Salmonella outbreaks: Assessing causes and trends

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Background Information

- What is *salmonella*?
  - Rod shaped bacteria
  - Causes 2 diseases called salmonellosis
    - enteric fever
    - acute gastric enteritis
  - Most common causes are raw meat, raw eggs, raw shellfish or unpasteurized animal products such as milk and cheese
  - Not harmful until it is ingested
  - Most harmful to compromised immune systems

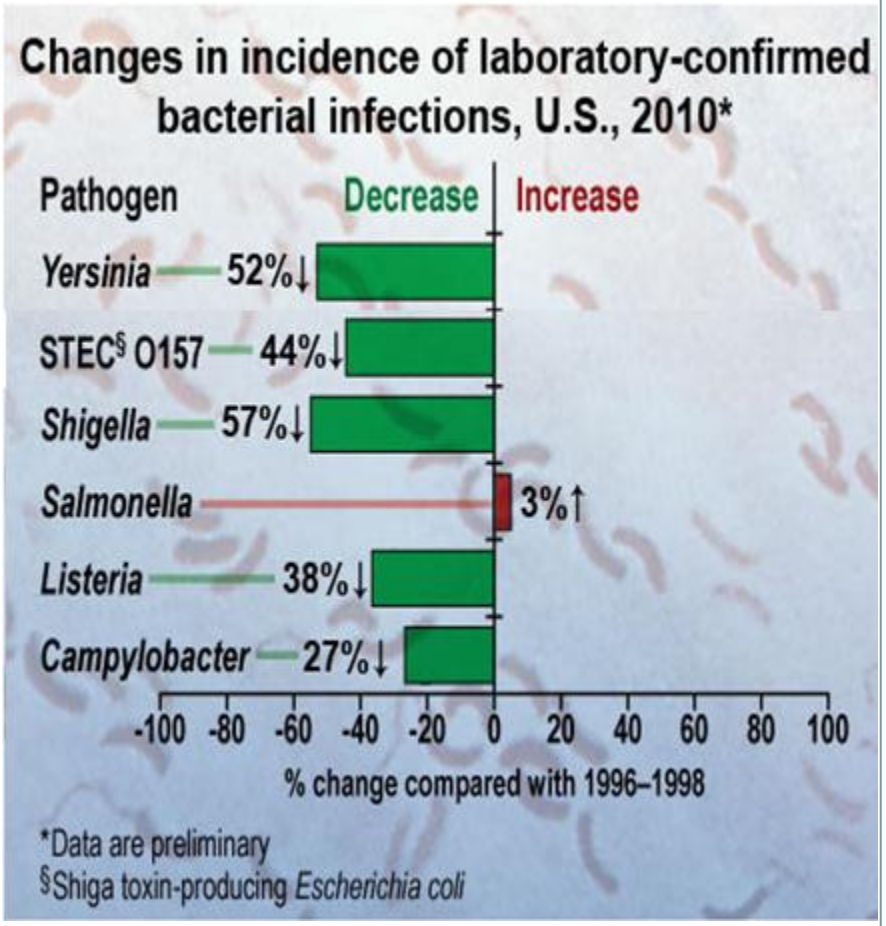
Background Information

- Symptoms:
  - Nausea
  - Vomiting
  - Abdominal pain
  - Diarrhea
  - Fever
  - Blood in the stool
  - 12-72 hours after ingestion

Severe cases of salmonella end up in dehydration, leading to a possible death.

Public Health Concern

- Actual number of infections could be thirty or more times greater (CDC)
- 1.2 million U.S. illnesses annually
- Most common cause of hospitalization and death tracked by FoodNet
- Incidence of Salmonella was nearly three times the 2010 national health objective target.
- Lab results since 1998 shows a positive trend

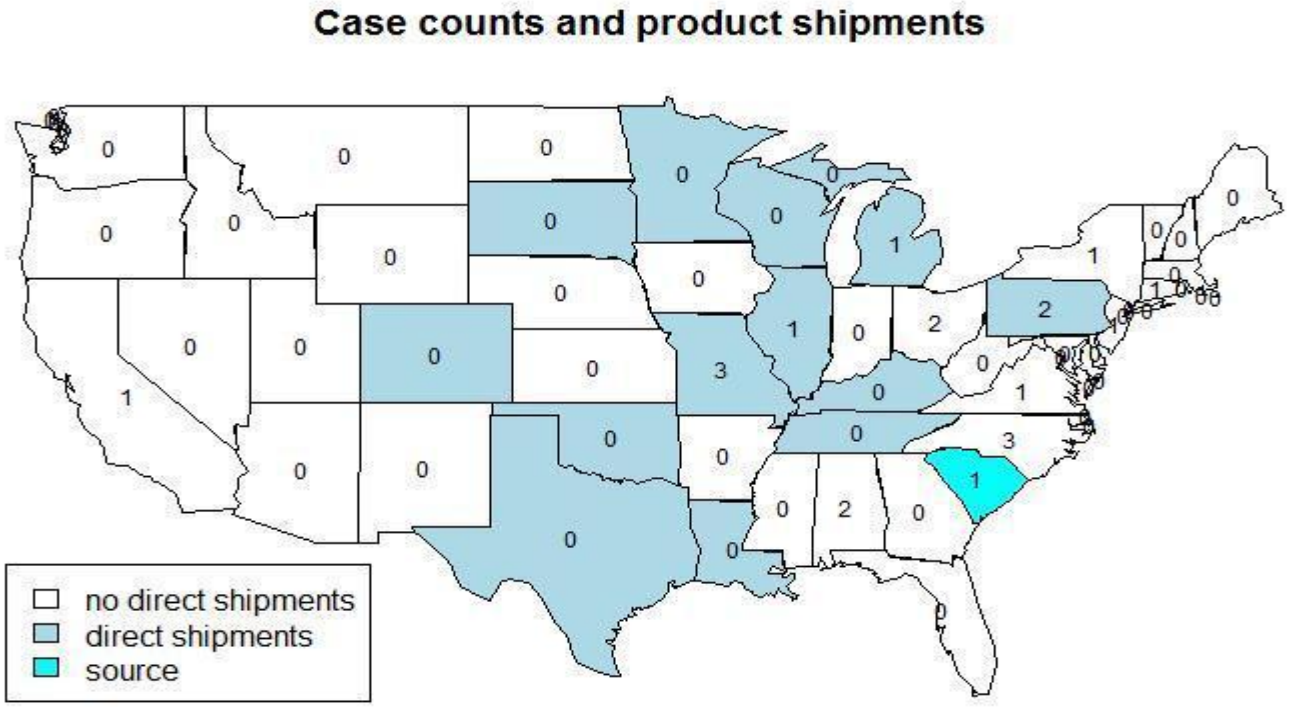


http://www.cdc.gov/foodborneburden/trends-in-foodborne-illness.html

Diamond Pet Food

- Manufacturer linked to *Salmonella Infantis* outbreak in humans
- Location: Gaston, SC
- Detected through random sampling –by MDARD
- Recall occurred April 2nd
- Infections identified from October 2011 – June 2012
- Illnesses caused by improper handling of pet food or feces

Infantis Outbreak(Diamond Pet Food)

