# Association of past dengue fever epidemics with the risk of Zika microcephaly at population level in Brazil

Supplementary material

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In this supplementary material, we provide the reproducible code to the manuscript, exploratory analysis and outputs.

## Required packages

```
library(tidyverse)
library(lubridate)
library(INLA)
```

## The data for modelling

```
dengue.df <- read_csv(
  file = "https://zenodo.org/record/3489428/files/dengueBR2001-2014.csv"
  )

micro.df <- read_csv(
  file = "https://zenodo.org/record/3489428/files/microBR2014-2016.csv"
  )
```

The file dengueBR2001-2014.csv contains the notified dengue cases by microregion per year. The included variables (and corresponding name) are:

- Microregion code (microreg);
- Year (Ano);
- Population (Pop);
- Number of notified dengue cases (counts);
- Dengue annual incidence per 100k inhab (DengueTx);

The file microBR2014-2016.csv contains the notified CZS cases in tree-year period from January 2014 to December 2016. The included variables (and corresponding name) are:

- Microregion code (microcod2);
- Number of notified CZS cases (Micro);
- Total of live-births (Nasc);

Now we have to define a "big" dengue epidemic for a given year and microregion, this is done by defining a threshold for the annual dengue incidence. For instance, lets assume that this threshold is 400 cases per 100,000 inhabitants. Hence that combined data frame is built by the following R code:

```
# Big dengue epidemic threshold
BIGEPI <- 400 # 100, 200, 300, 400, 500, 600

dengue.df2 <- dengue.df %>%
  # Creating auxiliary variables
  mutate(EpiHigh = ifelse(DengueTx > BIGEPI,1,0),
         Aux = EpiHigh * Ano) %>%
  # Grouping by microregion
  group_by(microreg) %>%
  summarise(
    # Counting the number of big dengue epidemics
    Xr = sum(EpiHigh, na.rm = T),
    # Defining when the last epidemic occur
    LastEpi = max(Aux, na.rm = T)) %>%
  # If there is no big epidemic we set it as 2000
  mutate(
    LastEpi = ifelse(LastEpi == 0, 2000, LastEpi),
    microcod2 = microreg,
    # Time since the last big dengue epidemic
    Zr = 2015 - LastEpi )

# Joining dengue and CZS dataframes
dengueCZS <- micro.df %>%
  left_join(dengue.df2, by = "microcod2")
```

## Model formulation

Let $Y_r$ be the number of notified CZS of microregion $r$ from 2015 and 2016, $N_r$ be the total of live-births in the same period, $X_r$ be the number of "big" dengue epidemics since 2000, and $Z_r$ be the time in years since the last "big" dengue epidemic.

The proposed model is the zero-inflated Poisson model defined as

$$Y_r \sim ZIP(\lambda_r, \pi),$$

where $\pi$ is a hyper-parameter defined as the probability of zero coming from a degenerated distribution, hence $1 - p$ is the probability of zero coming form a Poisson. The parameter $\lambda_r$

is defined as

$$\log(\lambda_r) = \log(N_r) + \alpha + \beta X_r + \gamma(Z_r) + \delta_r.$$

The coeffients $\alpha$ and $\beta$ are fixed effects, $\gamma(Z_r)$ is time-varying second-order random walk to emulate a spline-like function of $Z_r$, i.e. $\gamma(z) - 2\gamma(z-1) + \gamma(z-2) \sim N(0, \tau_\gamma)$, and $\delta_r$ is a microregion Gaussian random effect, i.e. $\delta_r \sim N(0, \tau_\delta)$.

