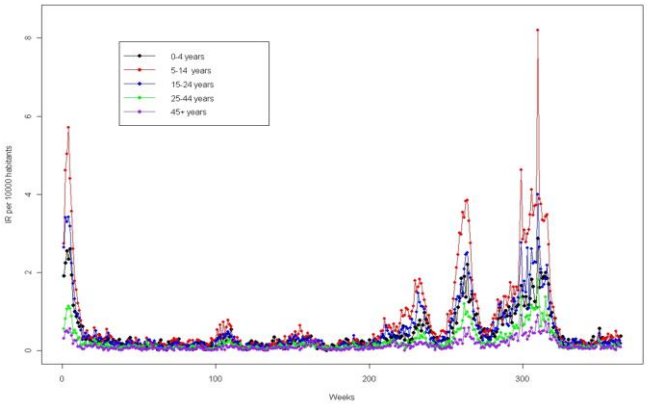
regression using WinBUGS with 100,000 iterations as a burn-in period, the point estimations are summarized on Table 2. The estimates based on the posterior means are listed on variables from b[1] to b[10]. The parameters coded between b[1] to b[6] represent the years: 2003, 2004, 2005, 2006, 2007 and 2008. In which year 2002 was considered as the baseline group. The variables from b[7] to b[10] represent the groups of age covering: 5 to 14, 15 to 24, 25 to 44 and age group of 45 or more, respectively (Figure 3).

Table 2. Posterior summary of the Bayesian NB approach using WinBUGS for RR of Dengue in Zulia, Venezuela, 2003-2008.

Estimates	Mean	RR	95% CI
Intercept	-5.92	-	-
beta[1]=year2003	-1.31	0.26	[0.23; 0.31]
beta[2]=year2004	-1.041	0.35	[0.30; 0.40]
beta[3]=year2005	-1.13	0.32	[0.27; 0.37]
beta[4]=year2006	0.0018	1.001	[0.87; 1.15]
beta[5]=year2007	0.7911	2.2058	[1.91; 2.53]
beta[6]=year2008	-0.2144	0.8070	[0.70; 0.92]
beta[7]=age group 5 to 14	0.4651	1.5921	[1.41; 1.79]
beta[8]=age group 15 to 24	0.0729	1.0756	[0.95; 1.21]
beta[9]=age group 25 to 44	-0.6485	0.5228	[0.46; 0.59]
beta[10]=age group 45 or more	-1.181	0.3069	[0.27; 0.34]

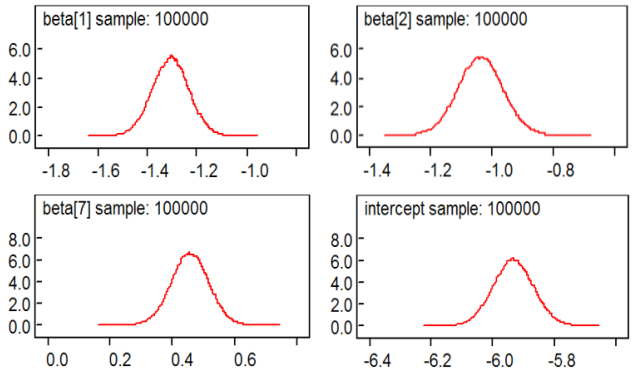
The findings revealed that children aged from 5 to 14 years old had 1.59-fold increased Relative Risk (RR) (95% CI 1.41-1.79) (Table 2) when compared to the baseline category aged from 0 to 4 years old (Figure 3). However, those aged 25 to 44 years old and 45 or more, have significantly less RR than the baseline category, RR 0.52 (95% CI 0.46-0.59) and 0.31 (95% CI 0.27-0.34) (Table 2). In addition, the year 2007 showed that Relative Risk increased by 2.20 times when compared to the baseline year 2002 (Figure 3).

Figure 3. Observed incidence rate of dengue weekly aggregated by age group in Zulia from 2002 to 2008.



