Multilevel models in epidemiology

An application to chikungunya and Zika epidemics

Advanced statistical methods for physicists

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Themes

Provide a real-world example of model development in relation to a scientific question:

- Mechanistic model (data-generating processes)
- Multilevel structure in relation to data structure
- Partial pooling of information

The global invasion of *Aedes* mosquitoes

Aedes mosquitoes (i)

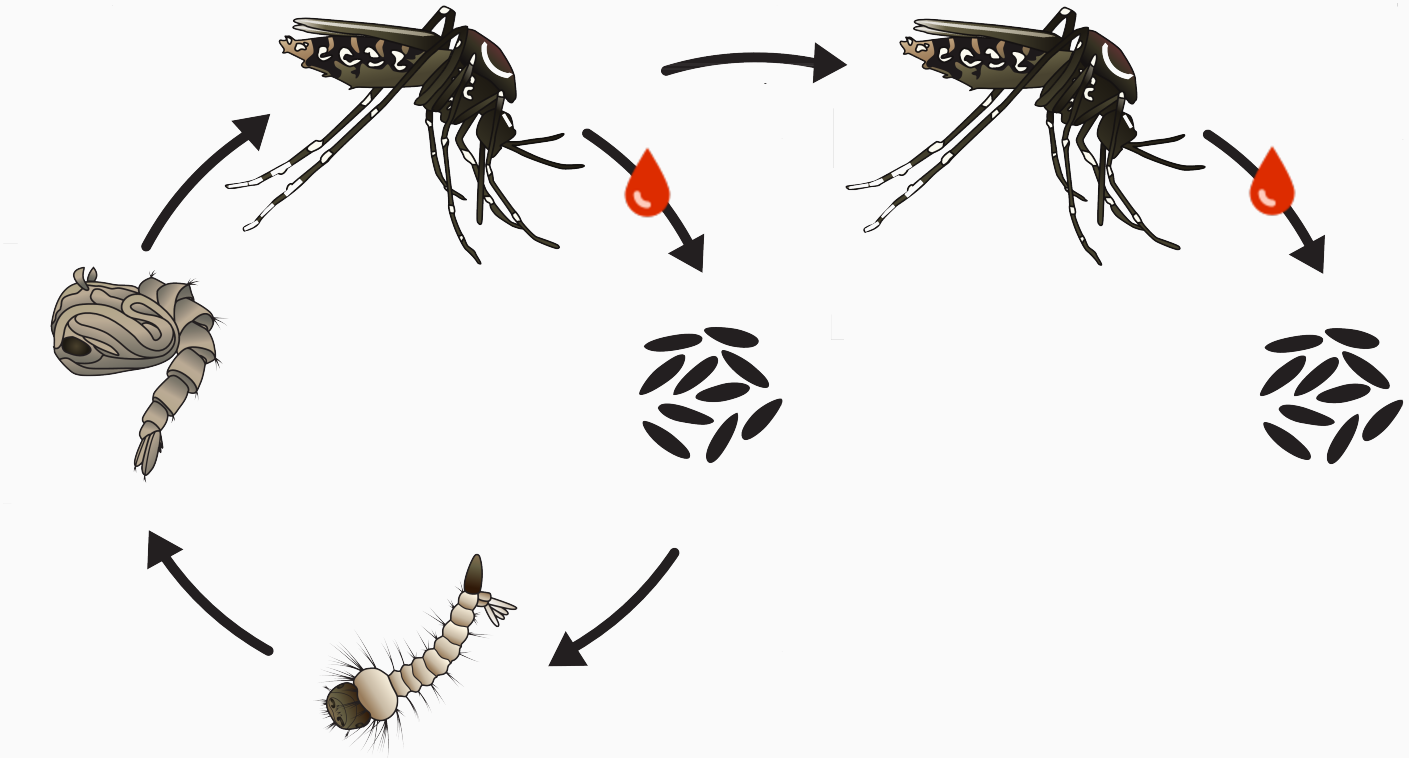


Figure 1: Life cycle of *Aedes* mosquitoes.

- Blood meal necessary to egg maturation
- Biting behaviour: gonotrophic cycle
- Transmission through saliva: specific vectorial competence

Aedes mosquitoes (ii)

Two species are important to human health:

- *Aedes aegypti* (tropical and subtropical areas)
- *Aedes albopictus* (subtropical et temperate areas)

Figure 2: Female adult specimens of *Aedes aegypti* (left) and *Aedes albopictus* (right).

The domestication of *Aedes aegypti*

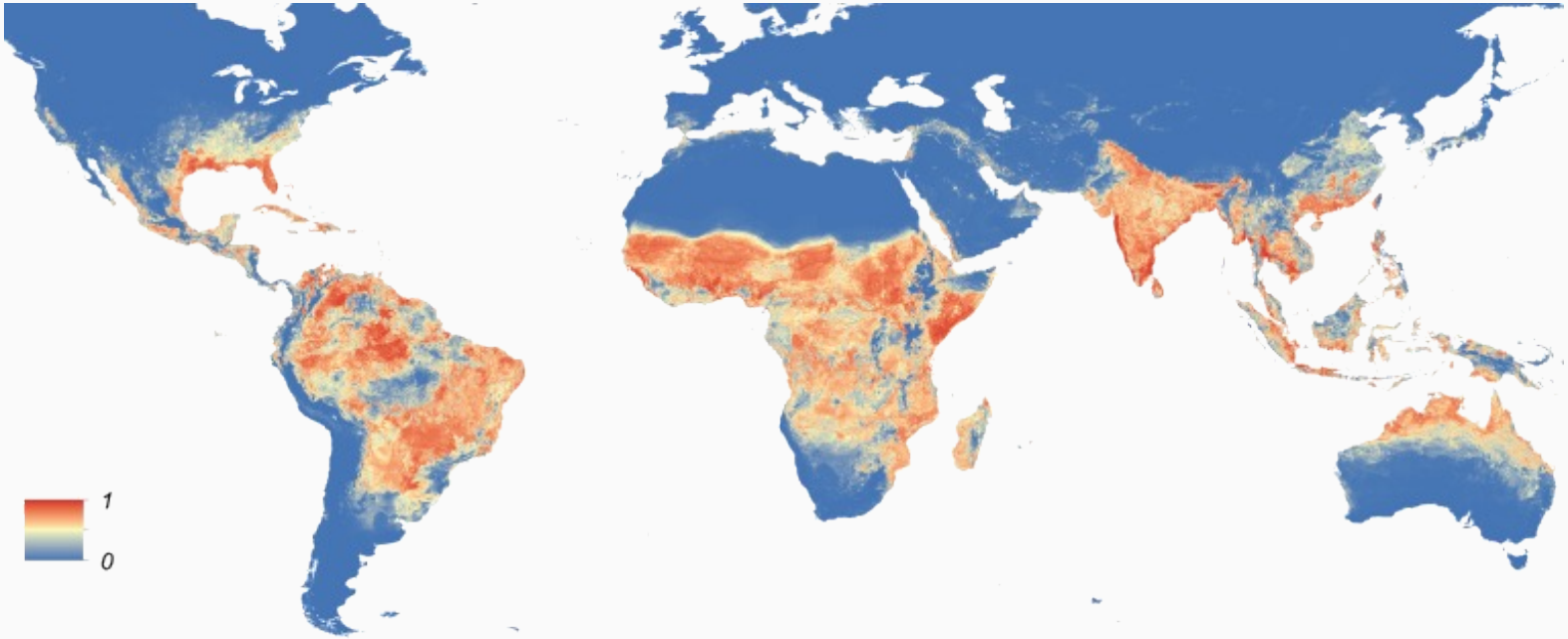


Figure 3: World distribution of *Aedes aegypti* [1].

- Originally from Africa, extension from the 15th century
- Urban and domestic species: adapted to human settlements[2]

[1] Kraemer et al., *eLife* (2015) ; [2] Powell et Tabachnick, *Memorias do Instituto Oswaldo Cruz* (2013)

