

# Automated and Early Detection of Disease Outbreaks

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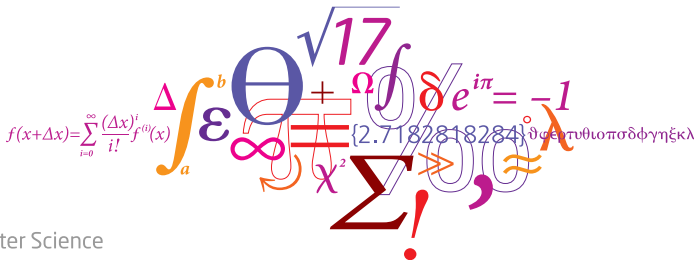
Master Thesis Project

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Technical University of Denmark

DTU Compute

Department of Applied Mathematics and Computer Science



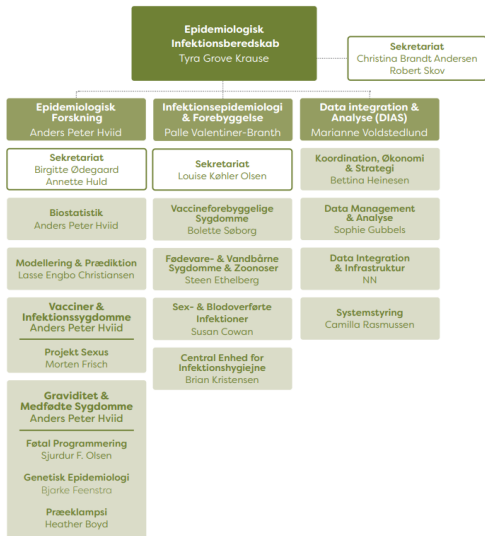
## Introduction

### About me

- MSc Eng., Quantitative Biology and Disease Modelling @ DTU
- Wife and three kids @ Vedbæk
- Passionate about e-Sports, particularly Counter Strike

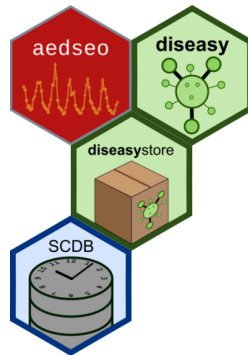


# Organisation of Epidemiological Infectious Disease Preparedness



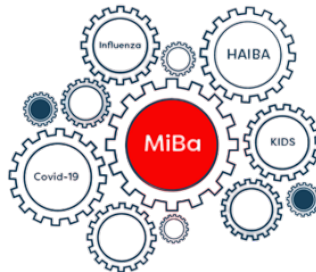
- A total of 39 employees
  - ... of which 6 are employed in Disease Dynamics & Forecasting
- High-quality research within
  - Genetic epidemiology
  - Pregnancy complications
  - Vaccine safety
  - Biostatistics
  - Modelling of the dynamics of infectious diseases

- Establish and maintain a model preparedness
  - Improve understanding of immunity over time
  - Manage lineages and mutations
- Wastewater monitoring
- Signal detection - automatically identify potential outbreaks
- Analyze and model excess mortality
- Antimicrobial resistance
  - Hospital network analysis - expansion of MiBAAlert
  - Focus on resistance in the population and its burden
- One Health





- Establishment of MiBa by SSI in 2010
- Great opportunity for data analysis
- No fully automated procedures in place at SSI



## State-of-the-art algorithms

State-of-the-art algorithms for aberration detection is presented in Salmon, Schumacher, and Höhle 2016 and implemented in the R package **surveillance**. The R package includes the method introduced by Farrington et al. 1996 together with the subsequently improved method proposed by Noufaily et al. 2013.

## Novel algorithm



The novel algorithm utilizes a generalized mixed effects model or a hierarchical mixed effects model as a modeling framework to model the count case observations  $\mathbf{y}$  and assess the unobserved random effects  $\mathbf{u}$ . These random effects are used directly to characterize an outbreak.