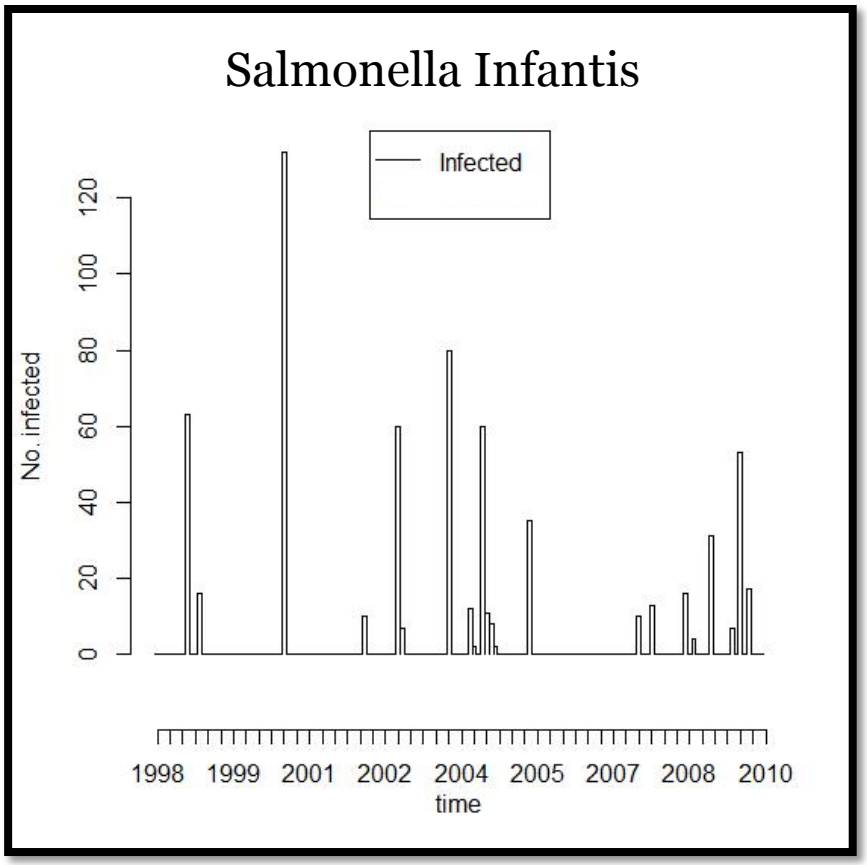


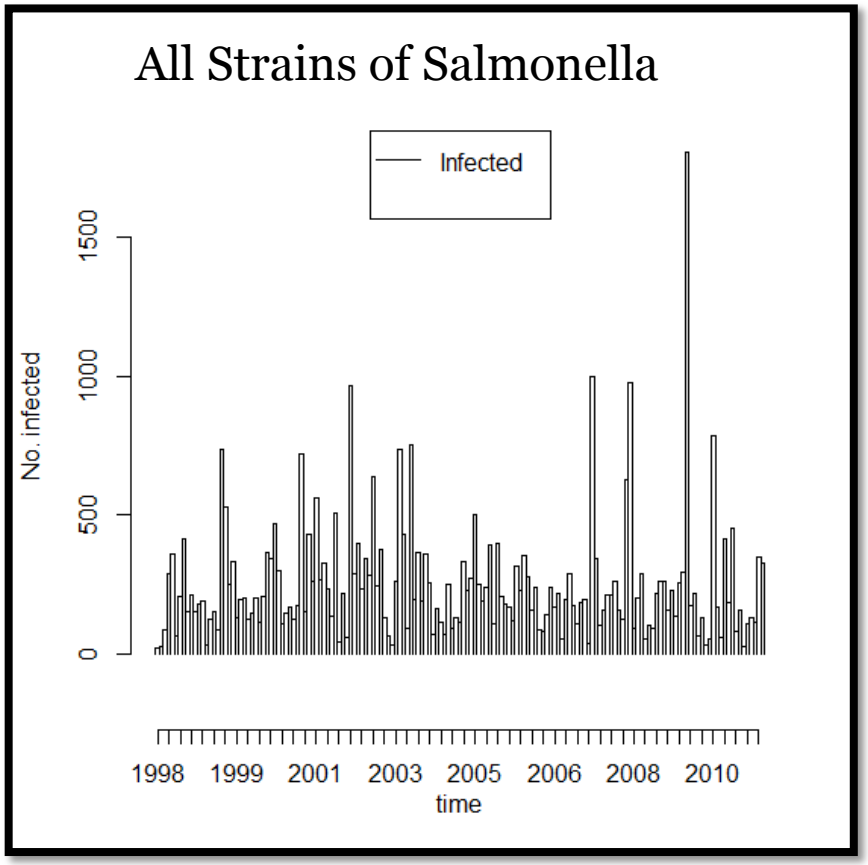
Cases:

- Number: 22
- Death: 0
- Hospitalizations: 6

Original S code by Richard A. Becker and Allan R. Wilks. R version by Ray Brownrigg. Enhancements by Thomas P Minka <surname@stat.cmu.edu>. (2012). maps: Draw Geographical Maps. R package version 2.2-6. http://CRAN.R-project.org/package=maps

Data





http://www.cdc.gov

Research Approach

Method: Bayesian Statistics

1. Analysis using Models:
   - Poisson Changepoint Model
     - *Fitted using Markov Chain Monte Carlo*
   - Poisson-Gamma Model
     - *Fitted Using Analytic Computation*

1. Simulation Study:
   - Simulate data comparable to our data set.
   - Run 1000 data sets for each set of parameters.

Research Approach

- Overall Goal:

  Understand outbreak trends of Salmonella Infantis

- Analysis Goals:
  - *Model comparison.*
  - *Data set comparison.*

- Simulation Goals:
  - *Determine most influential parameters.*
    - *Characteristics of the Data*
    - *How the analysis is conducted*
  - *Determine if we are correctly identifying the number of outbreaks in a time span.*

Research Approach

- Analysis Hypotheses:
  - *Our two models will produce similar results.*
- Simulation Hypotheses:
  - The frequency and magnitude of outbreaks will be the most influential factors in detecting the correct number of outbreaks.
  - A smaller upper bound probability will produce more accurate count of outbreaks.

Bayesian Statistics

- **Purpose:** *Provides a mathematically rigorous way of combining data from different sources to estimate model parameters and predict future data*

- **Model Quantities:**
  - λ = *parameter. (Poisson mean)*
  - Y = *preceding data point. (Poisson variable)*
  - Y_{new} = *data point that we are analyzing. (current month)*

Bayesian Statistics

- **Calculation Technique**: Bayes Rule

$$p(\lambda) = prior\ distribution$$

$$\downarrow$$

$$p(Y|\lambda) = likelihood$$

$$\downarrow$$

$$p(\lambda|Y) = posterior\ distribution$$

$$\propto prior\ *\ likelihood$$

$$\downarrow$$

$$p(Y_{new}|Y) = posterior\ predictive\ density$$

Bayesian Statistics

Posterior Predictive Distribution:

Formula:

$$P(Ynew|Y) = \int p(Ynew|\lambda) \cdot p(\lambda|Y)\ d\lambda,$$

Conditional Probabilities Defined:

- $P(Ynew|Y)$: posterior predictive probability dist.
- $P(Y|\lambda)$: likelihood distribution
- $P(\lambda|Y)$: posterior density

Poisson Changepoint Model

- Allows the parameters of the Poisson distribution to change over time
- MCMCpoissonChange generates a sample from the posterior distribution of a Poisson regression model with multiple changepoints.
- MCMCpoissonChange function defaults settings:
  - MCMCpoissonChange(
    formula, data = parent.frame(), m = 1, b0 = 0, B0 = 1, a= NULL,
    b = NULL, c0 = NA, d0 = NA, burnin = 1000, mcmc = 1000, thin = 1,
    verbose = 0, seed = NA, beta.start = NA , P.start = NA,
    marginal.likelihood = c("none", "Chib95"), ...)