The invasion of *Aedes albopictus*

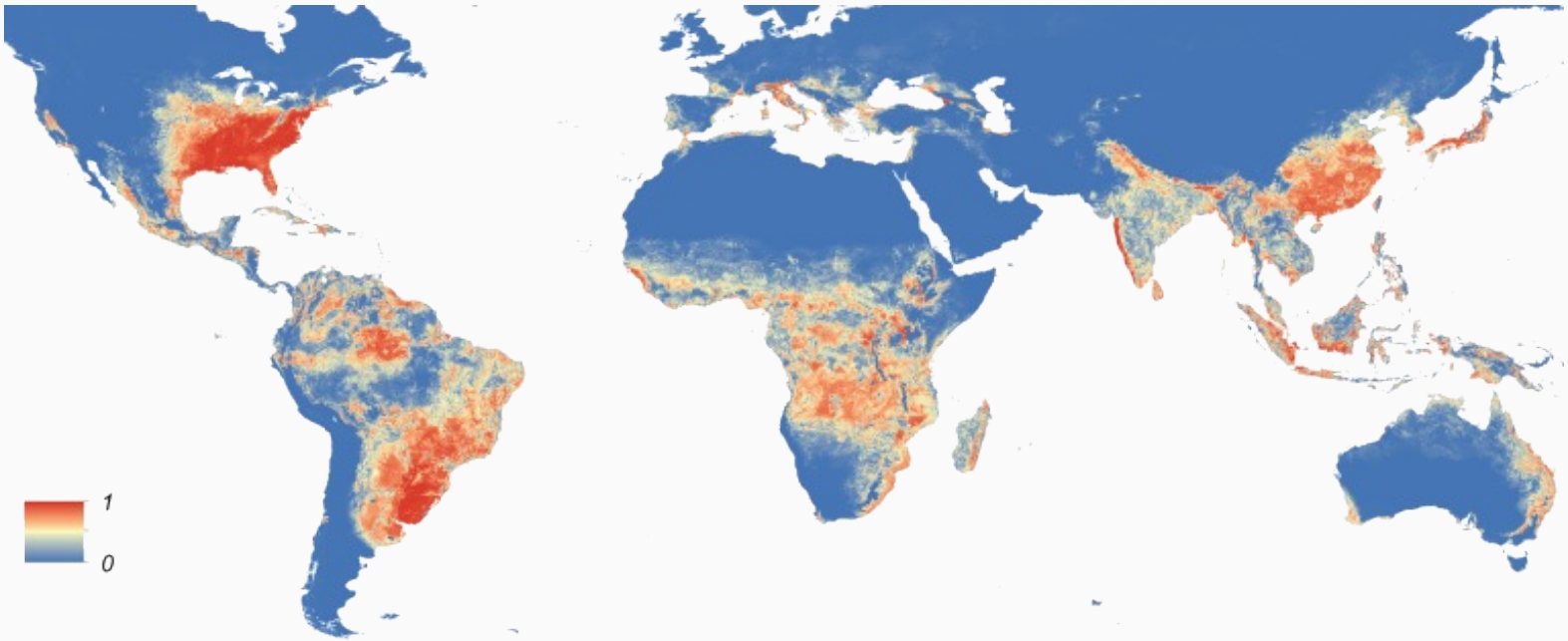
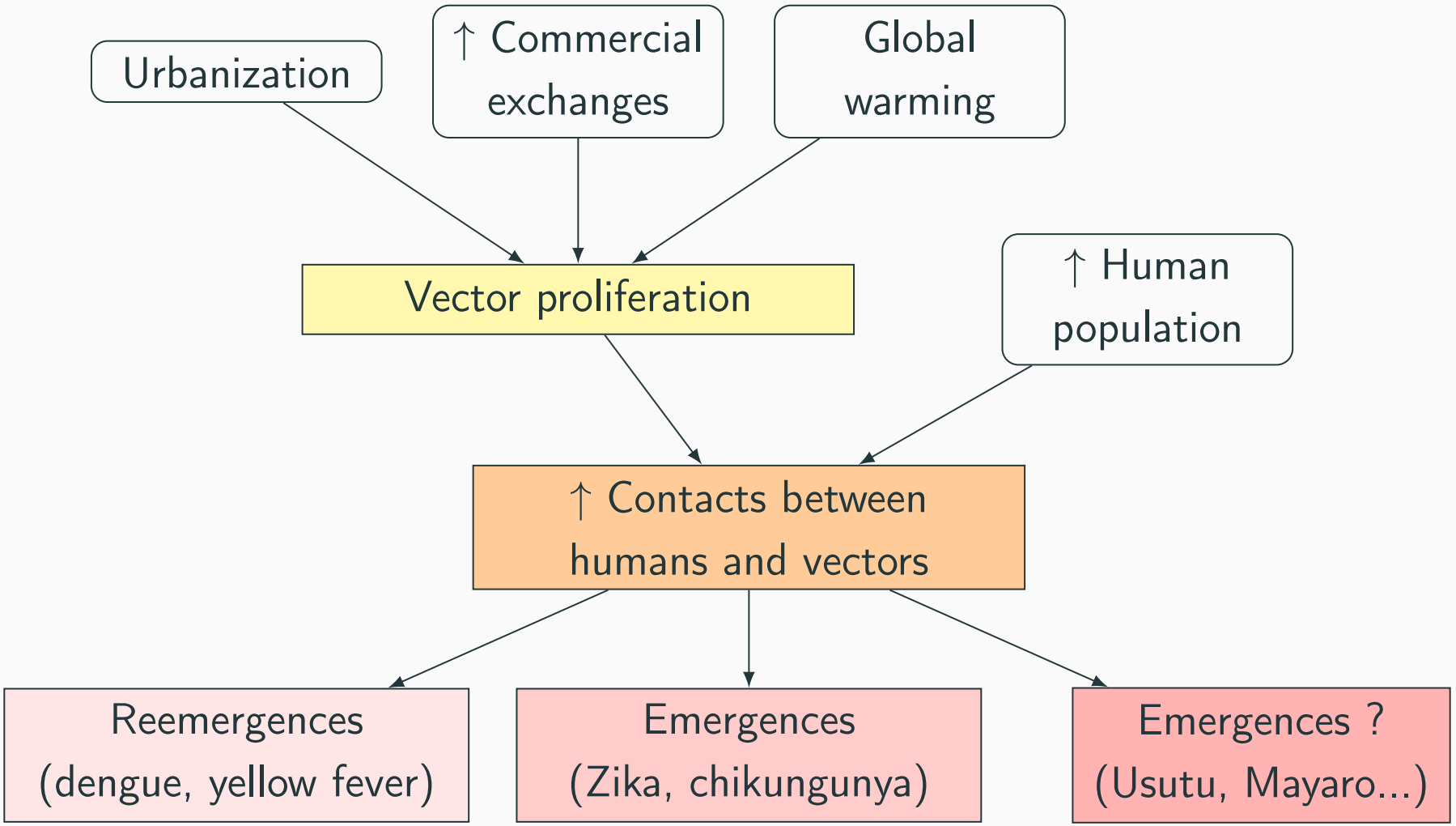


Figure 4: World distribution of *Aedes albopictus* [1].

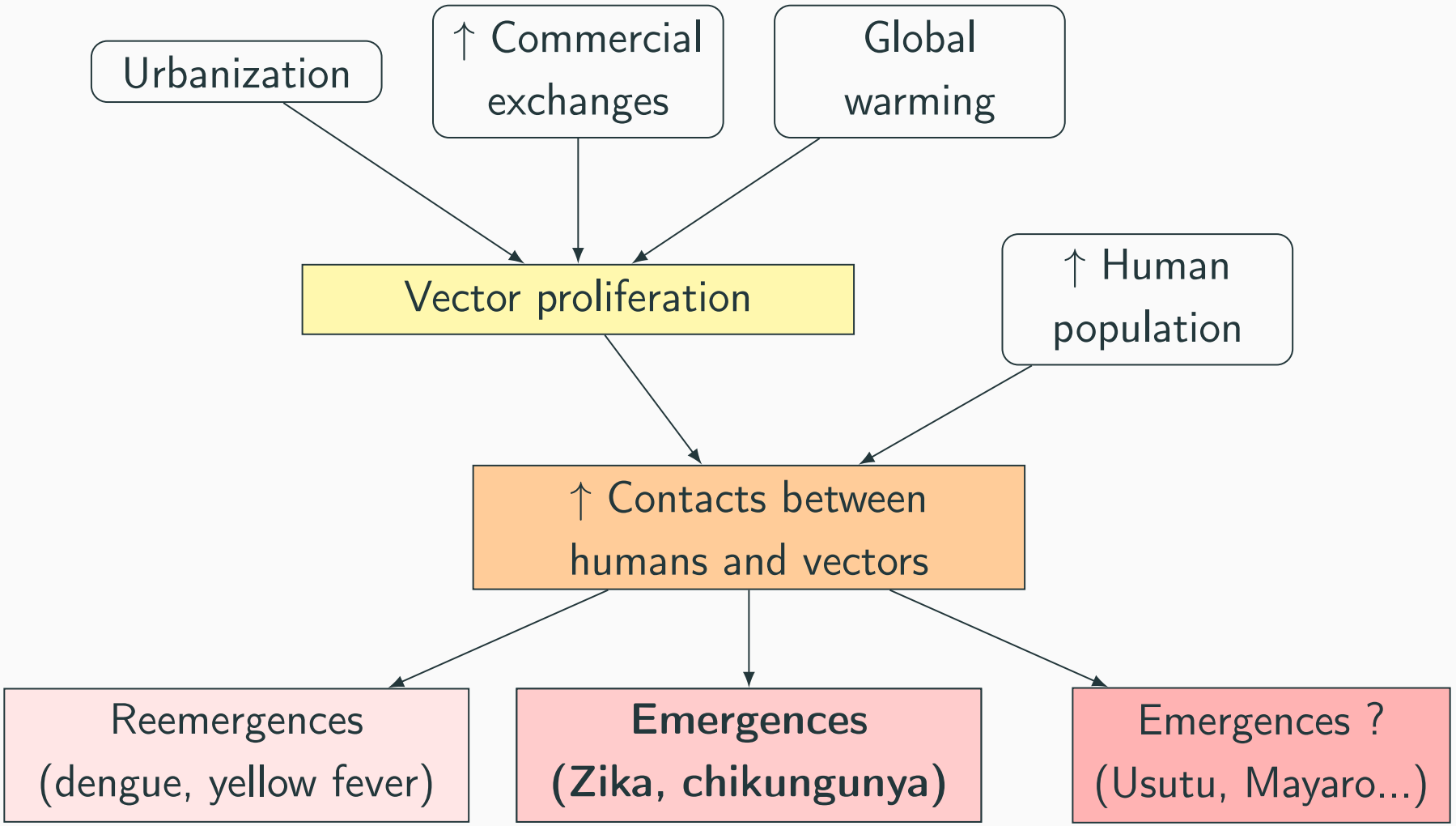
- Originally from Asia, extension from the 20th century[2]
- Invasive species: plasticity, competitive advantages[3]

