

Spatial Discrete-Time Infectious Disease Models for Surveillance Data

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Overview

Motivate discrete-time stochastic models for analysis of infectious disease **surveillance data**:

- **Review** of models.
- **Shortcomings** of current models.

Typical available information in a surveillance setting:

- **Demographic information** on each case, for example, age and gender.
- **Symptom onset** date.
- **Date of diagnosis**.
- **Clinical information**, for example, symptoms.
- Laboratory information on **virology**, perhaps on a subset of cases.
- Areal (ecological) **geographical information**.
- **Population information** at the areal level.

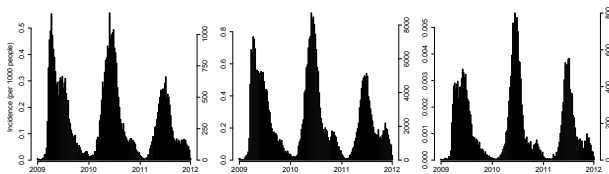
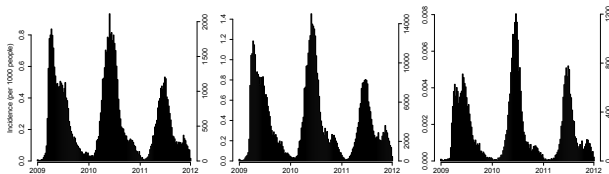
Motivating example: Hand, Foot and Mouth Disease (HFMD)

- HFMD caused by an acute contagious viral infection.
- Transmitted primarily via the fecal-oral route.
- Large-scale outbreaks in Asia during the past 20 years.
- Majority of cases are in children.
- Cases are most infectious during the first week of acute illness but may continue to shed virus in the stool for weeks.
- Incubation period is 3–5 days.

Each reported case of HFMD from the Chinese Center for Disease Control and Prevention (CCDC) infectious disease surveillance system consists of the patient's **geographical location**, **gender** and **age** and the **symptom onset date**.

For illustration, I present data from 59 prefectures in the Central North region of China over the period 2009–2011.

Weekly epidemic curves of HFMD cases by age group

(a) Female, $[0, 1)$ (b) Female, $[1, 6)$ (c) Female, ≥ 6 (d) Male, $[0, 1)$ (e) Male, $[1, 6)$ (f) Male, ≥ 6

Categories of infectious disease transmission models

Deterministic Models based on Differential Equations:

- Computation is efficient so system can be complex.
- Fit to data using ordinary least squares or variants, inference dicey.
- Interpretable parameters.
- Poor for small populations or when the disease is rare.

Discrete-Time Stochastic Models:

- Fitting via likelihood/Bayes is relatively straightforward.
- Interpretable parameters depends on the exact form.
- Computational efficiency not greatly affected by population size.
- Rigid data form (equally-spaced) typically required.

Continuous-Time Stochastic Models:

- Interpretable parameters.
- Computation not yet feasible in large populations.

Cartoon representation of SIR model

Let $x(t)$, $y(t)$, $z(t)$ be the number of **susceptibles**, **infectives**, **recovered** at time t in a **closed population**.

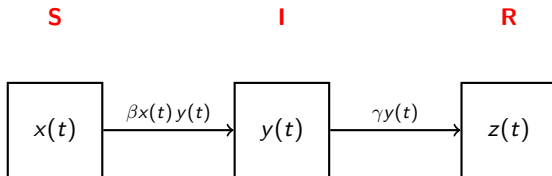


Figure 1 : Solid arrows show the movement from S to I to R.

Deterministic SIR model

Classic **mass-action**:

$$\begin{aligned}\frac{dx(t)}{dt} &= -\beta x(t)y(t) \\ \frac{dy(t)}{dt} &= \beta x(t)y(t) - \gamma Y(t) \\ \frac{dz(t)}{dt} &= \gamma y(t),\end{aligned}$$

with **per-contact infection rate** β and **recovery rate** γ .