## Formulation of hierarchical models



### Poisson Normal

$$Y|u \sim \text{Pois}(\lambda \exp(u))$$

$$u \sim N(\mathbf{0}, I\sigma^2)$$

### Poisson Gamma

$$Y|u \sim \text{Pois}(\lambda u)$$

$$u \sim G(\mathbf{1}/\phi, \phi)$$



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$$u \sim G(1/\phi, \phi)$$

$$Y \sim \text{NB}(1/\phi, 1/(\lambda\phi + 1))$$

**Step 1: Modeling framework**

- Assume a hierarchical Poisson Normal or Poisson Gamma model to reference data using a log link
- Incorporate covariates by supplying a model formula on the form

$$\log(\lambda_{it}) = \mathbf{x}_{it}\boldsymbol{\beta} + \log(n_{it}), \quad i = 1, \dots, m, \quad t = 1, \dots, T \quad (1)$$

- Account for structural changes in the time series using a rolling window of width  $k$

## Step 2: Inference of random effects

- Infer one-step ahead random effects  $\hat{u}_{it_1}$  for each group using the fitted model
- Define outbreak detection threshold  $U_{t_0}$  as a quantile of the second stage model's random effects distribution
- Use either a Gaussian or Gamma distribution with respective plug-in estimates

**Step 3: Parameter estimations and outbreak detection**

- Compare inferred random effects  $\hat{u}_{it_1}$  to a threshold  $U_{t_0}$
- Raise an alarm if the inferred random effect exceeds the threshold, i.e.  $\hat{u}_{it_1} > U_{t_0}$
- Omit outbreak related observations from future parameter estimation

# Shiga toxin (verotoxin)-producing *Escherichia coli* (STEC)

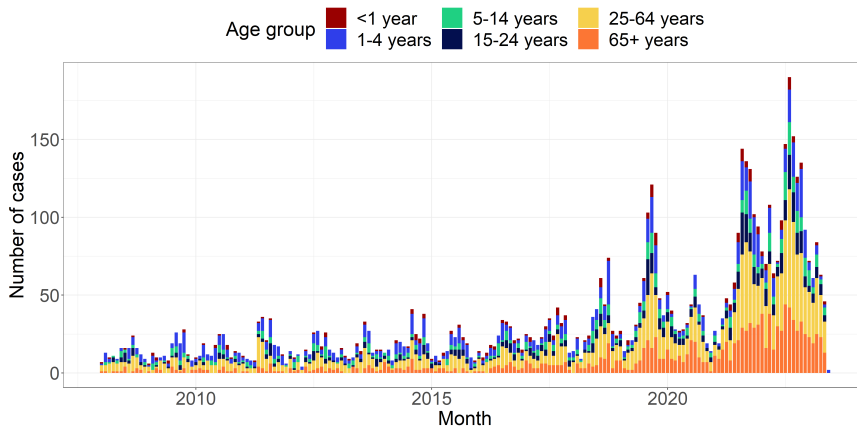


Figure: A stacked bar graph illustrating the number of monthly STEC cases observed in the period from 2008 to 2022 for the six age groups.

$$\log(\lambda_{it}) = \beta(\text{ageGroup}_i) + \log(n_{it}) \quad (2)$$

- $\lambda_{it}$  is the outbreak intensity at time  $t$  for age group  $i$
- $\beta(\text{ageGroup}_i)$  is the fixed effect specific to age group  $i$
- $\log(n_{it})$  acts as an offset, accounting for the population size at time  $t$  for age group  $i$

$$\log(\lambda_{it}) = \beta(\text{ageGroup}_i) + \beta_{trend}t + \log(n_{it}) \quad (3)$$

- In addition to constant model, includes a trend component
- $\beta_{trend}$  quantifies the rate of change in the outbreak intensity over time

$$\log(\lambda_{it}) = \beta(\text{ageGroup}_i) + \sin\left(\frac{2\pi \cdot \tau_t}{12}\right)\beta_{\sin} + \cos\left(2\frac{\pi \cdot \tau_t}{12}\right)\beta_{\cos} + \log(n_{it}) \quad (4)$$

- In addition to constant model, incorporates an annual seasonality pattern
- $\tau_t$  represents the time period  $t$  within a year (1-12)
- $\beta_{\sin}$  and  $\beta_{\cos}$  capture the effect of the seasonal pattern