Poisson Changepoint Model

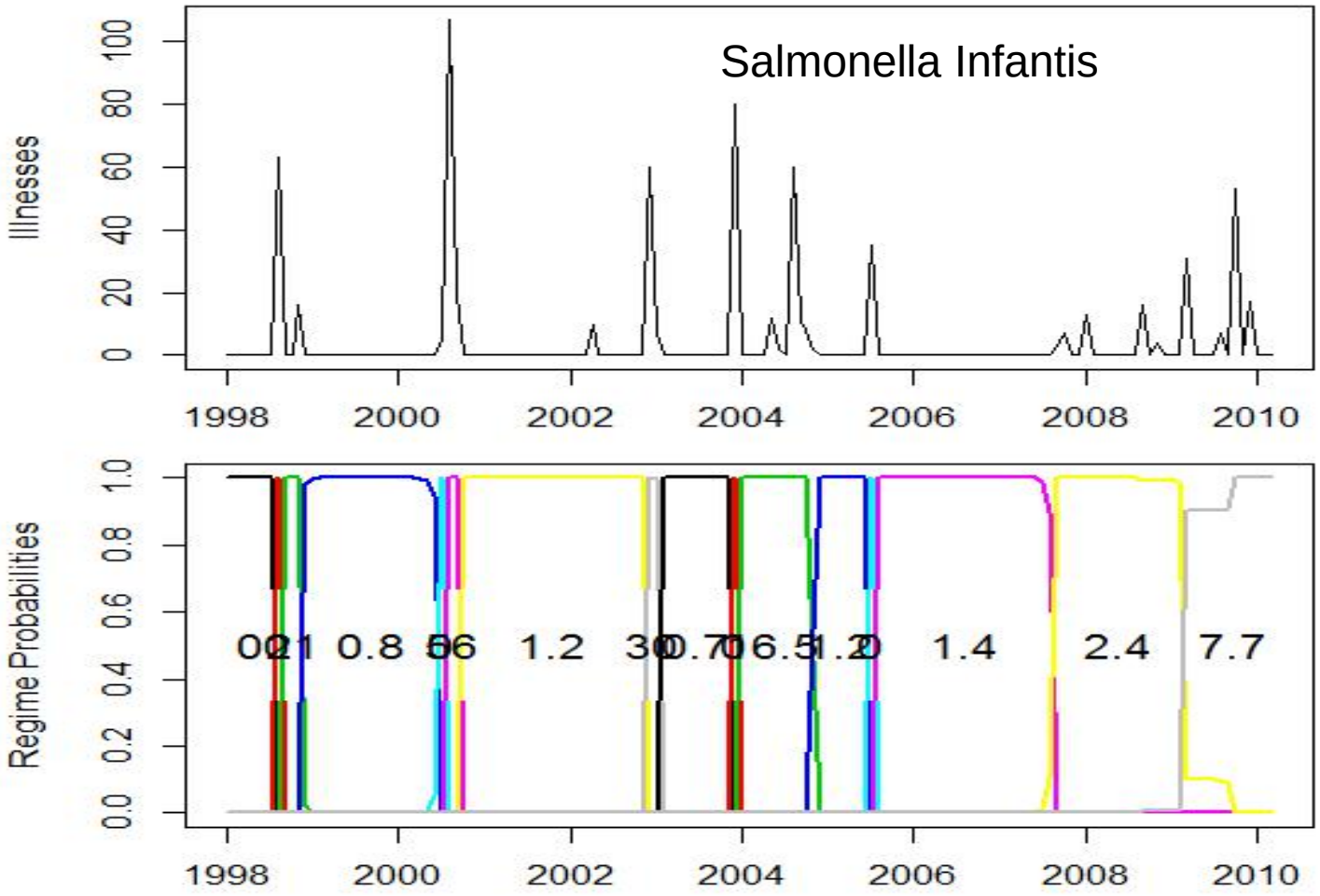
- BayesFactor(): best model is the model with highest log marginal likelihood (Method of Chib)

Andrew D. Martin, Kevin M. Quinn, Jong Hee Park (2011). MCMCpack: Markov Chain Monte Carlo in R. Journal of Statistical Software. 42(9): 1-21. URL http://www.jstatsoft.org/v42/i09/.

Sylvia Fruhwirth-Schnatter and Helga Wagner 2006. "Auxiliary Mixture Sampling for Parameter-driven Models of Time Series of Counts with Applications to State Space Modelling." Biometrika. 93:827–841.

Siddhartha Chib. 1998. "Estimation and comparison of multiple change-point models." Journal of Econometrics. 86: 221-241.