Continuous-time stochastic SIR model

Continuous-time Markov chain $\{X(t), Y(t), t \geq 0\}$ with **transition probabilities** for a susceptible becoming infective and an infective becoming recovered being:

$$\Pr \left(\begin{array}{l} X(t+h) \\ Y(t+h) \end{array} = \begin{array}{l} x-1 \\ y+1 \end{array} \mid \begin{array}{l} X(t) \\ Y(t) \end{array} = \begin{array}{l} x \\ y \end{array} \right) = \beta h x y + o(h)$$
$$\Pr \left(\begin{array}{l} X(t+h) \\ Y(t+h) \end{array} = \begin{array}{l} x \\ y-1 \end{array} \mid \begin{array}{l} X(t) \\ Y(t) \end{array} = \begin{array}{l} x \\ y \end{array} \right) = \beta h x y + o(h)$$

where the remainder term $o(h)$ is small.

The most appealing (at least to a statistician!) but quickly gets computationally hideous as the populations increase in size given the usual surveillance data, see the references in Fintzi et al. (2017).

Discrete-time stochastic SIR model

Choose the time scale to equal the transmission dynamic scale (e.g., 2 weeks for measles).

So we lose the **recovery rate** parameter.

Let X_t and Y_t be random variables representing the number of **susceptibles** and **infectives** at time t , $t = 1, \dots, T$.

Infectives are modeled and **susceptibles** are reconstructed from

$$X_t = X_{t-1} - Y_t,$$

assuming a closed population.

Discrete-time stochastic SIR model

Held et al. (2005) proposed an **epidemic-endemic** (frequency dependent¹) model:

$$\begin{aligned} E[Y_t | x_{t-1}, y_{t-1}] &= x_{t-1}(1 - e^{-\beta y_{t-1}/N}) \\ &\approx \beta x_{t-1} \frac{y_{t-1}}{N} \\ &\approx \beta y_{t-1}, \end{aligned}$$

if we approximate the number of susceptibles by total population.

Bjørnstad et al. (2002) describe a **Time-series SIR (TSIR)** (density dependent²) model:

$$E[Y_t | x_{t-1}, y_{t-1}] = \beta x_{t-1} (y_{t-1} + \delta_{t-1})^\alpha$$

where δ_{t-1} are immigrant infections and α allows flexibility in the transmission model.

Both use **negative binomial** data sampling models.

¹More on this later

²Ditto

Discrete-time stochastic SIR model extensions

From this point on we concentrate on discrete-time stochastic models.

The above models have been extended in various directions:

- Add a **spatial** component.
- **Age-gender stratum**.
- **Contact structure**.
- **Covariate models**: Ecological fallacy/change of support/modifiable areal unit issues?

A spatial discrete-time stochastic model

Let Y_{it} be the count of HFMD cases in area i and in week t , $i = 1, \dots, n$, $T = 1, \dots, T$ (assume no under-reporting or other sources of error).

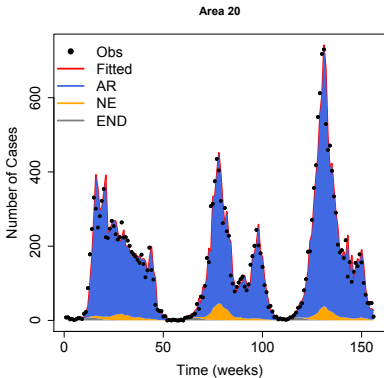
Data model:

$$Y_{it} | \mu_{it} \sim \text{NegativeBinomial}(\mu_{it}, \psi),$$

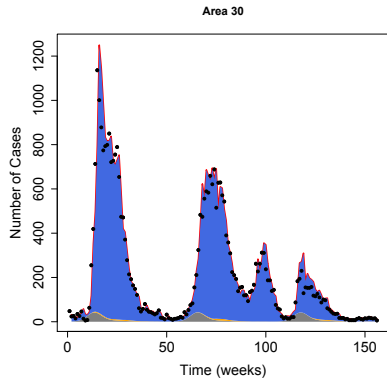
where $\mu_{it} = E[Y_{it} | y_{i,t-1}]$ is the conditional mean:

$$\mu_{it} = \underbrace{\lambda_{it}^{\text{AR}}}_{\text{Self Area}} y_{i,t-1} + \underbrace{\lambda_{i}^{\text{NE}}}_{\text{Neighboring Area}} \sum_{i'=1}^n \underbrace{w_{i'i}}_{\text{Proximity Matrix}} y_{i',t-1} + \underbrace{\lambda_{it}^{\text{EN}}}_{\text{Environmental}} .$$

This model is interesting but is there an infectious disease process formulation lurking behind the scenes, or it is just a flexible curve fitting exercise?