## Combined trend and seasonality model

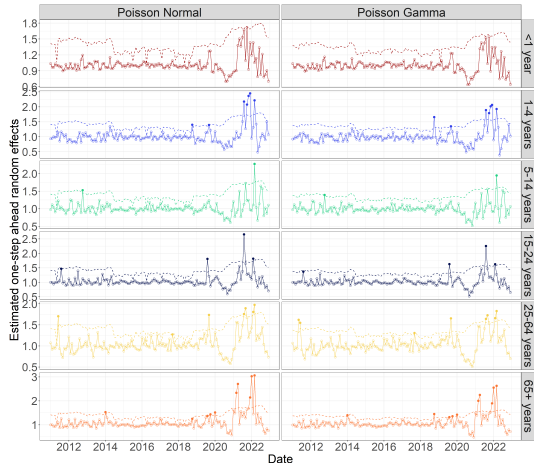
$$\log(\lambda_{it}) = \beta(\text{ageGroup}_i) + \beta_{trend}t + \sin\left(\frac{2\pi \cdot \tau_t}{12}\right)\beta_{\sin} + \cos\left(\frac{2\pi \cdot \tau_t}{12}\right)\beta_{\cos} + \log(n_{it}) \quad (5)$$

- Builds upon previous models, combining trend and seasonality components
- Includes both  $\beta_{trend}$ ,  $\beta_{\sin}$ , and  $\beta_{\cos}$  parameters

## Case study

## Estimated one-step ahead random effects

- A rolling window of width  $k = 36$  months is employed
- The combined model minimizes the logarithmic score
- Upper bound  $U_{t_0}$  is based on the 90% quantile of the random effects distribution
- If the one-step ahead random effects  $u_{it_1}$  exceeds  $U_{t_0}$  an alarm is raised
- 30 alarms are generated using the Poisson Normal framework, while 31 alarms are generated using the Poisson Gamma framework.
- A great number of alarms are generated in the period from March 2021 to March 2022



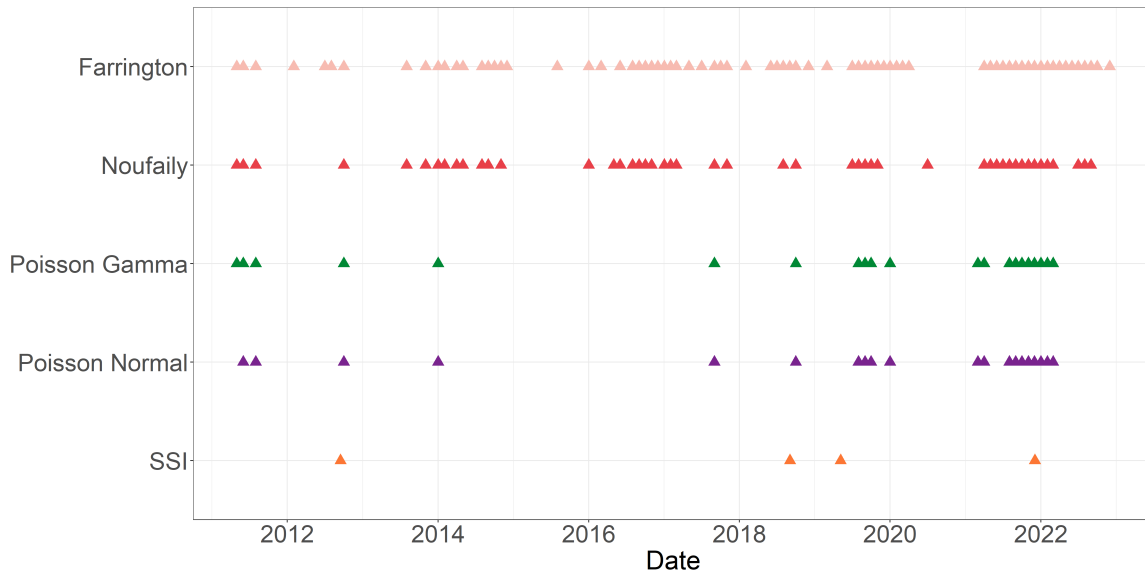
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# Performance of statistical outbreak detection algorithms