Changepoint Graph



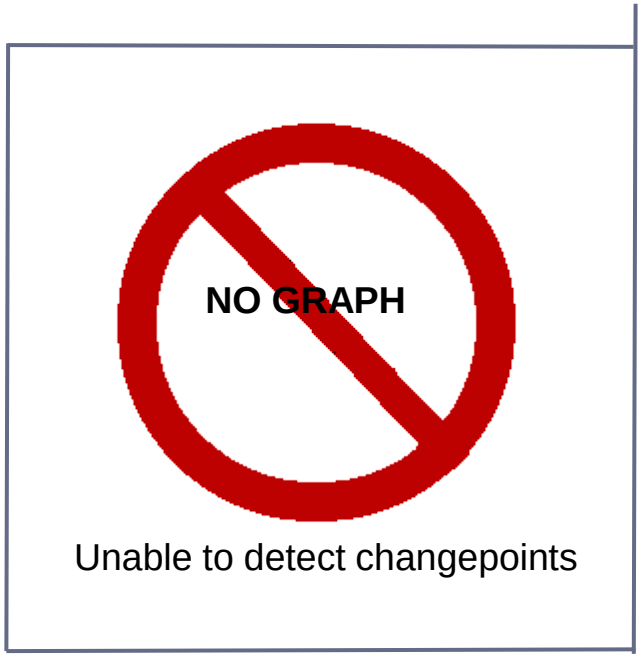
Poisson Means

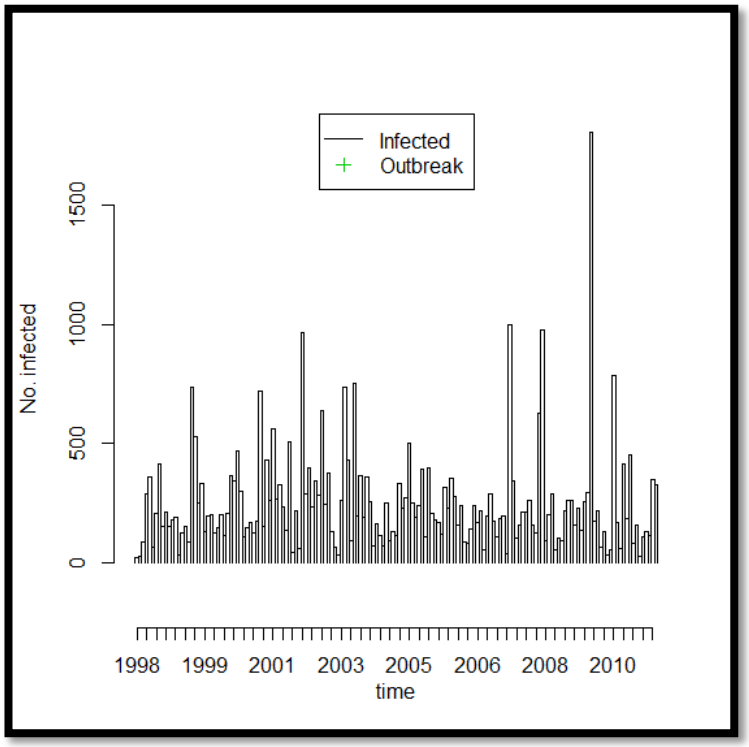
- 0
- 21
- 0.84
- 0
- 56
- 1.15
- 30
- 0.7
- 0
- 16.5
- 1.25
- 0
- 1.4
- 2.39
- 7.71

Package: MCMCpack

Changepoint Graph

Total Salmonella





Package: MCMCpack

Bayesian Poisson-Gamma

- Poisson likelihood; gamma prior; Negative Binomial posterior predictive
- Fits a poisson-gamma model to data to determine which timepoints are improbably large compared to previous data values
- Bayes Algorithm for surveillance
  - algo.bayes(disProgObj, control = list(range = range, b = 0, w = 6, actY = TRUE, alpha=0.05))

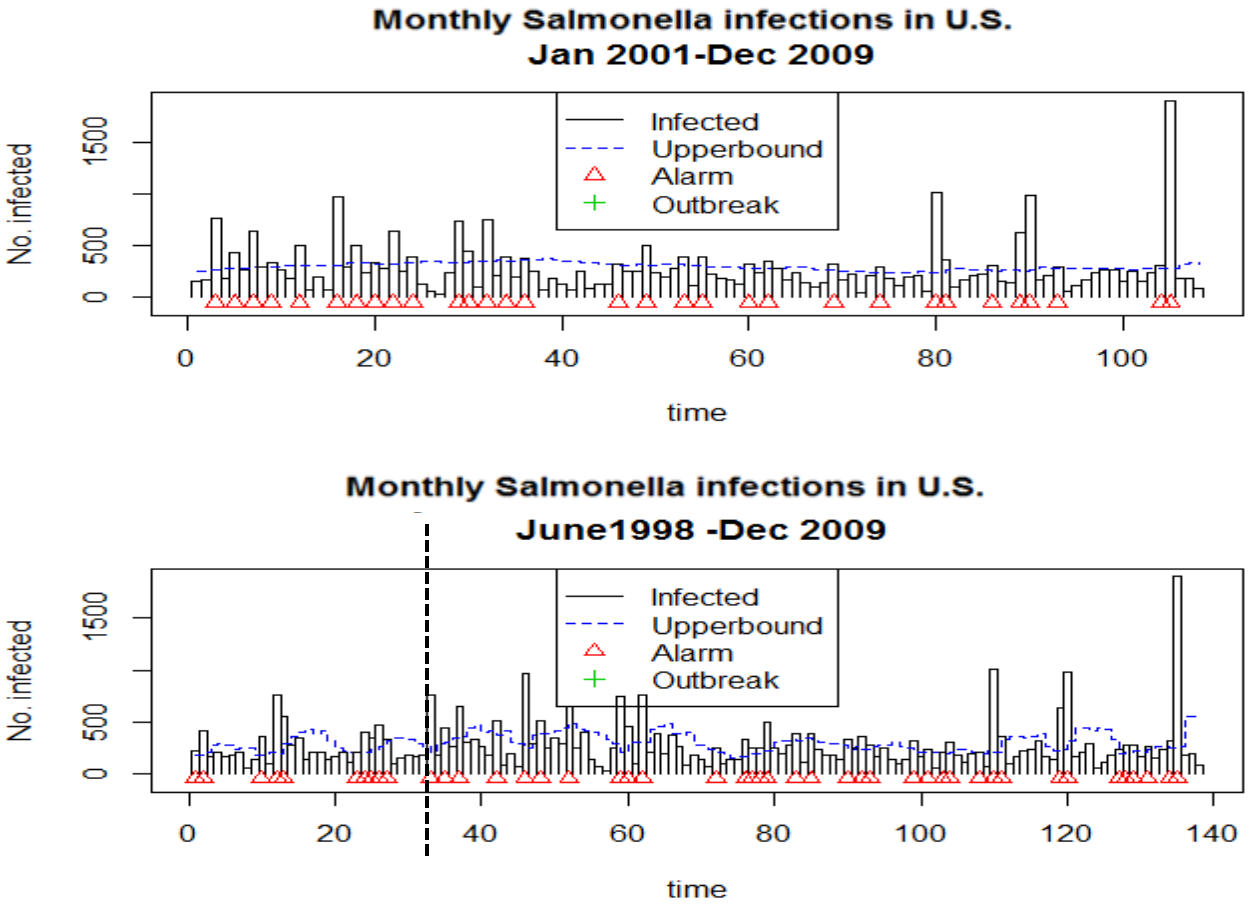
surveillance: An R package for the surveillance of infectious diseases (2007), M. Hoehle, Computational Statistics, 22(4), pp.571--582.

Riebler A (2004) Empirischer Vergleich von statistischen Methoden zur Ausbruchserkennung bei Surveillance
Daten. Bachelor's thesis, Department of Statistics, University of Munich