(a) Area 20



(b) Area 30

Figure 2 : Fitted and observed numbers of HFMD cases, with contributions by different components highlighted, for two provinces in the China central north region. The counts are summed over strata.

Derivation of the discrete-time stochastic model

For the moment, for simplicity, ignore space.

Model the probability that a susceptible individual at time $t - 1$ will become infected by time t .

For the moment, assume infected individuals are infectious for one time unit, before becoming removed, so that we have an **SIR model** with a fixed infectious period duration.

Given y_{t-1} infectives,

$$\underbrace{\lambda_t^\dagger}_{\text{Hazard}} = \underbrace{c(N)}_{\text{Contact Rate}} \times \underbrace{\frac{y_{t-1}}{N}}_{\text{Prevalence}} \times \underbrace{p}_{\text{Infection Prob}}$$

Contact rate can be

$$C(N) = \begin{cases} C_{\text{FD}} & \text{Frequency Dependent} \\ N C_{\text{DD}} & \text{Density Dependent} \end{cases}$$

We assume frequency dependent to give **hazard rate (force of infection)**:

$$\lambda_t^\dagger = \lambda y_{t-1} / N.$$

Derivation of the discrete-time stochastic model

Probability of infection in $[t - 1, t)$, given no infection at $t - 1$ is

$$1 - \exp(-\lambda y_{t-1}/N).$$

Leads to (under the usual assumptions):

$$Y_t | Y_{t-1} = y_{t-1} \sim \text{Binomial}[x_{t-1}, 1 - \exp(-\lambda y_{t-1}/N)].$$

If rare disease, and assume $x_{t-1} \approx N$:

$$Y_t | Y_{t-1} = y_{t-1} \sim \text{Poisson}(\lambda y_{t-1}).$$

This forms the basis of the Held et al. (2005) formulation.

A discrete-time stochastic model with age-gender strata and space

In the case of different possibilities for becoming infected, we can use the classic **competing risks** framework of Prentice et al. (1978), in which the hazard rates (forces of infection) are additive.

We let $\lambda_{itj}^{\text{TOT}}$ represent the overall hazard for a stratum j susceptible in area i at time t , and write

$$\lambda_{itj}^{\dagger, \text{TOT}} = \underbrace{\lambda_{itj}^{\dagger, \text{AR}}}_{\text{Self-Area}} + \underbrace{\lambda_{itj}^{\dagger, \text{NE}}}_{\text{Neighboring-Area}} + \underbrace{\lambda_{itj}^{\dagger, \text{EN}}}_{\text{Environmental}} .$$

Assuming $\lambda_{itj}^{\text{TOT}}$ is small, the probability of infection in $[t-1, t)$, for a single susceptible is,

$$1 - \exp(-\lambda_{itj}^{\text{TOT}}) \approx 1 - [1 - \lambda_{itj}^{\text{TOT}}] = \lambda_{itj}^{\text{TOT}} .$$

A discrete-time model with age-gender strata and space

Leads to conditional mean:

$$\mu_{itj} = \underbrace{\left(\sum_{j'=1}^J \lambda_{itjj'}^{\text{AR}} Y_{i,t-1,j'} \right)}_{\substack{\text{Self-Area} \\ \text{Different Strata}}} + \underbrace{\left(\sum_{i'=1}^n \sum_{j'=1}^J \lambda_{itjj'}^{\text{NE}} W_{i'i} Y_{i',t-1,j'} \right)}_{\substack{\text{Different Neighbors} \\ \text{Different Strata}}} + \underbrace{\lambda_{itj}^{\text{EN}}}_{\text{Environmental}}.$$

- We've allowed the rates to depend on **space**, **time** (to allow covariate modeling) and **strata**.
- In practice sparsity of information will lead to simplifications.
- Common to include area **random effects** (see later), which may or may not have spatial structure.