[1] Kraemer et al., *eLife* (2015) ; [2] Reiter, *Journal of the American Mosquito Control Assoc.* (1998) ; [3] Paupy et al., *Microbes and Infection* (2009)

Disease emergences



Disease emergences



World propagation of chikungunya (CHIKV)

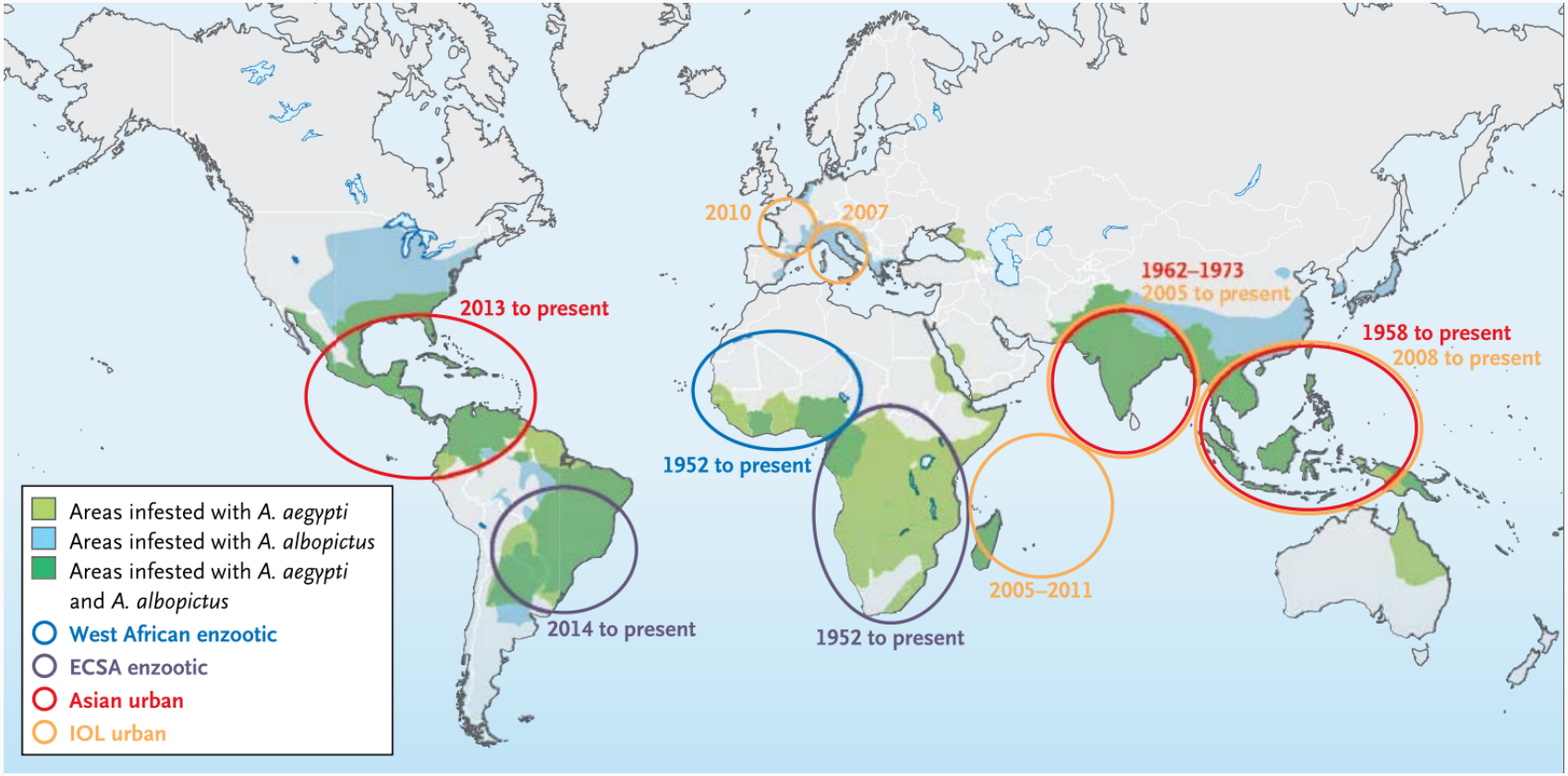


Figure 5: Origin and extension of the chikungunya virus and his vectors[1].

[1] Weaver et al., *New England Journal of Medicine* (2015)

World propagation of Zika (ZIKV)

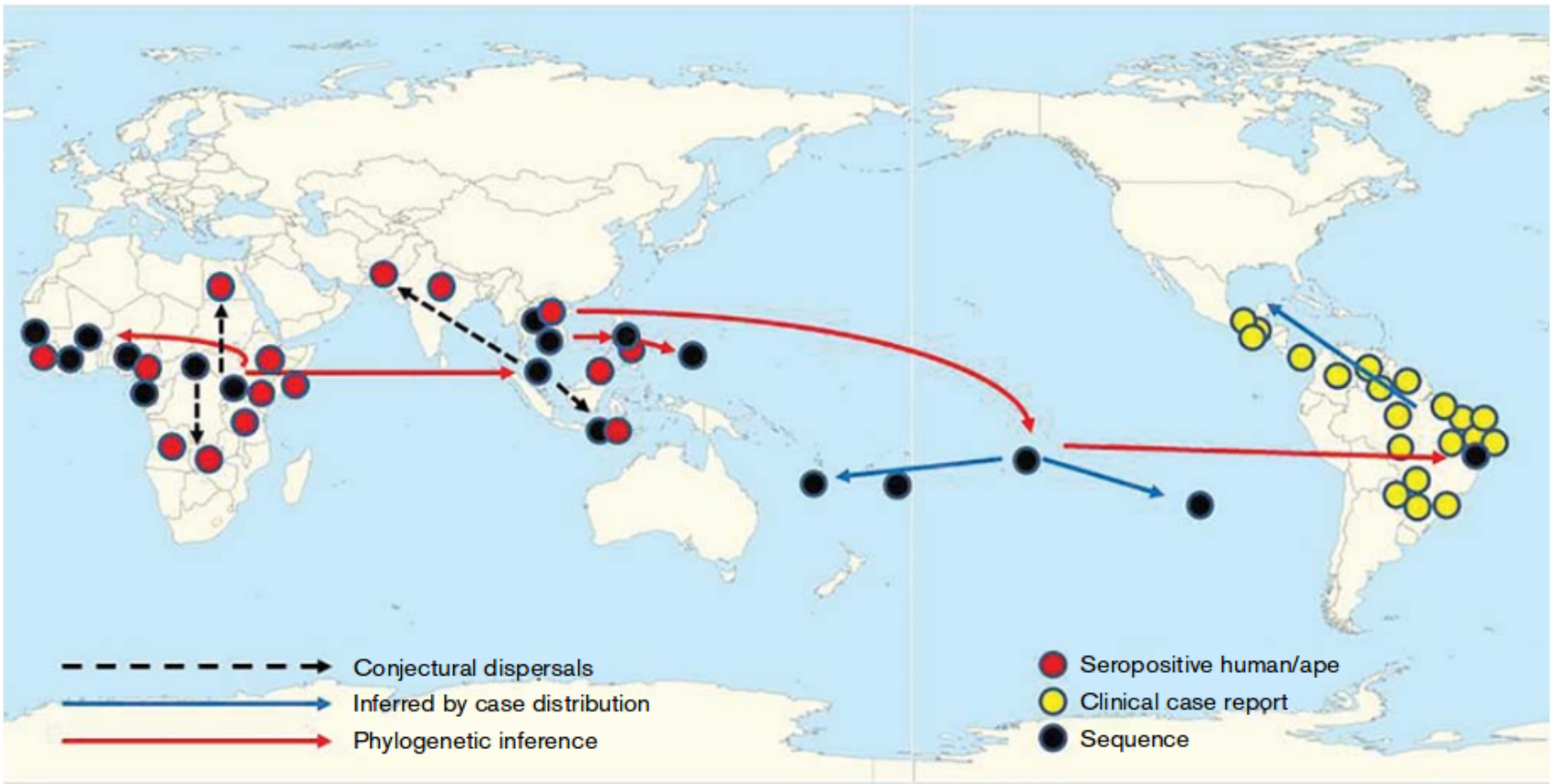


Figure 6: Origin and extension of the Zika virus[1].