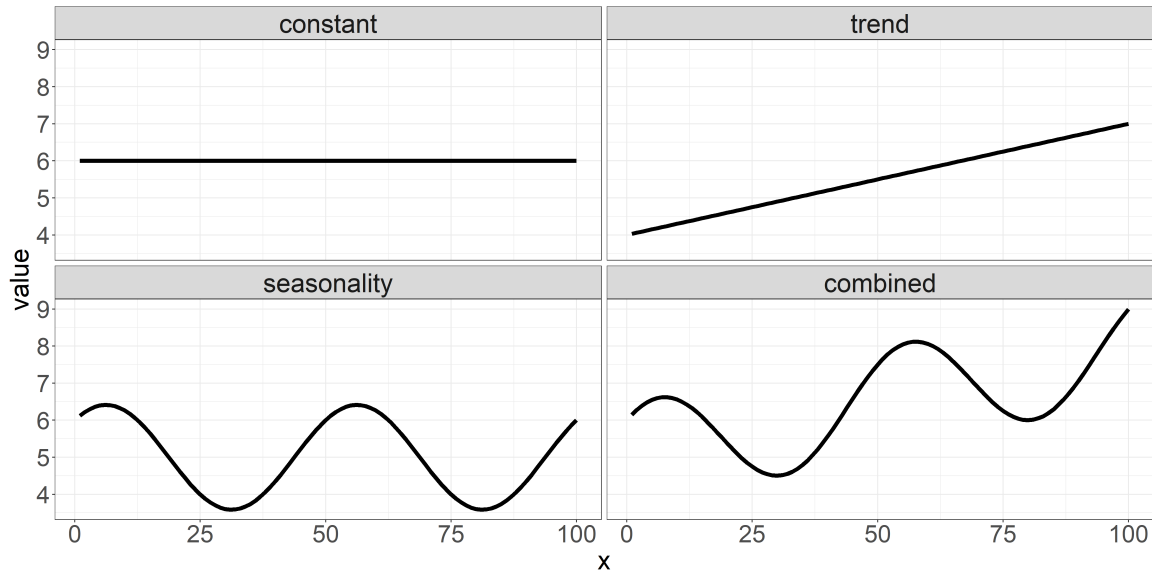


Simulated baseline data is generated according to a Negative Binomial distribution with mean  $\mu$  and a variance parameter  $\phi\mu$ . The equation for the mean  $\mu(t)$  is given as:

$$\mu(t) = \exp\left(\theta + \beta_{trend}t + \sum_{j=1}^m\left(\gamma_1 \cos\left(\frac{2\pi jt}{52}\right) + \gamma_2 \sin\left(\frac{2\pi jt}{52}\right)\right)\right) \quad (6)$$

Scenario	$\theta$	$\phi$	$\beta$	$\gamma_1$	$\gamma_2$	$m$	Trend
1	0.1	1.5	0.0000	0.00	0.00	0	0
2	0.1	1.5	0.0000	0.60	0.60	1	0
3	0.1	1.5	0.0025	0.00	0.00	0	1
4	0.1	1.5	0.0025	0.60	0.60	1	1
5	-2.0	2.0	0.0000	0.00	0.00	0	0
6	-2.0	2.0	0.0000	0.10	0.30	1	0
7	-2.0	2.0	0.0050	0.00	0.00	0	1
8	-2.0	2.0	0.0050	0.10	0.30	1	1
...	...	...	...	...	...	...	...
25	5.0	1.2	0.0000	0.00	0.00	0	0
26	5.0	1.2	0.0000	0.05	0.01	1	0
27	5.0	1.2	0.0001	0.00	0.00	0	1
28	5.0	1.2	0.0001	0.05	0.01	1	1

## Scenarios illustration



- Four outbreaks during baseline weeks (313-575), one outbreak during current weeks (576-624)
- Random constant value  $k$  is chosen
- Outbreak size  $v$  is generated from a Poisson distribution with mean equal to  $k$  times the standard deviation from the baseline data
- The  $v$  outbreak cases are distributed randomly in time according to a discretized log-normal distribution represented as  $Z \sim \lfloor \text{LN}(0, 0.5^2) \rfloor$