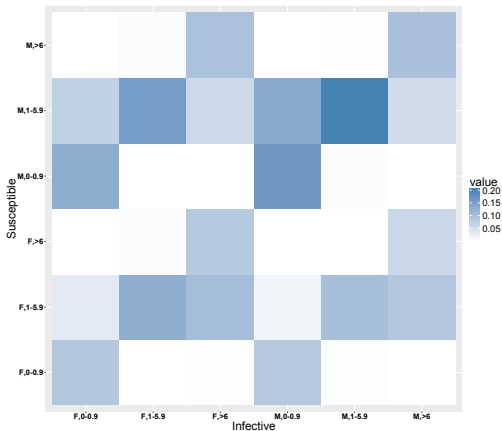


Figure 3 : Estimated [transmission rates](#) between age-gender strata for China central north weekly HFMD surveillance data, from Bauer and Wakefield (2017).

Modeling the neighborhood weights

Originally, weights were binary corresponding to spatial contiguity.

More recently (Meyer and Held, 2014), the weights are assumed to follow a [power law](#),

$$w_{i'i} = \frac{m_{i'i}^{-\rho}}{\sum_{k=1}^n m_{ki}^{-\rho}},$$

where $m_{i'i}$ is the number of areas that must be crossed when moving between areas i and i' , and ρ is a [power](#) that may be estimated.

The limit $\rho \rightarrow \infty$ corresponds to first-order dependency, and $\rho = 0$ gives equal weight to all areas.

The normalization ensures that $\sum_{k=1}^n w_{ki} = 1$ for all rows of the weight matrix (infecteds are being [allocated](#) to neighbors).

The power law allows “contact” between areas that are a large distance apart since it is “heavy-tailed”.

Neighborhood model in the TSIR formulation

Others (Xia et al., 2004) have used a **gravity model** within the TSIR framework:

$$E[Y_{it}|y_{i,t-1}] = \beta x_{i,t-1} (y_{i,t-1} + \delta_{i,t-1})^\alpha$$

$$\underbrace{\delta_{it}} \sim \text{Gamma}(m_{it}, 1)$$

Infections from
other areas

$$E[\delta_{i,t-1}] = m_{it}$$

$$= \theta N_i^{\tau_1} \sum_{i'=1}^n \frac{y_{i',t-1}^{\tau_2}}{d_{i'i}^\rho}$$

So with $\alpha = \tau_1 = \tau_2 = 1$ and $x_{i,t-1} \approx N_i$, we can write

$$\mu_{it} = N_i \lambda_t^{\text{AR}} y_{i,t-1} + \lambda^{\text{NE}} N_i \sum_{i'=1}^n \frac{y_{i',t-1}}{d_{i'i}^\rho}$$

where $\lambda^{\text{AR}} = \beta_t$, $\lambda^{\text{NE}} = \theta$ and we have a **distance-based weighting scheme**.

Effects of aggregation (Fisher and Wakefield, 2017)

The key to understanding **ecological bias** is to take an individual-level model and aggregate to the area-level (Wakefield, 2008).

Let Y_{itk} be disease indicator for a susceptible individual k in area i and week t .

Assume simple self-area model and a rare disease

$$Y_{itk} | \lambda_{itj} \sim \text{Bernoulli}(\lambda_{itk} Y_{i,t-1} / N_i).$$

Effects of aggregation

For a rare disease, covariates may be included via (say) the log-linear form

$$\lambda_{itk} = \exp(\alpha + \beta z_{itk}).$$

The implied **aggregate hazard rate** for area i and time t is

$$\bar{\lambda}_{it} = \exp(\alpha) \int_{A_i} \exp(\beta z) g_{it}(z) dz,$$

where A_i represents region i and $g_{it}(z)$ is the **within-area distribution** of z .

Simple example: A binary covariate so $z_{itk} = 0/1$.

Naive model: $\bar{\lambda}_{it} = \exp(\alpha^* + \beta^* \bar{z}_{it})$, where \bar{z}_{it} is the area-time average.

Aggregate consistent model: $\bar{\lambda}_{it} = N_i [(1 - \bar{z}_{it})e^\alpha + \bar{z}_{it}e^{\alpha+\beta}]$.