[1] Gatherer et Kohl, *Journal of General Virology* (2016)

Comparing Zika and chikungunya epidemics

Strategy

Successive waves of chikungunya and Zika epidemics:

- each circulating for the first time
- in the same areas
- within a short timespan

$\Rightarrow$ Comparison of epidemics of different viruses:

- in the same populations (immunologically naive)
- in the same environments (vectors)
- observed by the same surveillance systems

Data

Time-series of incidence data for 18 outbreaks of ZIKV and CHIKV:

- weekly number of reported cases CHIKV or ZIKV
- between 2013 and 2016
- in 9 islands with similar surveillance systems

```
> load("zikachik.Rdata")
> tibble(zikachik)
# A tibble: 537 x 1
   zikachik$record… $REGION $REGION_ID $ISLAND $ISLAND_ID $ISLAND_ABB $VIRUS $VIRUS_ID $DATE      $WEEK $YEAR $N_DAY $N_WEEK $NCASES  $POP $STATION
              <int> <fct>        <dbl> <chr>        <int> <fct>       <chr>      <dbl> <date>     <int> <int>  <dbl>   <dbl>   <int> <dbl> <chr>
 1              185 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-11-09    45  2014      0       0       1  7000 91954
 2              186 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-11-16    46  2014      7       1       7  7000 91954
 3              187 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-11-23    47  2014     14       2      17  7000 91954
 4              188 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-11-30    48  2014     21       3      54  7000 91954
 5              189 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-12-07    49  2014     28       4      81  7000 91954
 6              190 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-12-14    50  2014     35       5      93  7000 91954
 7              191 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-12-21    51  2014     42       6      70  7000 91954
 8              192 FP               0 AUSTRA…          6 AUS         CHIKV          0 2014-12-28    52  2014     49       7      65  7000 91954
 9              193 FP               0 AUSTRA…          6 AUS         CHIKV          0 2015-01-04     1  2015     56       8      65  7000 91954
10              194 FP               0 AUSTRA…          6 AUS         CHIKV          0 2015-01-11     2  2015     63       9      74  7000 91954
# … with 527 more rows, and 32 more variables: $NCASES_M1 <dbl>, $NCASES_M2 <dbl>, $NCASES_M3 <dbl>, $NCASES_M4 <dbl>, $NCASES_M5 <dbl>,
#   $CUM_NCASES <dbl>, $INC <dbl>, $CUMINC <dbl>, $TOT_NCASES <int>, $AR <dbl>, $TempAvgC_W0 <dbl>, $PrecCm_W0 <dbl>, $TempAvgC_W1 <dbl>,
#   $PrecCm_W1 <dbl>, $TempAvgC_W2 <dbl>, $PrecCm_W2 <dbl>, $TempAvgC_W3 <dbl>, $PrecCm_W3 <dbl>, $TempAvgC_W4 <dbl>, $PrecCm_W4 <dbl>,
#   $TempAvgC_W5 <dbl>, $PrecCm_W5 <dbl>, $TempAvgC_W6 <dbl>, $PrecCm_W6 <dbl>, $TempAvgC_W7 <dbl>, $PrecCm_W7 <dbl>, $TempAvgC_W8 <dbl>,
#   $PrecCm_W8 <dbl>, $temp <dbl>, $GT.mean <dbl>, $GT.sd <dbl>, $Ostar <dbl>
```

https://github.com/jriou/multilevel_models_epi

Data

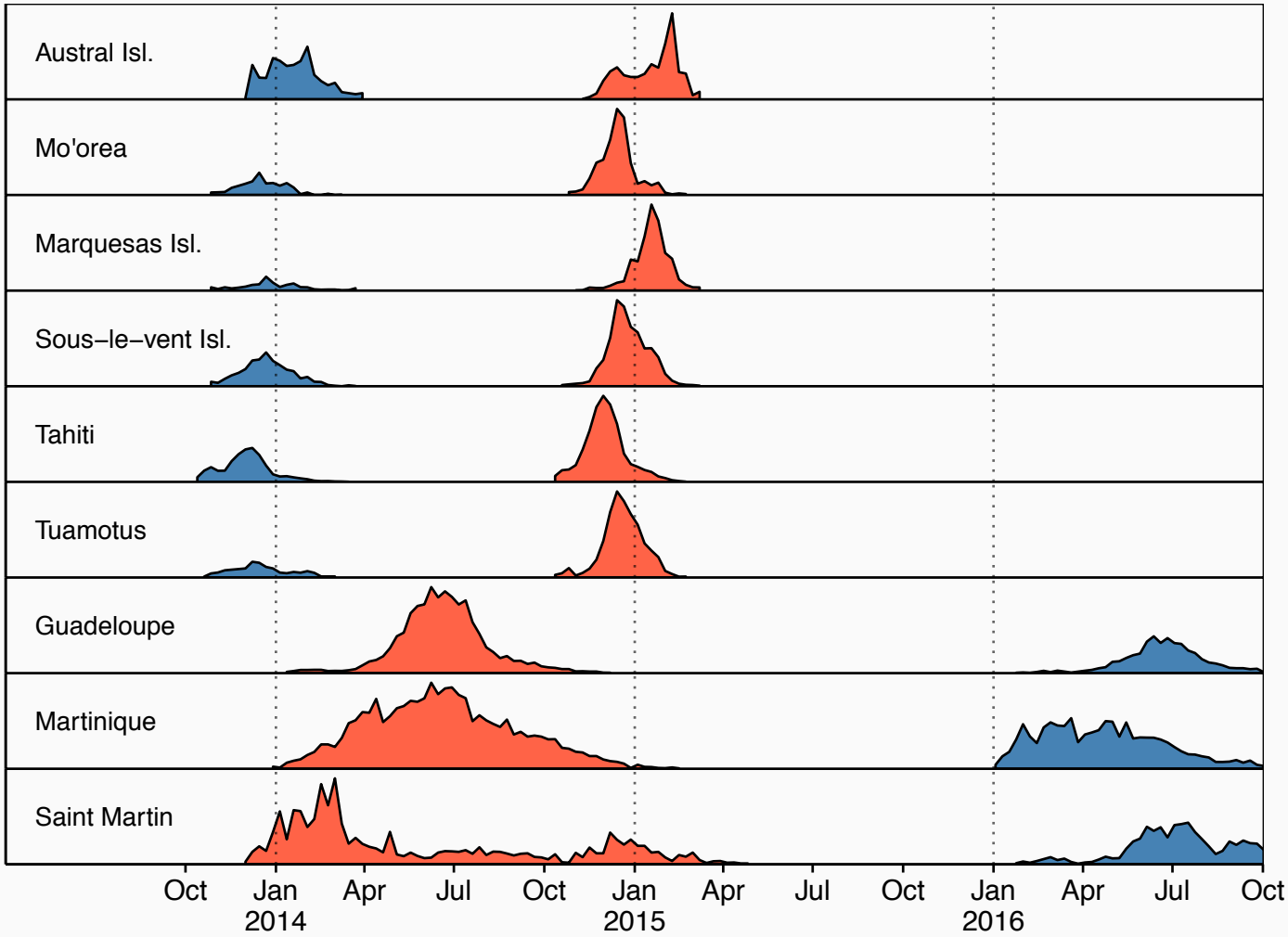


Figure 7: Profiles of CHIKV (red) and ZIKV (blue) incidence in nine territories during 2013–2016.

Data

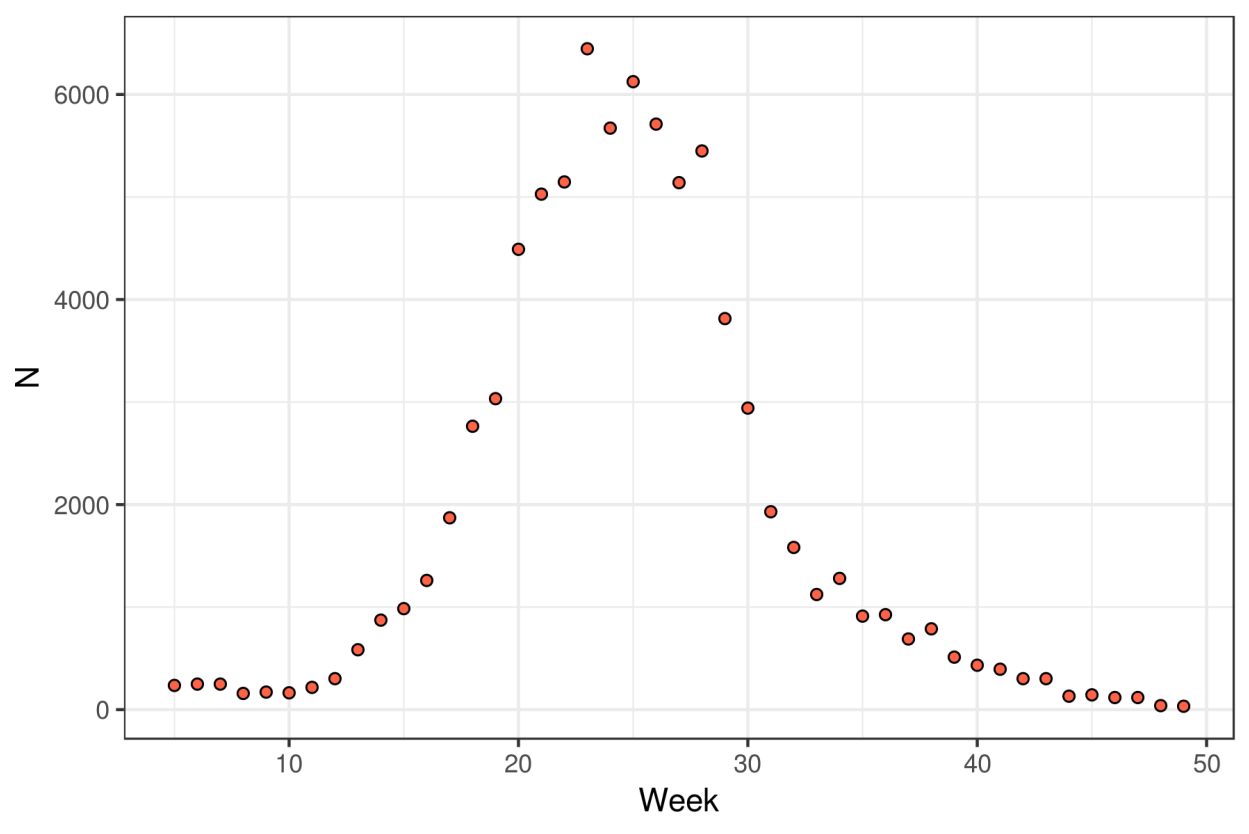


Figure 8: Weekly number of reported cases of chikungunya in Guadeloupe (Feb. – Dec. 2014).