Vague priors were defined for all hyper-parameters.

```
model.equation <- Micro ~ 1 + Xr +
  # Microregion effect
  f(microcod2, model = "iid") +
  # Time since last epidemic effect
  f(Zr, model = "rw2")

likelihood.family <- "zeroinflated.poisson.1"
# Other tested likelihoods
# "poisson", "nbinomial", "zeroinflated.nbinomial.1"

output <- inla(formula = model.equation,
               data = dengueCZS,
               family = likelihood.family,
               E = Nasc / 10000,
               control.compute = list(waic=TRUE) )
```

## Results

The results bellow are for the zero inflated Poisson likelihood and the threshold for big dengue epidemic set as 400 dengue cases per 100 thousand inhabitans.

### Fixed effects ($\alpha$ and $\beta$)

```
output$summary.fixed[,c(1,3,5)]
```

```
##                    mean 0.025quant 0.975quant
## (Intercept) 2.15297538 1.91727558  2.3845072
## Xr          0.07423508 0.01912741  0.1296944
```

### Hyperparameters ($\pi$, $\tau_\gamma$, $\tau_\delta$)

```
output$summary.hyperpar[,c(1,3,5)]
```

```
##                                                          mean
```

```
## zero-probability parameter for zero-inflated poisson_1  0.00581059
## Precision for microcod2                                  1.28351014
## Precision for Zr                                        57.37709006
##                                                           0.025quant
## zero-probability parameter for zero-inflated poisson_1 0.0007110325
## Precision for microcod2                                  1.0142237361
## Precision for Zr                                         9.5138896164
##                                                          0.975quant
## zero-probability parameter for zero-inflated poisson_1   0.019730
## Precision for microcod2                                   1.578808
## Precision for Zr                                        211.938835
```

### Random effect $\gamma(Z_r)$

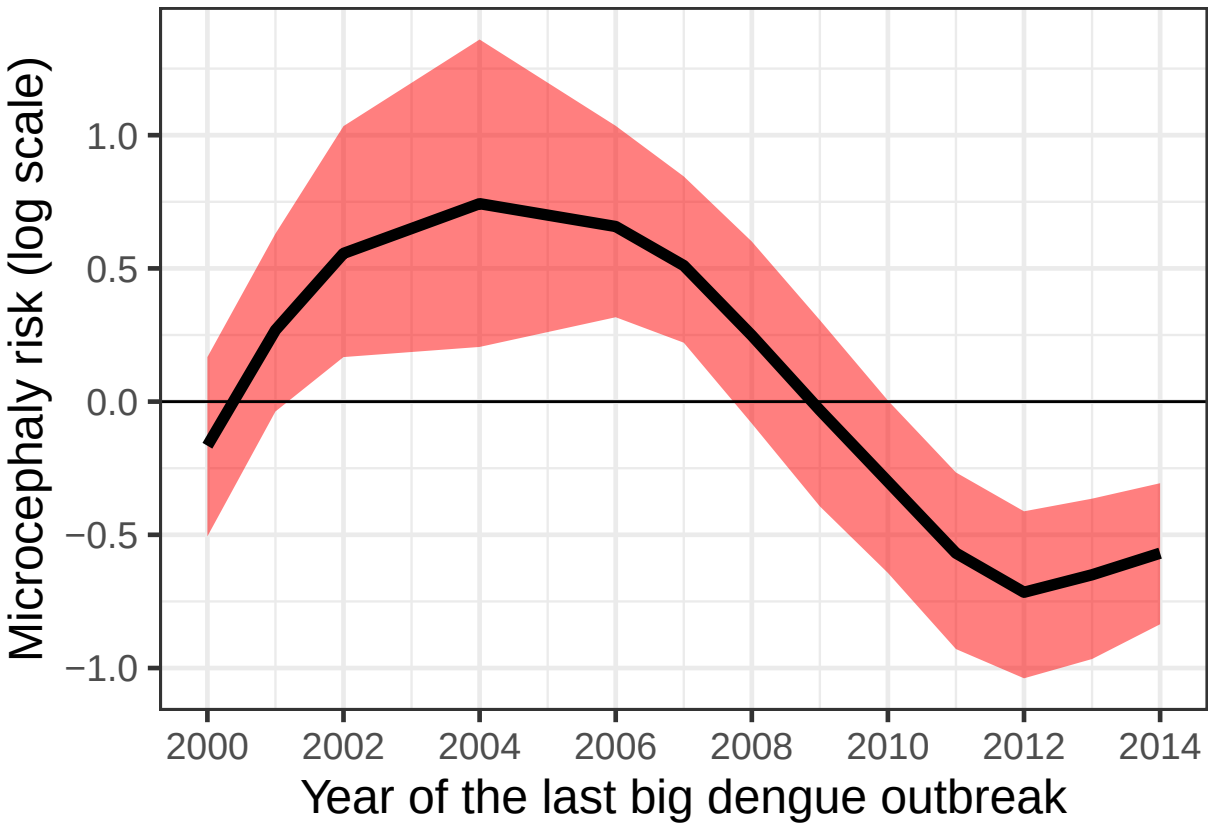
Effect of time since the last big dengue epidemic.

```
aux.plot <- output$summary.random$Zr

p <- ggplot(aux.plot, aes(x = ID, y = `0.5quant`,
                          ymax = `0.975quant`,
                          ymin = `0.025quant`)) +
  #geom_ribbon( fill = "gray") +
  geom_ribbon( alpha = .5, fill = "red") +
  geom_line(lwd = 2) +
  geom_hline(yintercept = 0) +
  theme_bw(base_size = 18) +
    xlab("Number of years since the last dengue epidemic") +
#  xlab("Number of years since the last largest dengue epidemic") +
  ylab("Microcephaly risk (log scale)") +
  scale_x_continuous(breaks = seq(1,15, by=2), trans = "reverse" )
```