Vaccination coverage and the ecological model

Herzog et al. (2011) and Meyer et al. (2016) include estimated vaccination coverage (z_i) in either the **epidemic** or **environmental** component of the Held et al. (2005) model:

$$Y_{it} | \mu_{it} \sim \text{Poisson}(\mu_{it}).$$

For example, when coverage is included in the **epidemic** term:

$$\mu_{it} = e^{\alpha_0} (1 - z_i)^{\alpha_1} y_{i,t-1} + N_{it} \nu_{it}$$

- $(1 - z_i)$ is a proxy for proportion of susceptibles in area i .
- $\alpha_1 > 0$ means higher proportion of susceptibles will boost the generation of new infections.
- Doubling of proportion of susceptibles is associated with a multiplicative change in the epidemic measles incidence of 2^{α_1} .

No biological motivation or interpretation for α_1 : we emphasize we want an **interpretable model**, not just a **predictive model**.

Modes of vaccine action on susceptibility

Let ϕ be vaccine effect, and z be the proportion vaccinated, so initially number of unvaccinated susceptibles is $S_{u0} = (1 - z)N$.

All-or-none vaccine:

- If successful, vaccinated individual has 100% lifetime immunity.
- Vaccine fails with probability $1 - \phi$.
- **Vaccinated susceptible** refers to those vaccine recipients for whom it failed, initially $S_{v0} = (1 - \phi)zN$.
- Risk of infection is same for vaccinated and unvaccinated susceptibles.

Leaky vaccine:

- Vaccinated individual's risk of infection reduced by multiplicative factor of $1 - \phi$, i.e. $\lambda_{vt}^{\dagger} = (1 - \phi)\lambda_{ut}^{\dagger}$.
- No one has 100% immunity, initially $S_{v0} = zN$.

All-or-none

Leaky

Initial susceptible population

$$S_{u0}(\phi) = (1 - z)N$$

$$S_{v0}(\phi) = (1 - \phi)zN$$

$$S_{u0} = (1 - z)N$$

$$S_{v0} = zN$$

Force of infection

$$\lambda_{ut}^\dagger = \lambda_t^\dagger, \quad \lambda_{vt}^\dagger = \lambda_t^\dagger$$

$$\lambda_{ut}^\dagger = \lambda_t^\dagger, \quad \lambda_{vt}^\dagger = (1 - \phi)\lambda_t^\dagger$$

Progression

$$Y_{u,t+1} | \lambda_{ut}^\dagger$$

$$\text{Bin}\left(S_{ut}(\phi), 1 - e^{-\lambda_t^\dagger}\right)$$

$$\text{Bin}\left(S_{ut}, 1 - e^{-\lambda_t^\dagger}\right)$$

$$Y_{v,t+1} | \lambda_{vt}^\dagger$$

$$\text{Bin}\left(S_{vt}(\phi), 1 - e^{-\lambda_t^\dagger}\right)$$

$$\text{Bin}\left(S_{vt}, 1 - e^{-(1-\phi)\lambda_t^\dagger}\right)$$

Implied aggregate model

$$Y_{t+1} | \lambda_t^\dagger$$

$$\text{Bin}\left(S_t(\phi), 1 - e^{-\lambda_t^\dagger}\right)$$

Convolution of binomials

Simplifying assumptions

Poissons approximate binomials

$$\text{Poi}\left(S_t(\phi)(1 - e^{-\lambda_t^\dagger})\right)$$

$$\text{Poi}\left(S_{ut}(1 - e^{-\lambda_t^\dagger}) + S_{vt}(1 - e^{-(1-\phi)\lambda_t^\dagger})\right)$$

Taylor approximation

$$1 - \exp(-\lambda_t^\dagger) \approx \lambda_t^\dagger$$

$$\text{Poi}\left(S_t(\phi)\lambda_t^\dagger\right)$$

$$\text{Poi}\left((S_{ut} + (1 - \phi)S_{vt})\lambda_t^\dagger\right)$$

Negligible number of infections

$$S_t(\phi) \approx (1 - \phi z)N$$

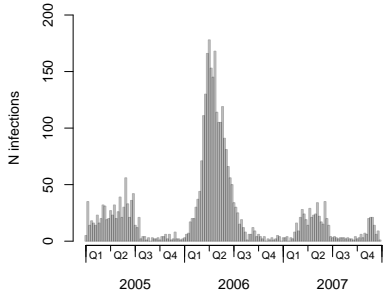
$$S_{ut} \approx (1 - z)N, \quad S_{vt} \approx zN$$