Data-generating processes: observation

How is the number of reported cases on week t (O_t) generated?

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At the observation level:

$$O_t \sim \text{Binom}(I_t, \rho)$$

$\Rightarrow$ Parameter ρ: probability of reporting

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At the transmission level:

$$I_t \sim \text{Binom}\left(S_t, \beta \boxed{\frac{1}{N}\sum_{n=1}^{5} w_{t,n} I_{t-n}}\right)$$

$\Rightarrow$ Parameter β: number of secondary cases by primary case ($\mathcal{R}_0$)

$\Rightarrow$ Exposure: depends on the serial interval w_t

The serial interval

Definition

Serial interval: the time between the disease onset of a primary case and one of its secondary cases[1]

Reconstruction using the full transmission cycle

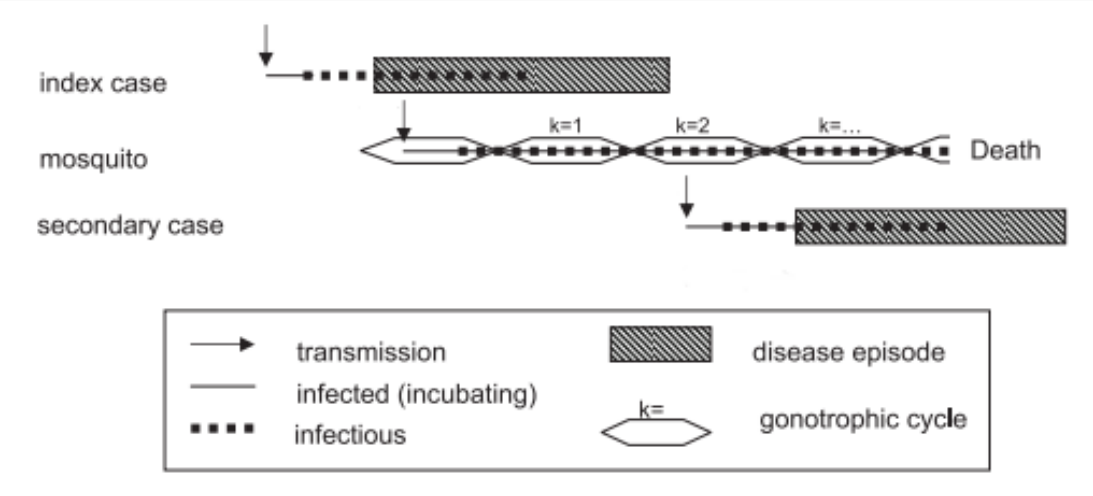

Figure 9: Framework for calculating the distribution of the serial interval[2].

[1] Svensson et al, *Math. biosciences* (2007); [2] Boëlle et al, *Vector-borne and zoonotic diseases* (2007)

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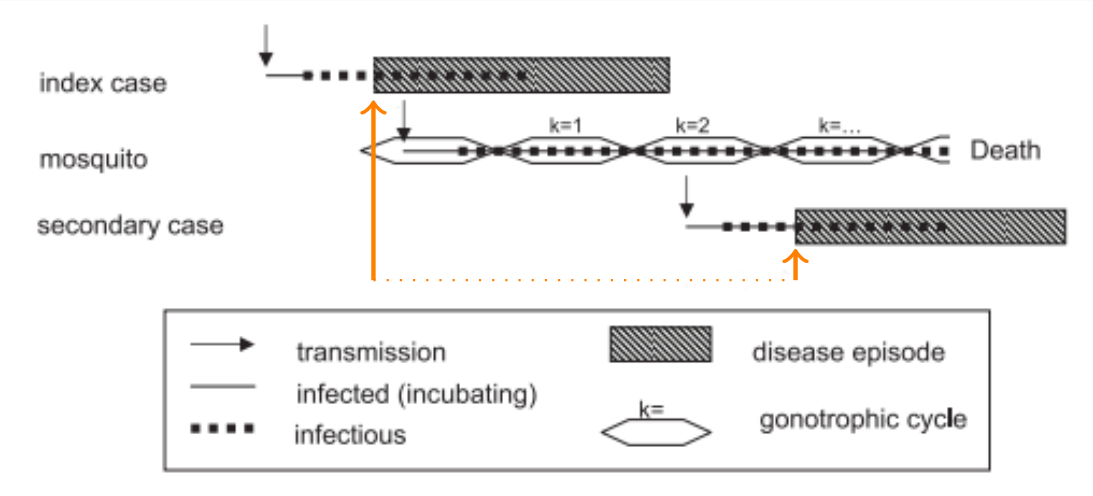

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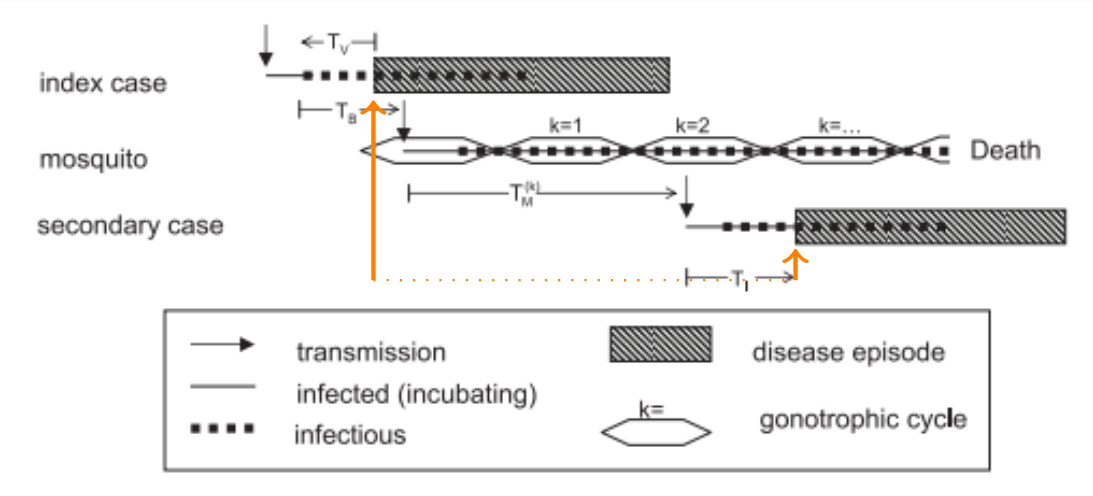

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The serial interval

Using published data on each stage (including dependence to local temperature T) we obtain:

$$T_{SI} = -T_V + T_B + T_M(T) + T_I$$

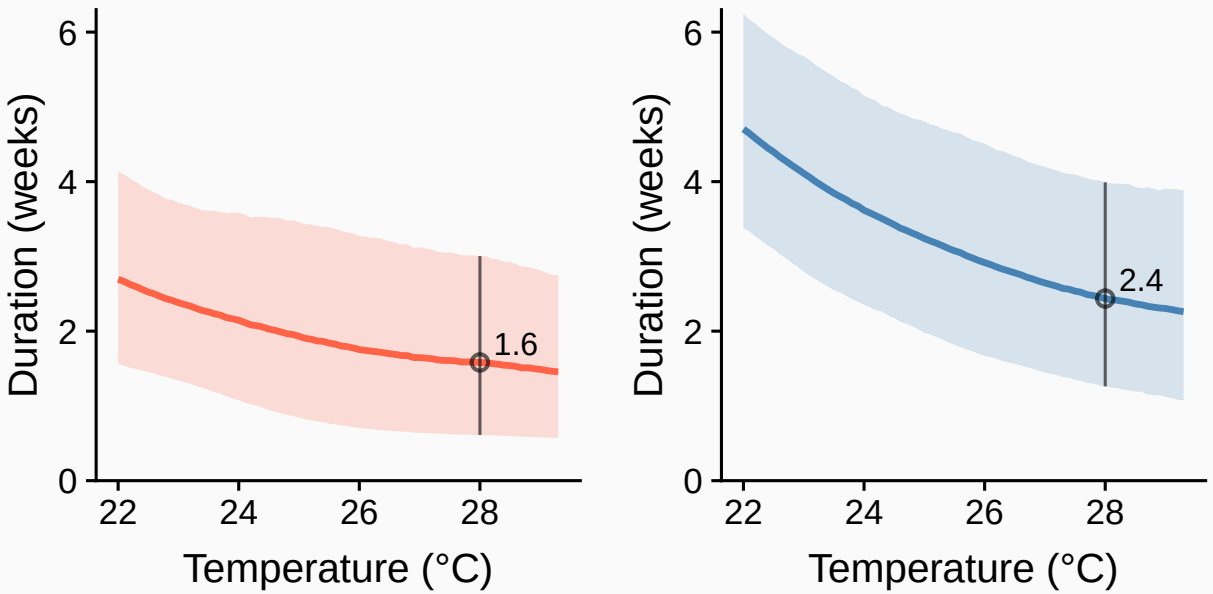

Figure 10: Distribution of the serial interval for CHIKV (red) and ZIKV (blue) according to temperature.