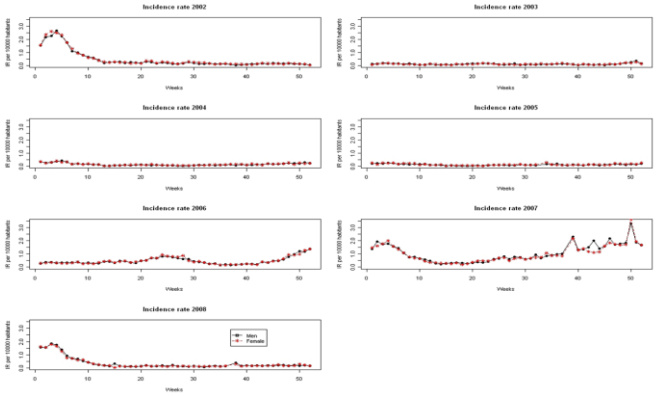
However, to validate those outcomes we graphically visualized the dynamics on the posterior distributions of the parameters under analysis. For instance, the posterior densities for the parameters: year 2003 defined as beta[1], year 2004 defined as beta[2] and group of age from 5 to 14 years old denoted as beta[7] showed clearly smooth and unimodal shapes (Figure 4).

Figure 4. WinBUGS output showing the posterior kernel densities of b[1]=year 2003; b[2]=year 2004 and b[7]=group of age from 5 to 14 years old.



It was also revealed that the remaining parameters had a similar pattern, including gender, where no significant differences were observed in the model across the years (Figure 5).

Figure 5. Observed incidence rates of dengue weekly aggregated by gender in the whole of Zulia from 2002 to 2008.



Furthermore, the trace patterns of all the estimates parameters were plotted against the number of iterations. It was seen quite dense chains, meaning a good mixing of the parameters. Moreover, the autocorrelation functions of every parameter indicated that the posterior distributions mixed slowly, which is a good pattern in terms of correlated values. Finally, the visual diagnostic revealed that the bivariate posterior scatter plots around

the mean was randomly distributed for all possible combination of parameters meaning that convergences were reached.

Discussion

Beyond emerging arboviral diseases, such as chikungunya and Zika [29], dengue still continues to be most important viral vector-borne disease globally, in terms of morbidity, mortality and disability. Then efforts to characterize, modelling and predict dengue are of utmost importance [24].

This study provided a better understanding of risk factors of age groups and gender associated with dengue transmission in Zulia state, Venezuela using epidemiological data from 2002 to 2008. The implementation of a Bayesian framework was conducted by adapting a Negative Binomial formulation via a Poisson-Gamma distribution structure [27,28]. However a limitation owing to the lack on epidemiological data stratified by age groups and gender at municipality level, restricted the construction of a spatio-temporal approach using those exposure factors. The findings revealed that children aged from 5 to 14 years old had a 1.59-fold increased Relative Risk (RR) when compared to the baseline category aged from 0 to 4 years. The severity of the disease was also observed within the stratum of the population from 15 to 24 years old. Those outcomes confirmed that groups at risk in Zulia state, Venezuela were children and young population. This statement was validated by similar studies conducted in different parts of the world in which the highest reported cases were observed amongst the youngest [30,13,8]. Given the opportunity of implementing strategies for the control and prevention of dengue fever in Zulia state, an effective initiative is needed involving scientists, health agencies and the local community aimed to coordinating an integrated vector programme against dengue transmission. In this context, the WHO has proposed disseminating scientific information about dengue transmission in order to educate people about the techniques that could help to protect or prevent dengue infection [31]. The WHO also recommends effective interventions to reorganize the public health centers and provide timely access of resources to affected population during outbreaks of dengue fever [31].

The findings of this study also showed that the year 2007 had the largest RR increased by 2.20 times when compared to the baseline year 2002. Detailed examination of the outcomes also showed that the previous year (2006) had a high Relative Risk factor, but it was low in the preceding years, 2003, 2004 and 2005. This pattern leads us to investigate the reasons for the evolution of dengue fever transmission over time. It has been argued that epidemics of dengue fever are followed by endemic cycles periodically observed every 3 to 5 years [32]. Although the evolution of dengue fever in Zulia state from 2002 to 2008 supported this assertion, more studies are needed to properly understand spatial and temporal variations of dengue fever in the state.

In addition, although those findings were based on a NB Hierarchical Bayesian model using non-informative or vague prior information in which the posterior distribution was dominated by the likelihood of observed date [23]. More studies are needed to explore potential alternatives of prior distributions in future studies [33].