Ecologically-consistent vaccine model

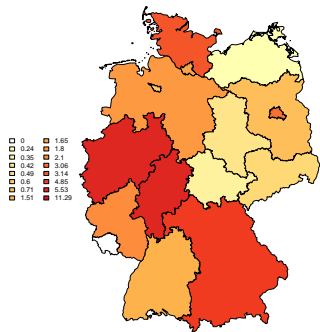
$$Y_{t+1} | \lambda_t^\dagger, \phi \sim \text{Poisson}\left(\lambda_t^\dagger(1 - \phi z)N\right)$$

Measles in Germany: Toy illustration

Cases by week



Cases per 100,000



Ecological Measles Model

Include area-specific random effects and seasonal effects in the endemic component.

Data Model: Y_{it} are counts over a 2-week period:

$$Y_{it} | \mu_{it} \sim \text{Poisson}(N_i(1 - \phi z_i) \mu_{it}),$$

$$\mu_{it} = \lambda_i \frac{y_{i,t-1}}{N_i} + \nu_{it},$$

Prior Model:

$$\log \lambda_i = \alpha_{AR} + a_i,$$

$$\log \nu_{it} = \alpha_{EN} + b_i + \gamma \sin(2\pi t/26) + \delta \cos(2\pi t/26),$$

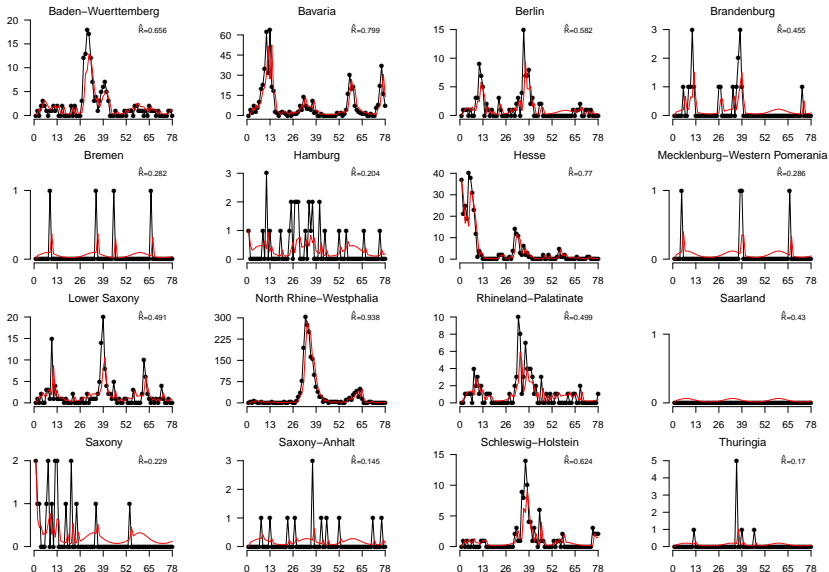
$$a_i \sim \text{N}(0, \sigma_{AR}^2),$$

$$b_i \sim \text{N}(0, \sigma_{EN}^2),$$

$$\phi \sim \text{Beta}(10, 2.5),$$

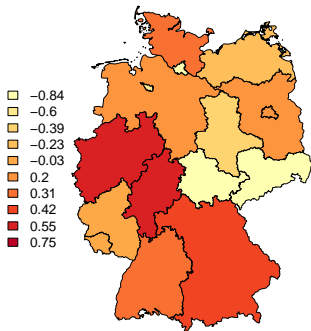
Fit using Hamiltonian Monte Carlo implemented in **Stan** (Carpenter et al., 2016).