One disease, one island: model

Let O_t be the observed incidence in one epidemic on week t:

- at the observation level:

$$O_t \sim \text{Binom}(I_t, \rho)$$

Reporting rate

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Transmission

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$$I_t \sim \text{Binom}\left(S_t, \beta \frac{1}{N} \sum_{n=1}^{5} w_{t,n} I_{t-n}\right)$$

- both levels simplify into:

Overdispersion

$$O_t \sim \text{Neg-Binom}\left(S_t \frac{\beta}{N} \sum_{n=1}^{5} w_{t,n} \frac{O_{t-n}}{\rho}, \phi\right)$$

One disease, one island: inference

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- maximum likelihood $\rightarrow$ point-estimate + interval
- Bayesian approach $\rightarrow$ posterior distributions:

$$\Pr(\rho, \beta, \phi|O_t) \propto \Pr(O_t|\rho, \beta, \phi) \Pr(\rho, \beta, \phi)$$

One disease, one island: priors

We need to choose prior distributions for $\{\rho, \beta, \phi\}$:

- informative priors: reflect our prior knowledge about the values

[2] Gelman et al, The Annals of Applied Statistics (2008)

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One disease, one island: priors

We need to choose prior distributions for $\{\rho, \beta, \phi\}$:

- informative priors: reflect our prior knowledge about the values
- non-informative priors: flat priors (problematic)
- weakly-informative priors[2]: reflect our knowledge about the magnitude of the values

$$\rho \sim \text{Beta}(1, 1)$$

$$\beta \sim \text{Exponential}(0.1)$$

$$\phi \sim \text{Half-Cauchy}(2.5)$$

[2] Gelman et al, The Annals of Applied Statistics (2008)

One disease, one island: priors

We check the adequacy of these choices by conducting a prior predictive check[3]:

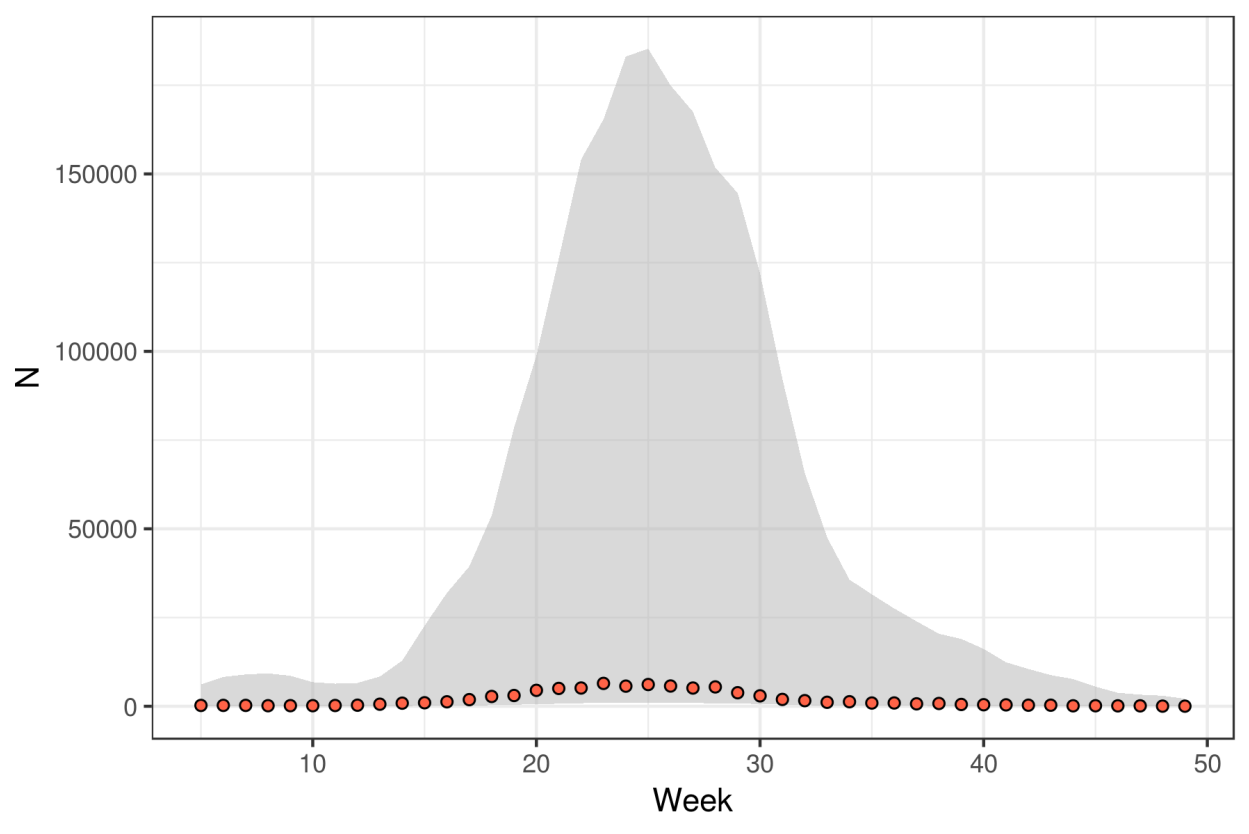

Figure 11: Prior predictive check for the epidemic of Zika virus in Guadeloupe.

[3] Gabry et al, Journal of the Royal Statistical Society (2019)

One disease, one island: implementation in Stan

In a separate `.stan` file:

- Data block:

```
data {
  int<lower=1> W; // number of records
  int<lower=0> O_t[W]; // number of reported cases at time t
  real<lower=0> Ostar_t[W]; // exposure at time t
  int<lower=0> sumO_t[W]; // cumulative number of reported cases at time t
  int<lower=0> pop; // island population
}
```

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}
```

- Parameters block:

```
parameters {
  real<lower=0> beta;
  real<lower=0,upper=1> rho;
  real<lower=0> phi;
}
```

One disease, one island: implementation in Stan

- Transformed parameters block:

```
transformed parameters {
  real<lower=0> lp[W];
  real<lower=0> sampledisp[W];
  for(i in 1:W) {
    lp[i] = ( 1 - sumO_t[i] / (rho * pop)) * beta * Ostar_t[i] ;
    sampledisp[i] = lp[i]/phi;
  }
}
```

NB: $S_t \frac{\beta}{N} \sum_{n=\mathbf{1}}^{\mathbf{5}} w_{t,n} \frac{O_{t-n}}{\rho} = \left(1 - \frac{\sum_t O_t}{\rho N}\right) \beta O_t^*$

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- Model block:

```
model {
  beta ~ exponential(0.1);
  rho ~ beta(1,1);
  phi ~ cauchy(0,2.5);
  // likelihood
  target += neg_binomial_2_lpmf(O_t|lp,sampledisp);
}
```

One disease, one island: implementation in Stan

Control `Stan` from `R` with `library(rstan)`:

```
## Select CHIKV in Guadeloupe
GUAD = filter(zikachik,ISLAND=="GUADELOUPE",VIRUS=="CHIKV",WEEK>=5)
## Format data for rstan
GUAD_L = list(W=dim(GUAD)[[1]],
              O_t=GUAD$NCASES,
              Ostar_t=GUAD$Ostar,
              sumO_t=GUAD$CUM_NCASES,
              pop=GUAD$POP[[1]])
## Sample
S_GUAD = stan("TSIR_one_island.stan",data=GUAD_L)
```

One disease, one island: implementation in Stan

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```
## Select CHIKV in Guadeloupe
GUAD = filter(zikachik,ISLAND=="GUADELOUPE",VIRUS=="CHIKV",WEEK>=5)
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              pop=GUAD$POP[[1]])
## Sample
S_GUAD = stan("TSIR_one_island.stan",data=GUAD_L)
```

Results: posterior distributions of β, ρ and ϕ

```
> print(S_GUAD,pars=c("beta","rho","phi"))
Inference for Stan model: TSIR_one_island.
4 chains, each with iter=2000; warmup=1000; thin=1;
post-warmup draws per chain=1000, total post-warmup draws=4000.

      mean se_mean    sd  2.5%   25%   50%   75% 97.5% n_eff Rhat
beta  1.54    0.00  0.06  1.42  1.50  1.53  1.58  1.66  1632    1
rho   0.33    0.00  0.02  0.30  0.32  0.33  0.34  0.38  1539    1
phi  51.04    0.24 11.47 33.31 42.74 49.42 57.74 77.75  2258    1

Samples were drawn using NUTS(diag_e) at Tue May 28 13:04:45 2019.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).
```