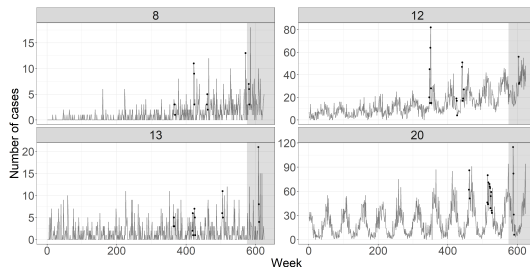
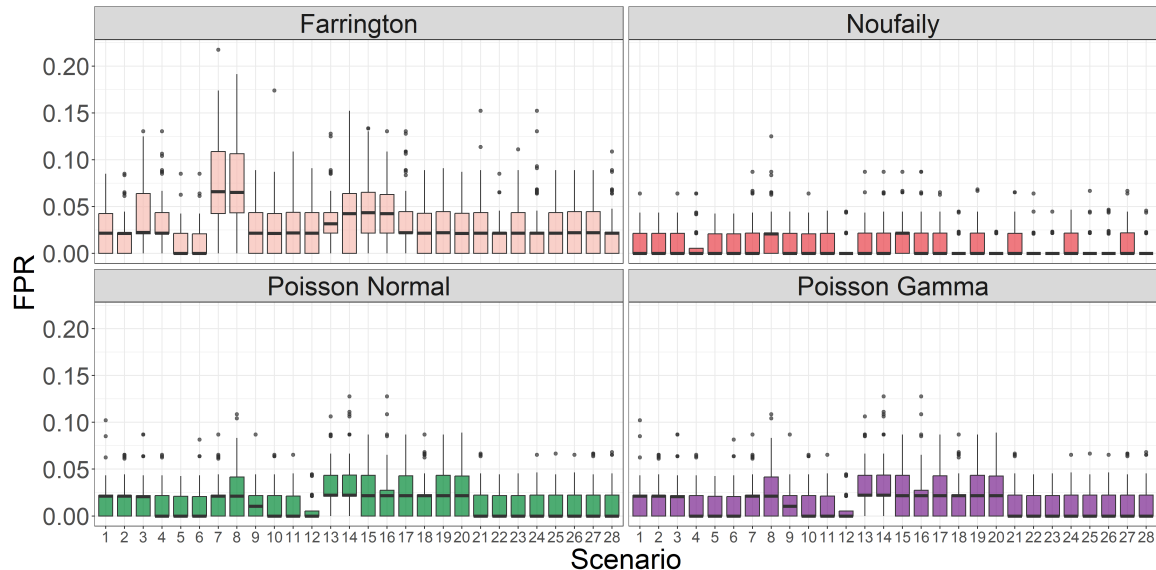


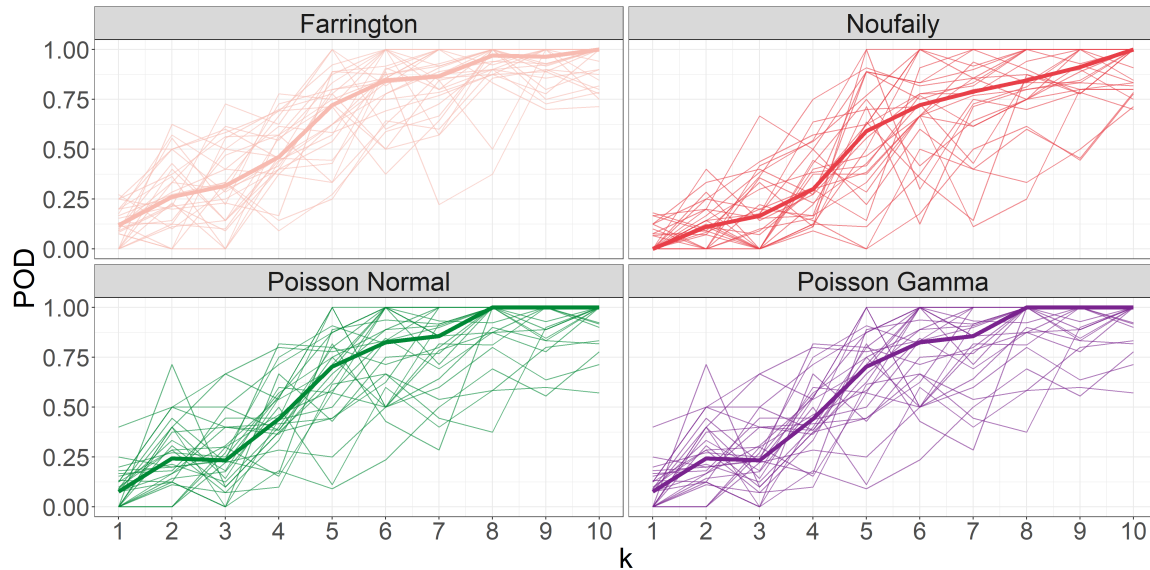
Figure: Plots of one randomly chosen realization for scenario 8, 12, 13, and 20.