Fitted values for measles in Germany

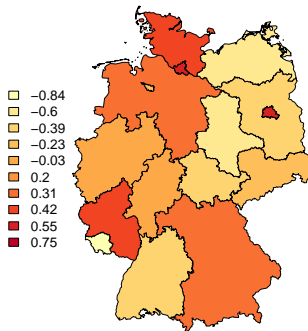


Component-specific random effect estimates

Self-area random effects \hat{a}_i



Environmental random effects \hat{b}_i



Estimates for measles in Germany

	Median	2.5%	97.5%
α_{AR}	0.87	-0.30	1.65
ϕ	0.91	0.64	0.99
α_{EN}	3.52	2.53	4.17
γ	0.71	0.55	0.86
δ	-0.20	-0.36	-0.04
σ_{AR}	0.70	0.28	1.66
σ_{EN}	0.53	0.27	0.96
R_0	2.38	0.74	5.22

- $\hat{\phi}$ agrees with known MMR vaccine effect.
- \hat{R}_0 is much smaller than known R_0 .
- Vaccination coverage is estimated.
- Frequency versus density dependent.
- Other values seem to be reasonable.

Table 1 : Posterior medians and 95% credible intervals for the measles biweekly data.

Discussion

So far, the Held et al. (2005) framework has not been extensively used to address policy (e.g., vaccination strategies), rather used as for labeling areas as **high**, or for **prediction** or **covariate** modeling (e.g., meteorological covariates are common).

Herzog et al. (2011) examined measles vaccination levels, but as we have seen the model used has limited interpretability.

Azman et al. (2012) investigated different vaccination campaigns for Cholera in Haiti, using a discrete-time model similar to Held et al. (2005).

Van Boeckel et al. (2016) examine vaccination strategies for HFMD using a TSIR model.

Discussion

Still needs further development:

- **Under-reporting**; some work with the integer autoregressive (INAR) model (Fernández-Fontelo et al., 2016).
- **Non-constant infectious period** (Wang et al., 2011).
- Fast implementations.
- **Social contact** data (Meyer and Held, 2017).
- **Ecological aspect**: fundamental problem is that we don't observe exact locations of cases.
- Combining disease and population data with other data sources, for example, from satellites.
- More **policy-driven** analyses.

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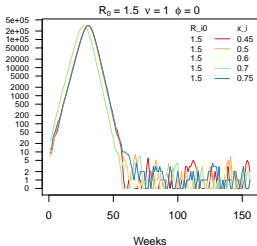
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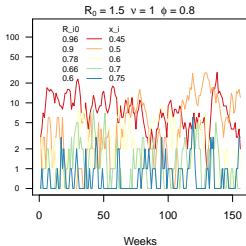
Partially vaccinated populations

We simulate data under either all-or-none or leaky assumption and compare following model fits:

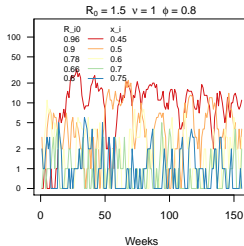
None



All-or-none

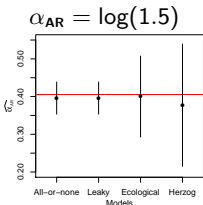


Leaky

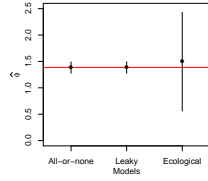
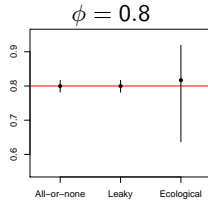
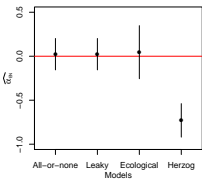
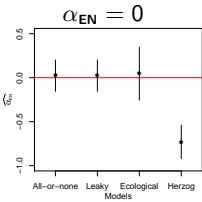
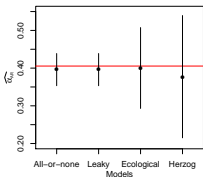


Compare results for fully observed all-or-none model, fully observed leaky model, ecological vaccine model, and Herzog epidemic model.

All-or-none



Leaky



- Ecological vaccine model has similar estimates as the fully observed models
- Fully observed models have smaller intervals compared to the ecological vaccine model (due to loss of information)
- Herzog is not estimating the same parameters