One disease, one island: implementation in Stan

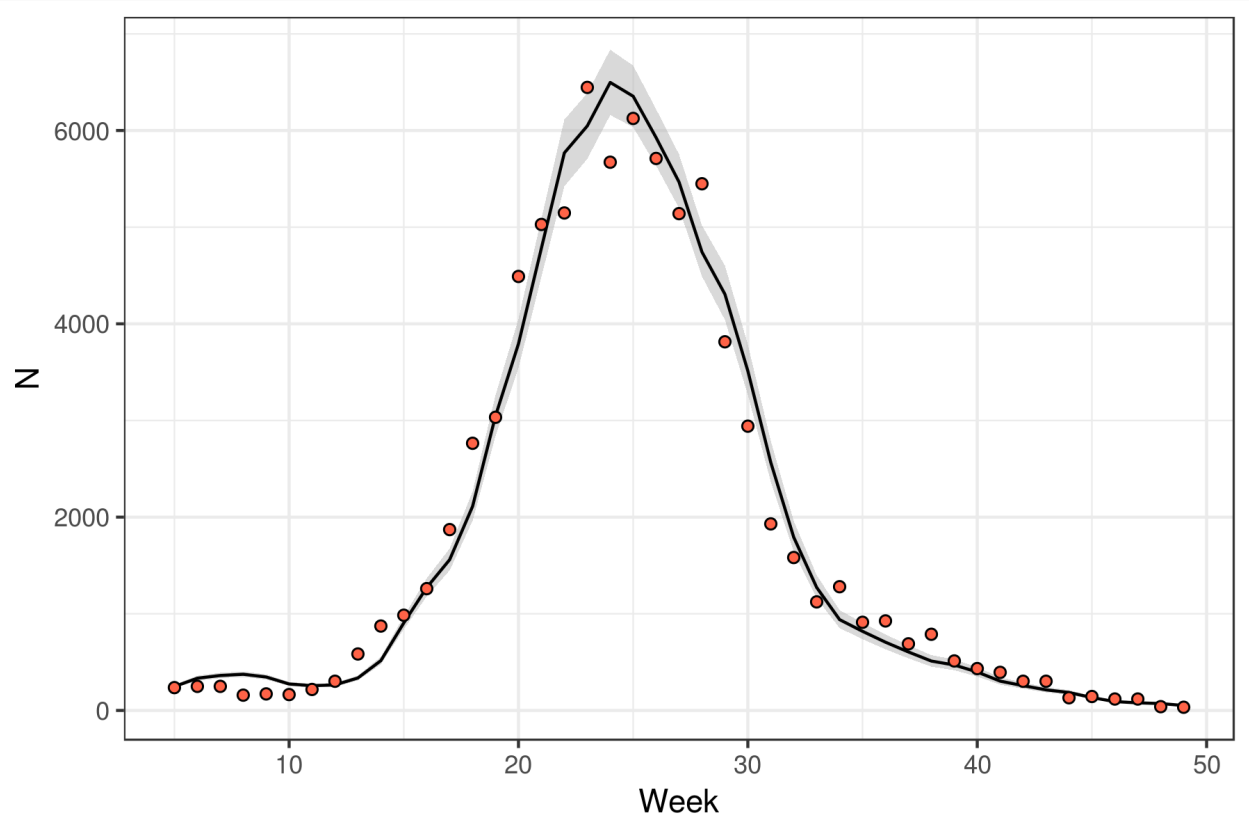

Figure 12: Model fit for the epidemic of Zika virus in Guadeloupe.

Now for 9 islands

Degrees of pooling:

- independent β_i and ρ_i for each island: no pooling

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Degrees of pooling:

- independent β_i and ρ_i for each island: no pooling
- the same β and ρ for all islands: complete pooling
- *correlated* β_i and ρ_i for each island: partial pooling
  $=$ multilevel or hierarchical

Now for 9 islands

For the epidemic in island i, we have:

- a transmission parameter β_i which depends on hyperparameters μ_β and σ_β:

$$\ln \beta_{i,j=0} \sim \mathcal{N}(\mu_\beta, \sigma_\beta^2)$$

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- a reporting parameter ρ_i which depends on hyperparameters μ_ρ and σ_ρ:

$$\ln \frac{\rho_{i,j=0}}{1-\rho_{i,j=0}} \sim \mathcal{N}(\mu_\rho, \sigma_\rho^2)$$

Now for 9 islands

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- a reporting parameter ρ_i which depends on hyperparameters μ_ρ and σ_ρ:

$$\ln \frac{\rho_{i,j=0}}{1-\rho_{i,j=0}} \sim \mathcal{N}(\mu_\rho, \sigma_\rho^2)$$

$\Rightarrow$ We now also estimate μ_β, μ_ρ, σ_β and σ_ρ

Now for 9 islands and 2 diseases

We now model together the epidemics of ZIKV ($j = 1$) and CHIKV ($j = 0$) assuming proportionality:

- on the transmission parameters of ZIKV and CHIKV:

$$\beta_{i,j=1} = \eta \times \beta_{i,j=0}$$

- on the reporting parameters of ZIKV and CHIKV (on the logit scale):

$$\frac{\rho_{i,j=1}}{1 - \rho_{i,j=1}} = \omega \times \frac{\rho_{i,j=0}}{1 - \rho_{i,j=0}}$$

Now for 9 islands and 2 diseases

We now model together the epidemics of ZIKV ($j = 1$) and CHIKV ($j = 0$) assuming proportionality:

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- on the reporting parameters of ZIKV and CHIKV (on the logit scale):

$$\frac{\rho_{i,j=1}}{1 - \rho_{i,j=1}} = \omega \times \frac{\rho_{i,j=0}}{1 - \rho_{i,j=0}}$$

$\Rightarrow$ We now also estimate η and ω

Now for 9 islands and 2 diseases

The model fit is acceptable for CHIKV:

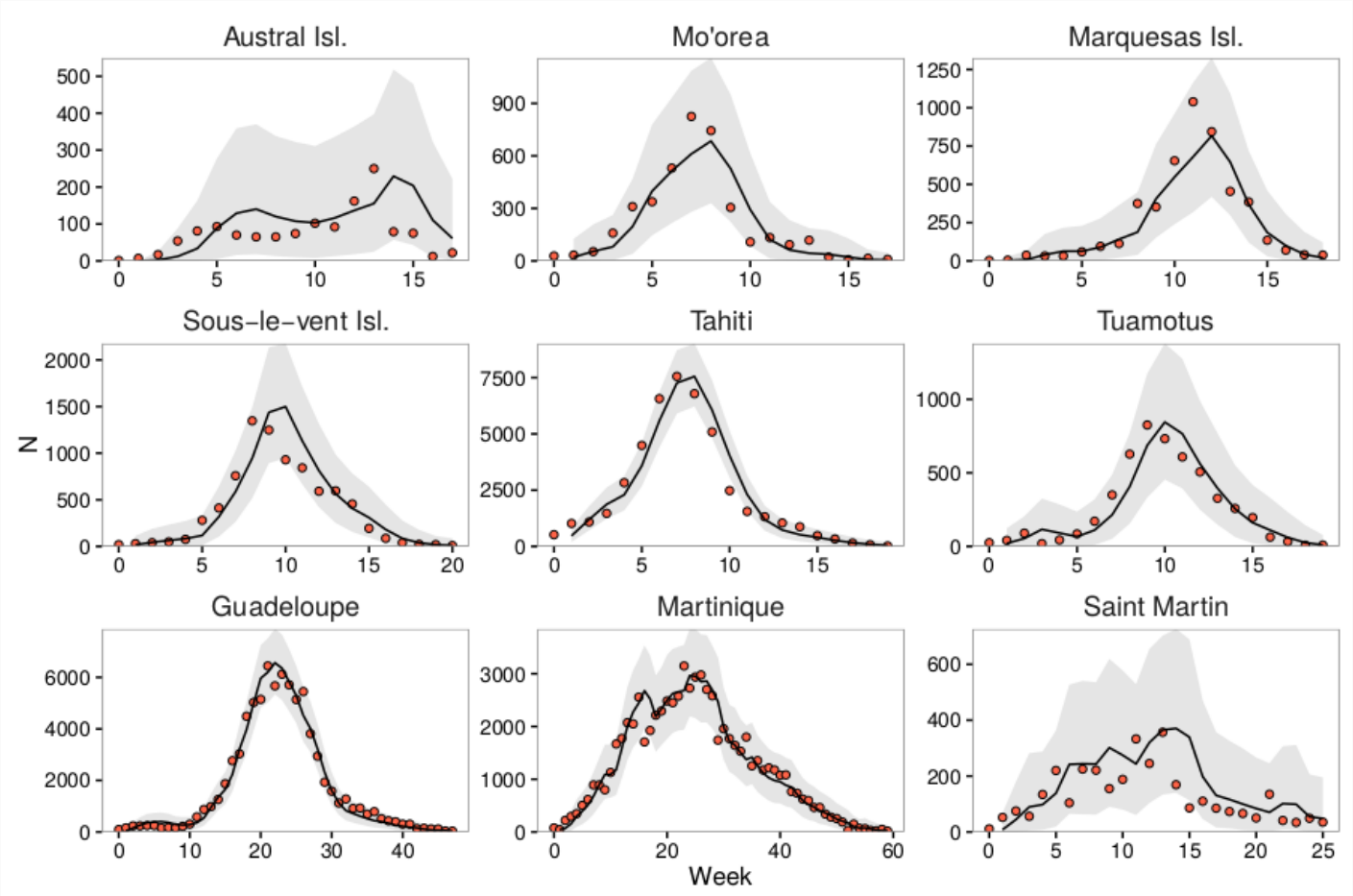

Figure 13: Model fit for the CHIKV epidemics.