Effect of time since the last big dengue epidemic.

```
ggplot(aux.plot, aes(x = ID, y = `0.5quant`,
                          ymax = `0.975quant`,
                          ymin = `0.025quant`)) +
  #geom_ribbon( fill = "gray") +
  geom_ribbon( alpha = .5, fill = "red") +
  geom_line(lwd = 2) +
  geom_hline(yintercept = 0) +
  theme_bw(base_size = 18) +
  xlab("Year of the last big dengue outbreak") +
  ylab("Microcephaly risk (log scale)") +
  scale_x_continuous(breaks = seq(1,15, by=2), labels = seq(2014,2000, by=-2), trans =
```



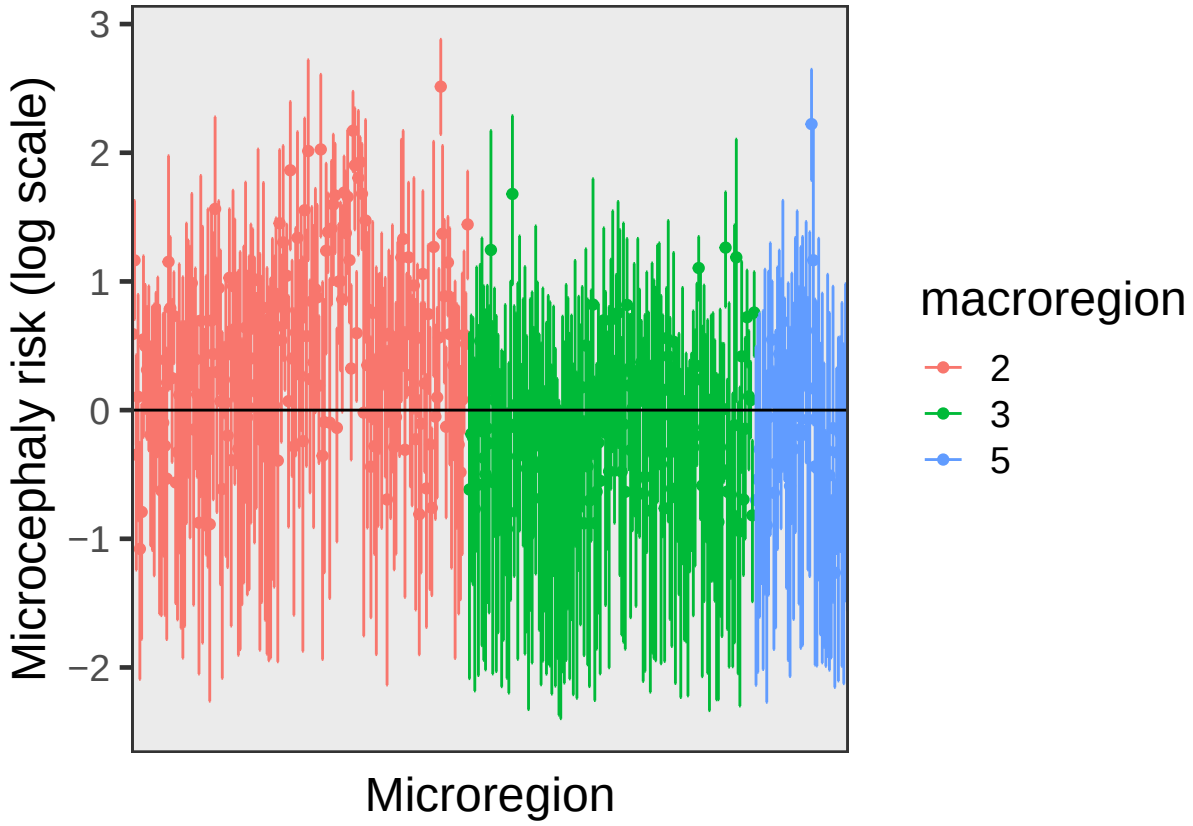

**Random effect** $\delta_r$

Microregion random effect. The microregion region code is the official code of the Brazilian Institute of Statistics and Geography (IBGE), so the random effects could be spatially represented in a map. In the plot bellow the data order is arbitrary however the colors represent different macroregions, 2 for NE region, 3 for SE, and 5 for CW.

```
aux2.plot <- output$summary.random$microcod2[,c(1,5,4,6)]
aux2.plot$macroregion <- substr(aux2.plot$ID, start = 1, stop = 1)

ggplot(aux2.plot,
             aes(x = as.character(ID),
                 y = `0.5quant`,
                 ymax = `0.975quant`,
                 ymin = `0.025quant`,
                 color = macroregion)) +
  geom_point() + geom_errorbar() +
  geom_hline(yintercept = 0) +