Predicting Alarms

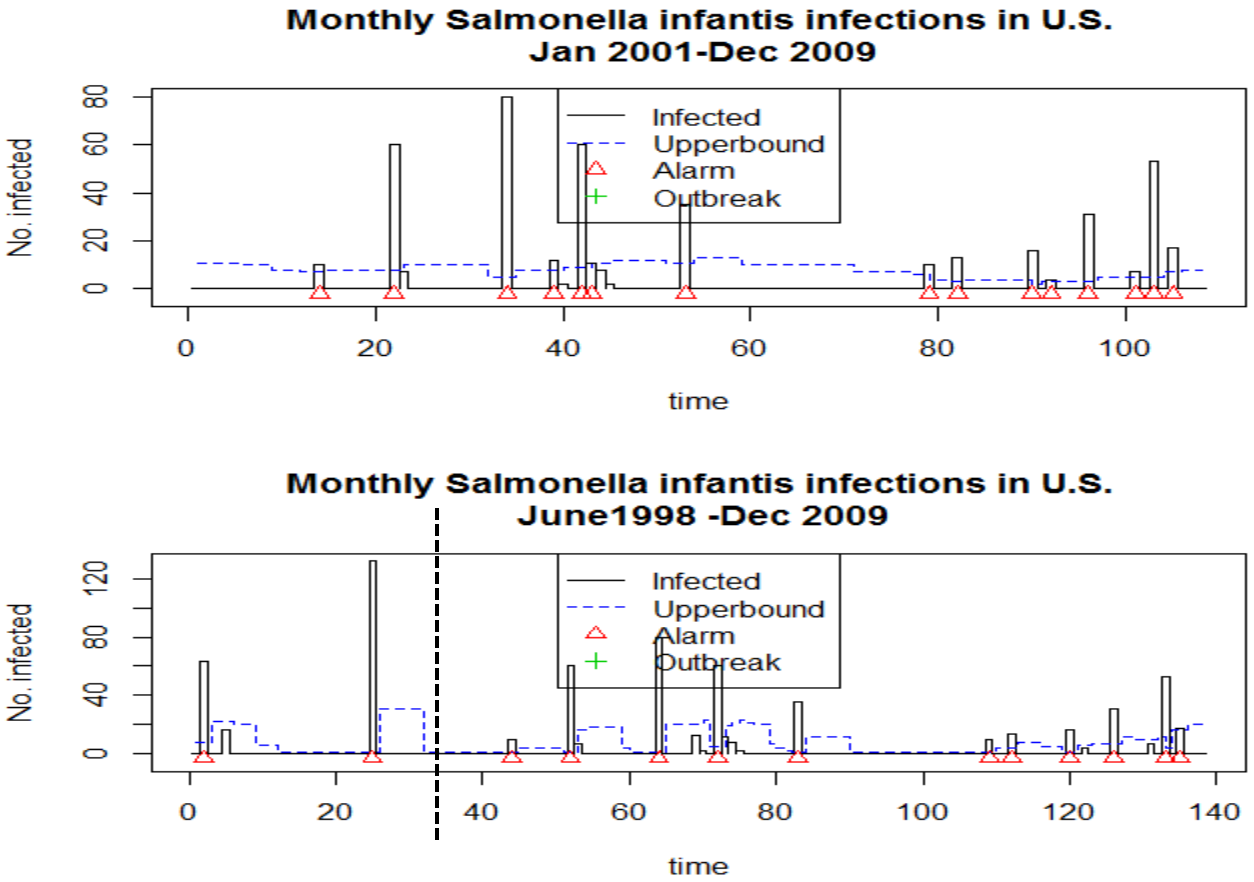
- Based on posterior predictive distribution, Bayes algorithm creates a maximum typical value
- Depends on probability level set by user (α)
- Based on preceding data, there is a $(1-\alpha)$ probability that the current month case count will be at or below the upper bound
- If value is above upper bound, flagged as alarm