On the other hand, the major advantage of using a Bayesian framework is the relatively straightforward specification of the models provided that care is taken in the calculation of priors and posteriors [34]. In addition it is because of the growing development of computational software via the Markov Chain Monte Carlo (MCMC) algorithms, which facilitates modelling implementation [9, 18, 21, 23, 35-37]. Finally uncertainties over epidemiological data on the type of serotypes circulating during the period of time under analysis, was a limitation within the surveillance information provided in this study. Experts postulate a temporal cycle of serotypes circulating in geographical contexts [32] which could have a direct effect across the various strata of the population categorized by age. Consequently, a deeper analysis is needed to explore some other factors [38-42] associated with the spread of the disease in Zulia state, looking for spatial and temporal effects on dengue transmission. In this respect, a generalized additive mixed model was previously implemented using dengue cases of Zulia state, which would provide additional highlighting points [43]. In addition, future evaluations need to be done towards the construction of an Early Warning System [39] in Zulia state, Venezuela. These tools for detailed analyses are highly relevant in public health.

Given the social and ecoepidemiological conditions of Zulia, as well most of the states of Venezuela are prone across the whole territory for arboviral diseases. Then, the applicability of this study would be directly oriented also to other emerging arboviral diseases that occurred in Venezuela in after 2014, such as chikungunya and Zika [40], where there is a lack of studies assessing its incidence, spatial epidemiology and modelling among others [41]. Operative research for that, including evidence-based policies are urgently required in the country. Venezuela requires immediate intersectoral

action and investment to halt this unnecessary and increasing burden for dengue, but also on chikungunya and Zika [42]. Other emerging and reemerging diseases, such as Mayaro, Oropouche and West Nile Virus are circulating in the Americas and be responsible for new epidemics in Venezuela [43].

Current migration scenario of Venezuela implies that these arboviral diseases occurring in Venezuela have consequences for the region. In the country conditions of forced migration, people are moving forward to Colombia, Brazil, Peru, United States of America, and other countries in the region and abroad [42].

Finally, Venezuela, once considered the richest and most developed of the region, today represents an epicenter of the resurgence of multiple vector-borne and other infectious diseases with numerous ongoing, co-occurring epidemics [39]. Most of these epidemics directly and/or indirectly intersect on their social, biological and epidemiological determinants sharing as common ground a country whipped by an unprecedented humanitarian and political crisis that has led to a massive collapse of its healthcare system along with a large-scale impoverishment of its population among other social forces which have contributed to their origin and persistence [42]. These findings have also implications in other arboviral diseases that have affected Zulia and Venezuela, but have not yet studied in detail, such is the case of chikungunya and Zika [45,46].

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Author Contributions

MC, GT, VSN, FCL and AJRM, participated in design, collecting and analysing data. MC and AJRM wrote the first and second draft. PEA and LEAA contributed in the review of results and critical improvements of the manuscripts. All authors read subsequent versions of the manuscripts. All approved the submitted version.

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Supplemental Material
The following is the code of Bayesian Hierarchical Negative Binomial Model in WinBUGS:

```
##############################################
##       Incidence rate per year in each agegroup          ##
##############################################
model
{
for (I in 1:84) {                # amount of data
count [i]~dpois(mustar[i]) # response variable
mustar[i]<-rho[i]*mu[i]    # product log link
log (mu[i]<-log(popsize[i])+intercept+
yeargrp2[i]*beta[1]+
yeargrp3[i]*beta[2]+
yeargrp4[i]*beta[3]+
yeargrp5[i]*beta[4]+
yeargrp6[i]*beta[5]+
yeargrp7[i]*beta[6]+
yeargrp2[i]*beta[7]+
yeargrp3[i]*beta[8]+
yeargrp4[i]*beta[9]+
yeargrp5[i]*beta[10]+

rho[i]~dgamma(alpha,alpha)  #overdispersion
}
# Prior distributions
intercept~dnorm(0,1.0E-6)     #Flat priors
beta[1]~dnorm(0,1.0E-6)       #Vague normal priors
beta[2]~dnorm(0,1.0E-6)       #Vague normal priors
beta[3]~dnorm(0,1.0E-6)       #Vague normal priors
beta[4]~dnorm(0,1.0E-6)       #Vague normal priors
beta[5]~dnorm(0,1.0E-6)       #Vague normal priors
beta[6]~dnorm(0,1.0E-6)       #Vague normal priors
beta[7]~dnorm(0,1.0E-6)       #Vague normal priors
beta[8]~dnorm(0,1.0E-6)       #Vague normal priors
beta[9]~dnorm(0,1.0E-6)       #Vague normal priors
beta[10]~dnorm(0,1.0E-6)      #Vague normal priors
alpha<-exp(logalpha)
logalpha~dnorm(0,1.0E-6)
}
```