## Simulation study

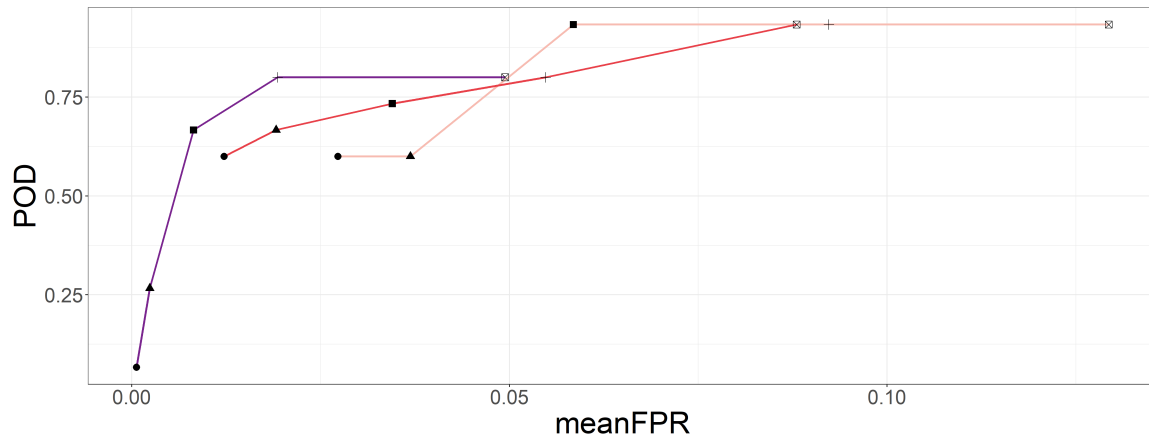
## False Positive Rates



**Probability an outbreak is detected**

## Simulation study

## Profile of POD vs FPR

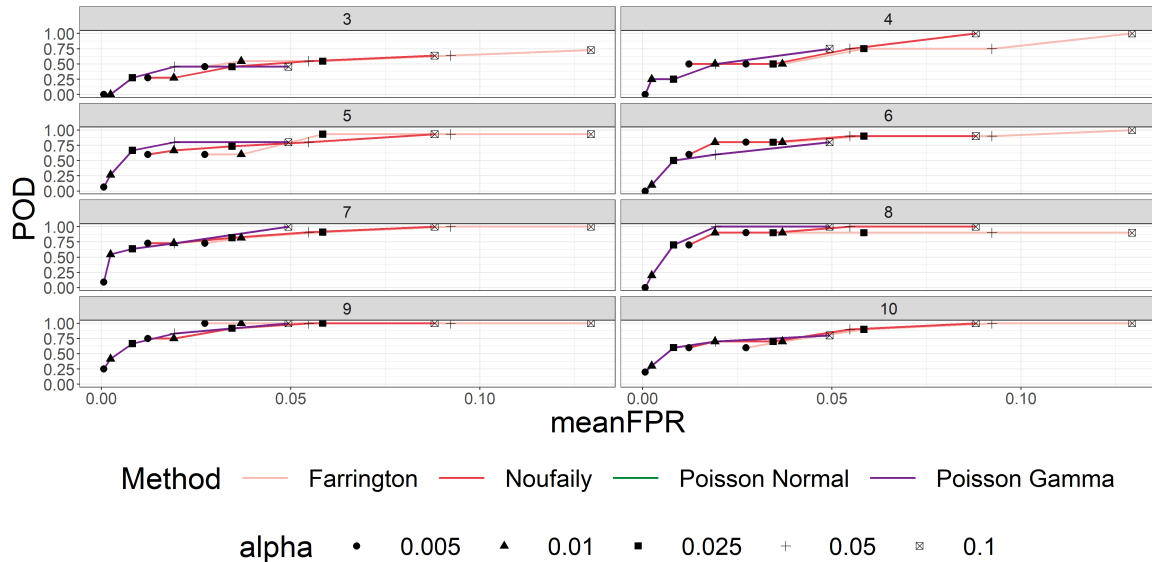


Method — Farrington — Noufaily — Poisson Normal — Poisson Gamma

alpha • 0.005 ▲ 0.01 ■ 0.025 + 0.05 ☒ 0.1

# Simulation study

## Profile of POD vs FPR for different outbreak sizes



- Easy incorporation of **covariates**
- Estimates are **consistent** across the two modeling frameworks
- Positively **identified outbreaks** coinciding with well-documented outbreaks
- Effectively **control the number of "false alarms"**
- Great potential in utilizing **MiBa-based surveillance**