Total Salmonella Epi Curve



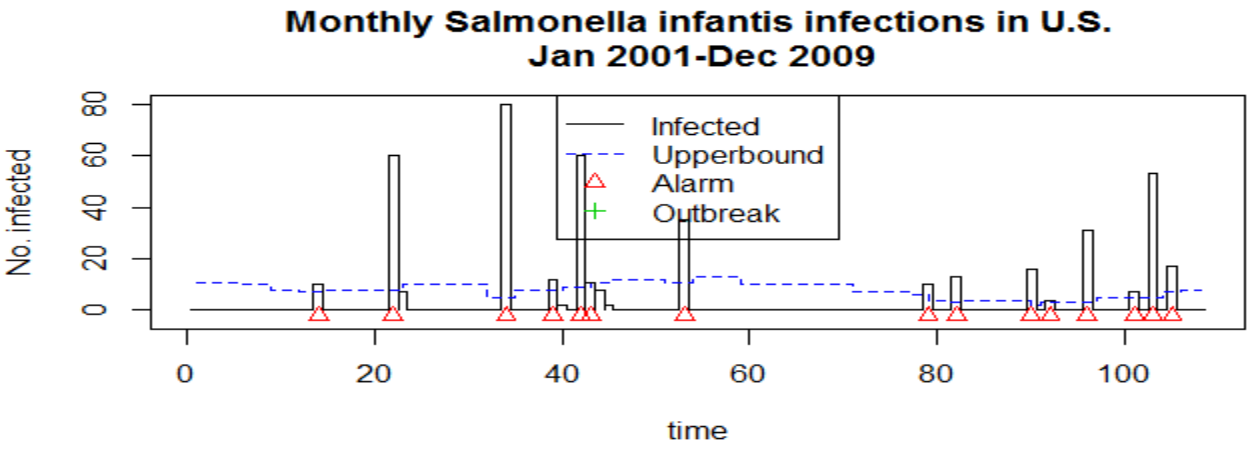
Window width: 6 versus 36 months

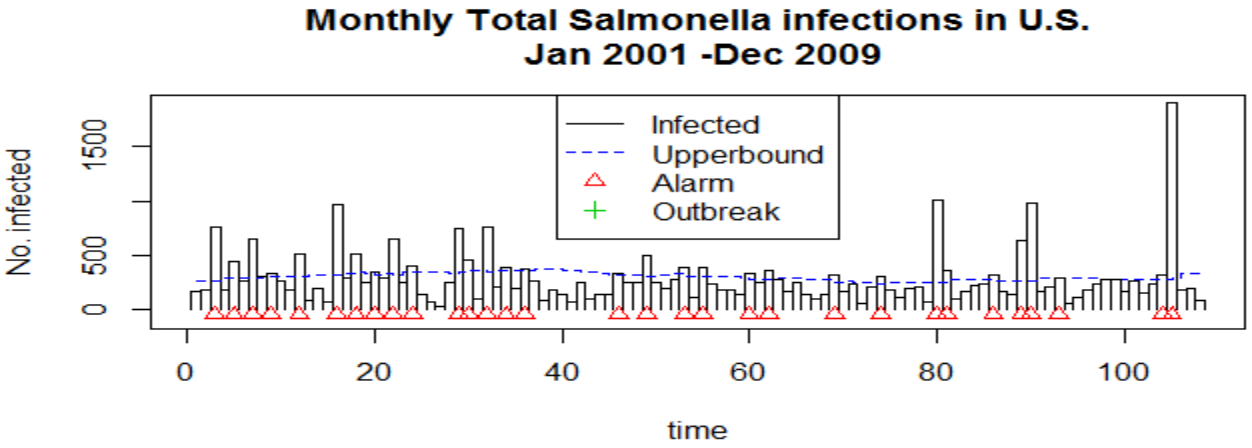
Infantis Epi Curve



Window width: 6 versus 36 months

Epi Curves





Window width: 36 months ; Salmonella versus Salmonella Infantis

Package: Surveillance

Simulation Study

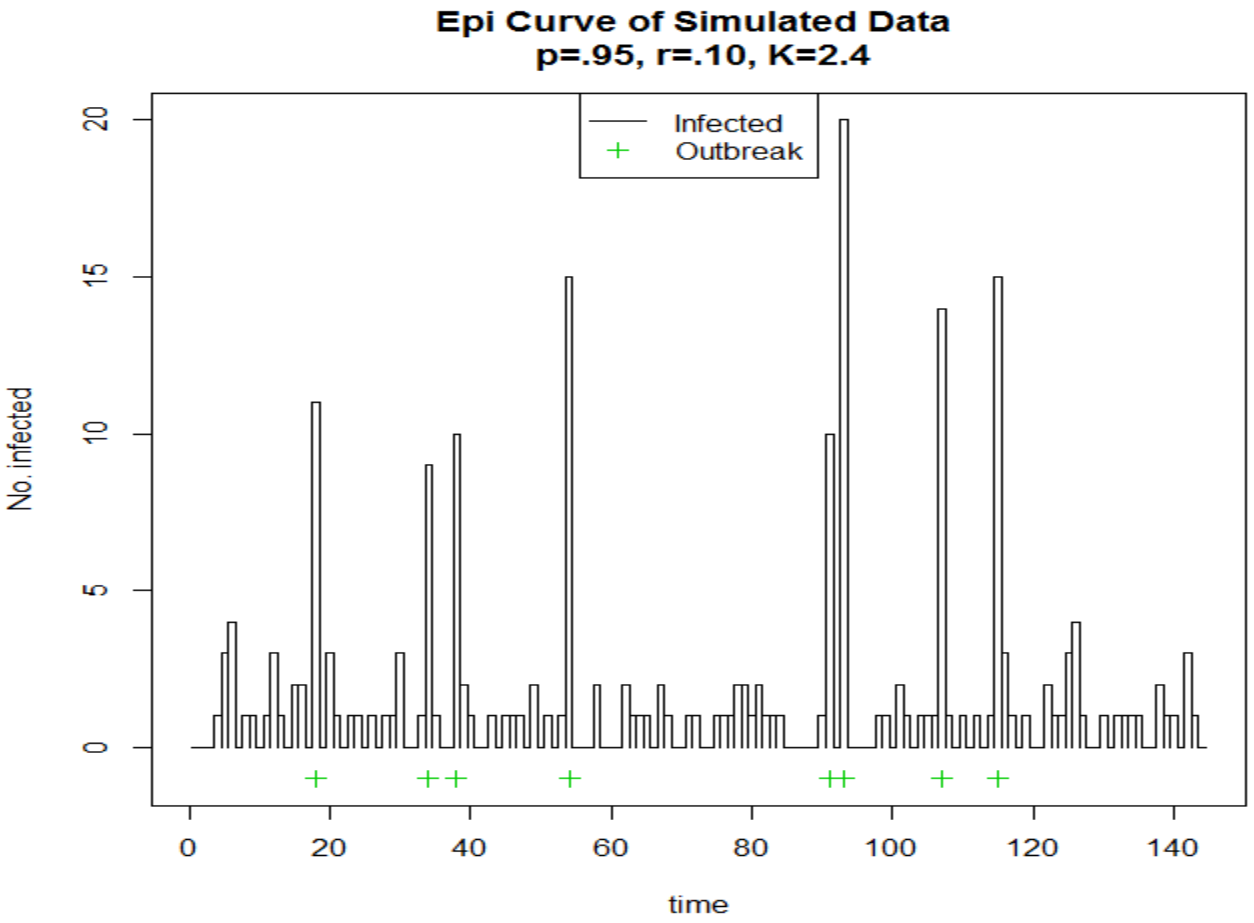
- Test performance of the Poisson-Gamma method
- Using surveillance package
  - Sim.pointSource – simulates
  - Algo.bayes – analyzes
- Use to determine which factors are most influential in detecting an outbreak
- Sim.pointSource
  - sim.pointSource(p = 0.99, r = 0.5, length = 400, A = 1, alpha = 1, beta = 0, phi = 0, frequency = 1, state = NULL, K = 1.7)

surveillance: An R package for the surveillance of infectious diseases (2007), M. Hoehle, Computational Statistics, 22(4), pp.571--582.

Simulation Study

- Parameters that describe the data
  - P= probability of not being in an outbreak, given that there is no current outbreak (frequency of outbreaks)
  - R= probability of staying in an outbreak, given that there is an outbreak (duration of outbreaks)
  - K= factor by which the background incidence rate is multiplied to obtain the outbreak incidence rate (magnitude of outbreaks)
- Parameters that describe the analysis
  - W=window of data (estimating background rate of incidence)
  - α= upper bound probability for detecting outbreaks
- Hypothesis: P and K will be most influential

Example of Simulated Data



Simulation Study: Code

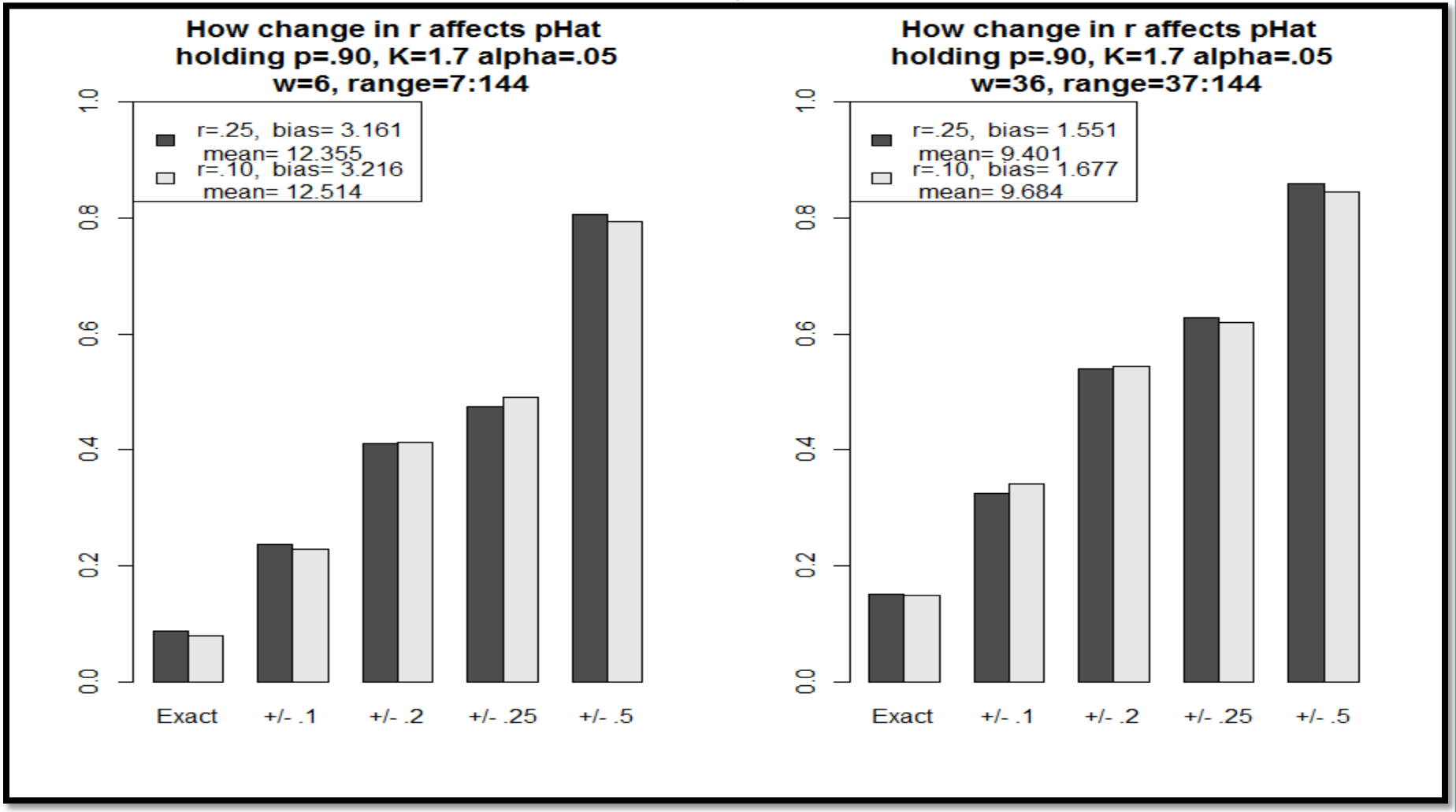
```
survsim=function(p,r,k,nsets, alpha,w){
        trueCount<-rep(NA, nsets)
        estCount<-rep(NA,nsets)
        for (i in 1:nsets){
            #Simulate the disProg object using specified parameters
                object<-sim.pointSource(p=p, r=r, length=144, A=0, alpha=.001,
                        beta=0, phi=0, frequency=12, state=NULL, K=k)
                #Counts number of actual outbreaks in simulated object
                #If more than one outbreak month in a row, only counts it once
                 trueCount[i]<-sum(diff(c(object$state[(w+1):144],0))==-1)
                #Performs algo bayes analysis on simulated object
                res <- algo.bayes(object, control=list( w=w, range=(w+1):144, alpha=alpha))
                #Counts number of detected outbreaks in simulated object
                #If more than one outbreak month in a row, only counts it once
                 estCount[i]<-sum(diff(c(res$alarm,0))==-1)        }
        #Returns list of true counts, estimated counts, as well as
        #specified parameters to identify simulation
        return(list(trueCount=trueCount, estCount=estCount, p=p, r=r, k=k))
}
```