  theme_bw(base_size = 18) +
  ylab("Microcephaly risk (log scale)") +
  xlab("Microregion") +
  theme(axis.text.x=element_blank(),
```

```
        axis.ticks.x=element_blank() )
```




## WAIC table of all tested models

The table below presents the WAIC for all tested models by varying the likelihood (Poisson, Negative binomial, Zero-inflated Poisson, and Zero-inflated negative binomial) and the epidemic threshold for defining a big dengue epidemic, values varying from 100 to 600. You can notice that the ZIP model with a threshold of 400 cases per 100 thousand inhabitants is the best one according to this criterion, the smaller the better.

| Likelihood | 100 | 200 | 300 | 400 | 500 | 600 |
|---|---|---|---|---|---|---|
| Pois | 1712.22 | 1713.75 | 1710.00 | 1705.93 | 1706.86 | 1710.32 |
| Nbin | 2063.60 | 2076.43 | 2066.50 | 1766.01 | 2067.50 | 2062.14 |
| ZIP | 1710.27 | 1713.22 | 1708.27 | 1704.39 | 1708.24 | 21232.14 |
| ZINB | 2065.74 | 2079.14 | 2070.58 | 1783.26 | 1797.69 | 2009.46 |

Table 1: Watanabe-Akaike information criterion for different models varying the likelihood (rows) and the big dengue epidemic threshold (columns).

You may also notice a very large value for WAIC for the ZIP model with a threshold of 600, this occur because the model didn't fit properly due to numerical instability problems.