- Farrington, C. P. et al. (1996). "A Statistical Algorithm for the Early Detection of Outbreaks of Infectious Disease". In: *Journal of the Royal Statistical Society. Series A (Statistics in Society)* 159.3, pp. 547–563. ISSN: 09641998, 1467985X. URL: <http://www.jstor.org/stable/2983331> (visited on 01/27/2023).
- Noufaily, Angela et al. (2013). "An Improved Algorithm for Outbreak Detection in Multiple Surveillance Systems". en. In: *Online Journal of Public Health Informatics* 32.7, pp. 1206–1222.
- Salmon, Maëlle, Dirk Schumacher, and Michael Höhle (2016). "Monitoring Count Time Series in R: Aberration Detection in Public Health Surveillance". In: *Journal of Statistical Software* 70.10, pp. 1–35. DOI: 10.18637/jss.v070.i10. URL: <https://www.jstatsoft.org/index.php/jss/article/view/v070i10>.

$$\begin{aligned} P[Y = y] &= g_Y(y; \beta, \phi) \\ &= \frac{\lambda^y}{y! \Gamma(1/\phi) \phi^{1/\phi}} \frac{\phi^{y+1/\phi} \Gamma(y + 1/\phi)}{(\lambda\phi + 1)^{y+1/\phi}} \\ &= \frac{\Gamma(y + 1/\phi)}{\Gamma(1/\phi) y!} \frac{1}{(\lambda\phi + 1)^{1/\phi}} \left( \frac{\lambda\phi}{\lambda\phi + 1} \right)^y \\ &= \binom{y + 1/\phi - 1}{y} \frac{1}{(\lambda\phi + 1)^{1/\phi}} \left( \frac{\lambda\phi}{\lambda\phi + 1} \right)^y, \quad \text{for } y = 0, 1, 2, \dots \end{aligned} \tag{7}$$

where the following convention is used

$$\binom{z}{y} = \frac{\Gamma(z + 1)}{\Gamma(z + 1 - y) y!} \tag{8}$$

The marginal distribution of  $Y$  is a negative binomial distribution,  $Y \sim \text{NB}(1/\phi, 1/(\lambda\phi + 1))$

The probability function for the conditional distribution of  $Y$  for given  $u$

$$f_{Y|u}(y; u, \beta) = \frac{(\lambda u)^y}{y!} \exp(-\lambda u) \quad (9)$$

and the probability density function for the distribution of  $u$  is

$$f_u(u; \phi) = \frac{1}{\phi \Gamma(1/\phi)} \left( \frac{u}{\phi} \right)^{1/\phi-1} \exp(-u/\phi) \quad (10)$$



Given (9) and (10), the probability function for the marginal distribution of  $Y$  is determined from

$$\begin{aligned} g_Y(y; \beta, \phi) &= \int_{u=0}^{\infty} f_{Y|u}(y; u, \beta) f_u(u; \phi) du \\ &= \int_{u=0}^{\infty} \frac{(\lambda u)^y}{y!} \exp(-\lambda u) \frac{1}{\phi \Gamma(1/\phi)} \left(\frac{u}{\phi}\right)^{1/\phi-1} \exp(-u/\phi) du \\ &= \frac{\lambda^y}{y! \Gamma(1/\phi) \phi^{1/\phi}} \int_{u=0}^{\infty} u^{y+1/\phi-1} \exp(-u(\lambda\phi + 1)/\phi) du \end{aligned} \quad (11)$$

In (11) it is noted that the integrand is the *kernel* in the probability density function for a Gamma distribution,  $G(y + 1/\phi, \phi/(\lambda\phi + 1))$ . As the integral of the density shall equal one, we find by adjusting the norming constant that

$$\int_{u=0}^{\infty} u^{y+1/\phi-1} \exp\left(-u/(\phi/(\lambda\phi + 1))\right) du = \frac{\phi^{y+1/\phi} \Gamma(y + 1/\phi)}{(\lambda\phi + 1)^{y+1/\phi}} \quad (12)$$

and then (7) follows