Simulation Study: Code

```
survinterval<- function(a){
        exact<- sum(a$estCount==a$trueCount)/length(a$trueCount)
        int1<- sum((.9*a$trueCount<=a$estCount)&(a$estCount<=1.1*a$trueCount))/length(a$trueCount)
        int2<- sum((.8*a$trueCount<=a$estCount)&(a$estCount<=1.2*a$trueCount))/length(a$trueCount)
        int3<- sum((.75*a$trueCount<=a$estCount)&(a$estCount<=1.25*a$trueCount))/length(a$trueCount)
        int4<- sum((.5*a$trueCount<=a$estCount)&(a$estCount<=1.5*a$trueCount))/length(a$trueCount)
        phat<- c(exact, int1, int2, int3, int4)
        #compute a 95% confidence interval for the population proportion using pHat as a point  estimator
        res<-matrix(rep(NA, 2*length(phat)), ncol=2)
        dimnames(res)<- list(c("exact", "+/- .1", "+/- .2", "+/- .25", "+/- .5"),
                c("Lower Bound", "Upper Bound"))
        for(i in 1: length(phat)){
                res[i,]<-phat[i]+c(-1,1)*1.96*sqrt(phat[i]*(1-phat[i])/length(a$trueCount))
        }
        #Compute bias
        bias<- mean(a$estCount)-mean(a$trueCount)
            return(list(p=a$p, r=a$r, K=a$k,MinTrueCount= min(a$trueCount),MedTrueCount=
median(a$trueCount),                    MaxTrueCount= max(a $trueCount),pHat= phat, bias= bias, CI=res))
}
```

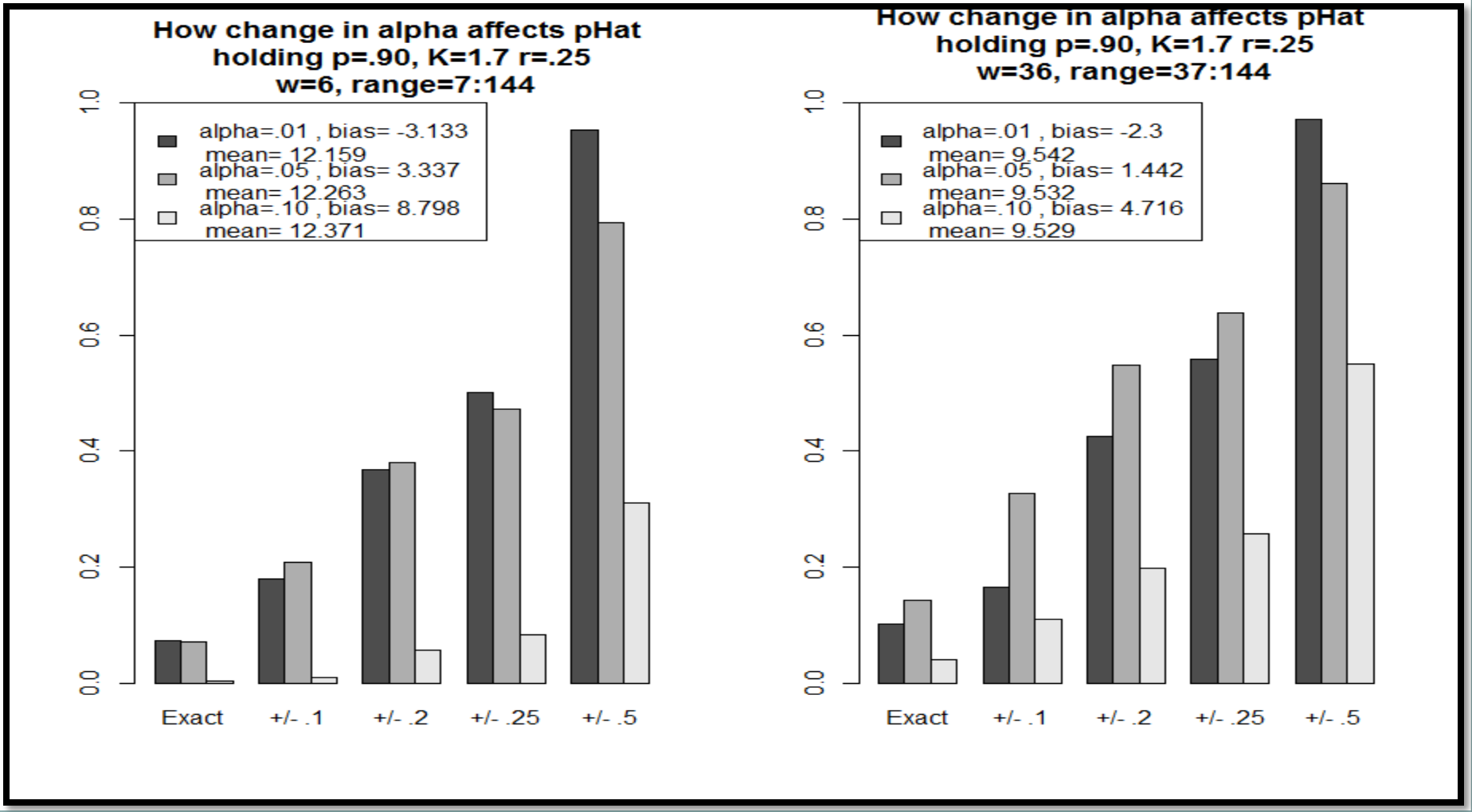
Simulation Study: Results

R: probability of staying in an outbreak given that there is already an outbreak (duration of outbreaks)