Now for 9 islands and 2 diseases

And for ZIKV:

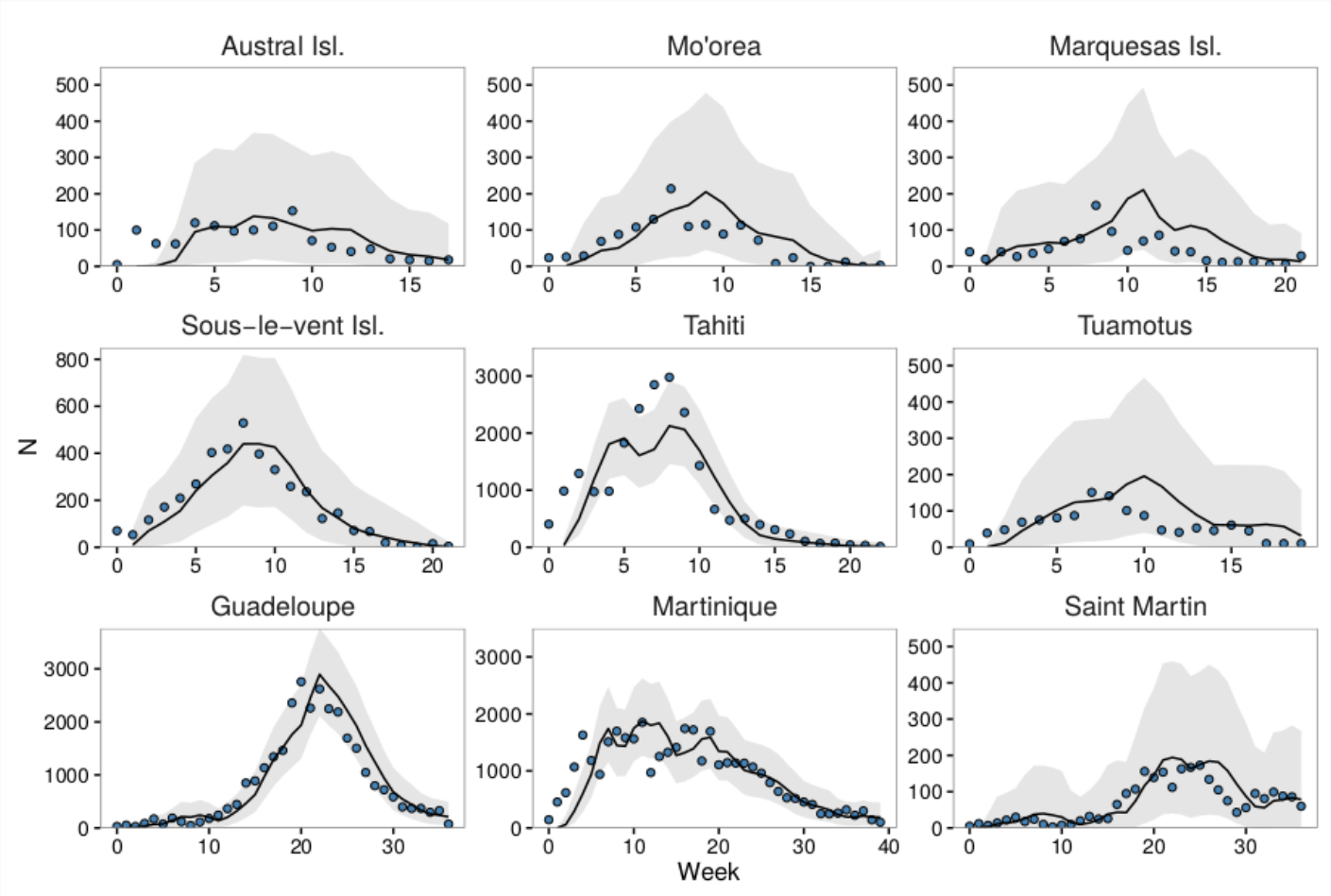

Figure 14: Model fit for the ZIKV epidemics.

Now for 9 islands and 2 diseases

The main results are:

- a similar transmissibility of CHIKV and ZIKV within an area
  - $\eta|\text{data} = 1.04\ [0.97 - 1.13]$
- a lower reporting rate for ZIKV
  - $\omega|\text{data} = 0.37\ [0.34 - 0.40]$

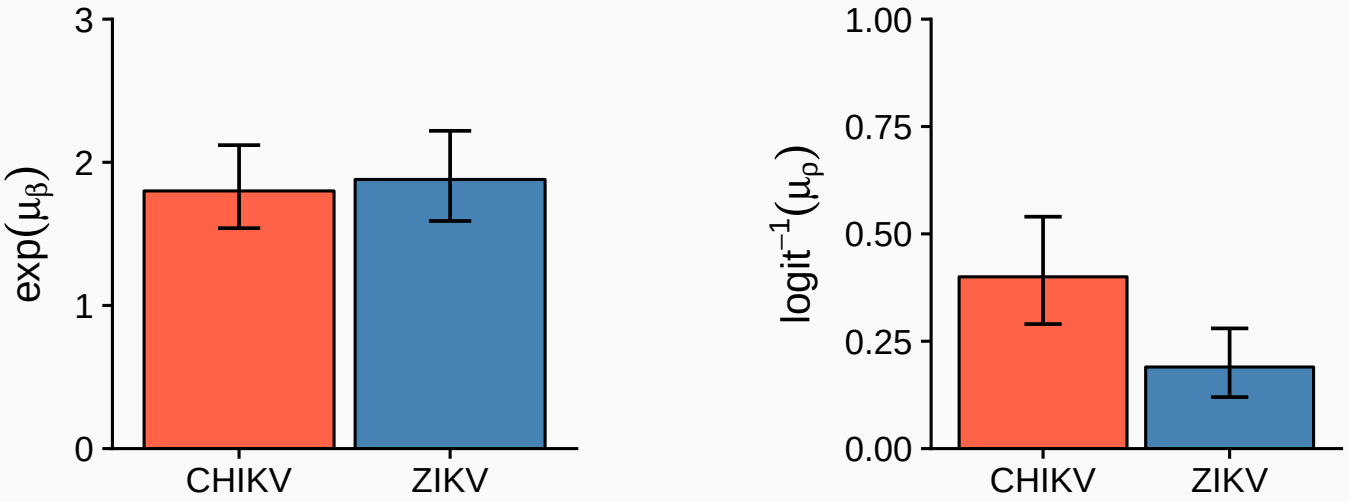

Figure 15: Posterior estimates of μ_β and μ_ρ for CHIKV and ZIKV.

Now for 9 islands and 2 diseases

We also find heterogeneity between areas:

- $\sigma^2_\beta|\text{data} > 0$, lower β in the French West Indies
- $\sigma^2_\rho|\text{data} > 0$, higher ρ in small islands and in Martinique

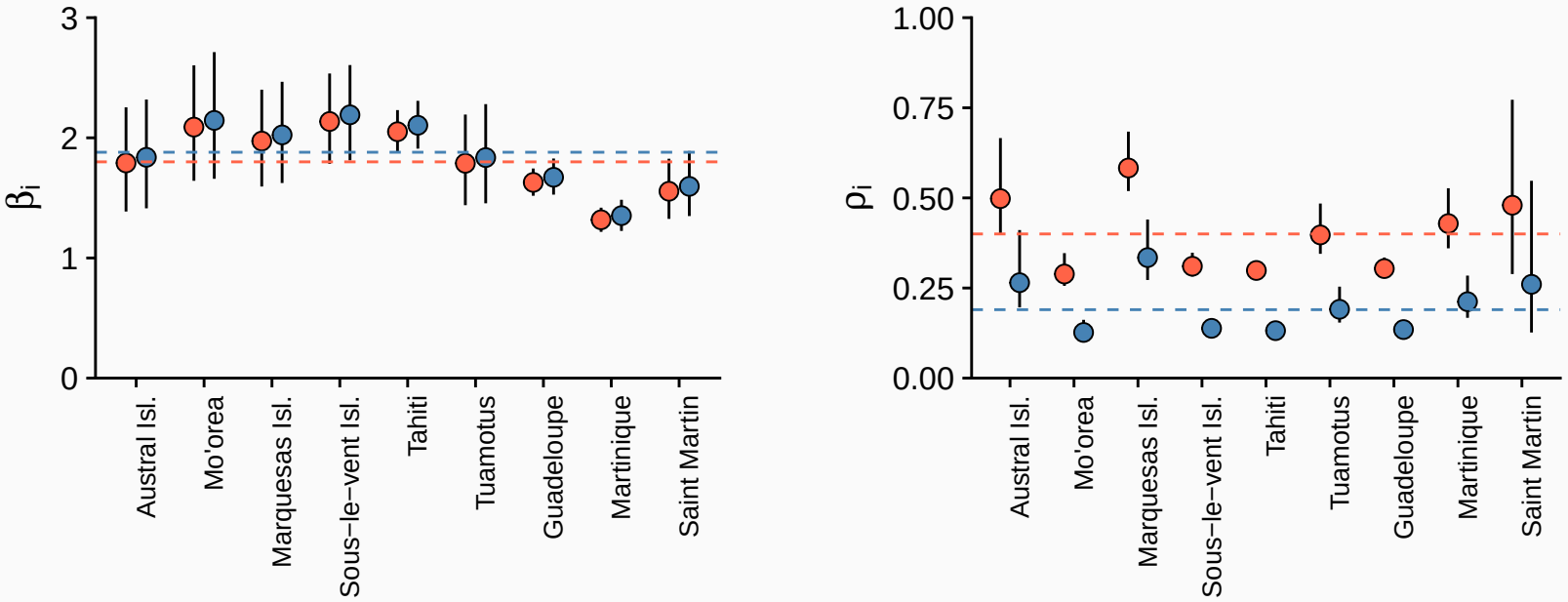

Figure 16: Island-specific posterior estimates of β and ρ for CHIKV (red) and ZIKV (blue).

Conclusion

Remember about:

- Data-generating mechanisms
- Prior predictive checks
- Plot model predictions (fit)
- Multi-level structure following data structure (partial pooling)