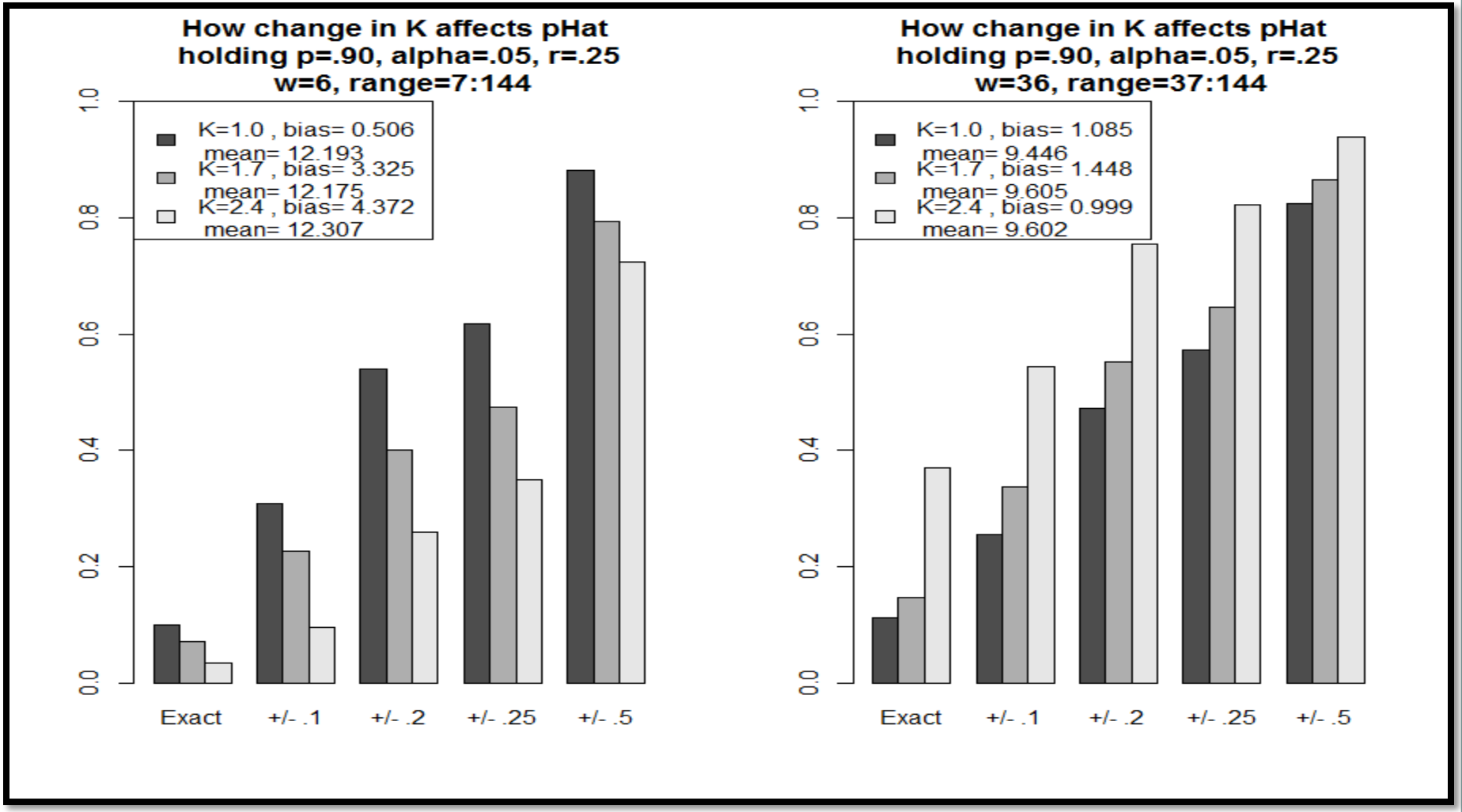
Simulation Study: Results

α=upper bound probability level for Bayes algorithm
(larger α = more sensitive)



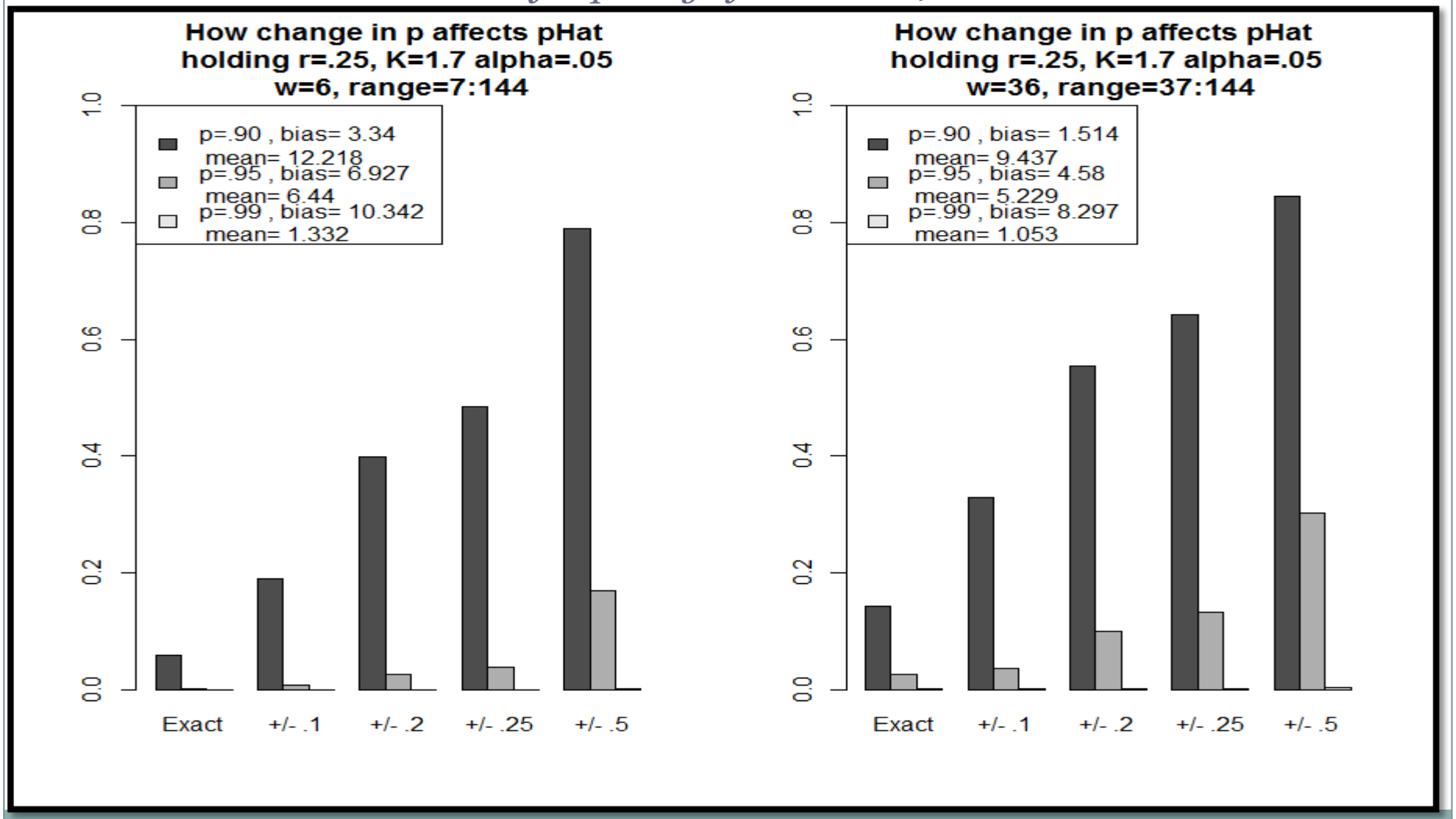
Simulation Study: Results

K: Difference between outbreak infections and background infections



Simulation Study: Results

P: probability of not being in an outbreak given that there is no outbreak (frequency of outbreaks)



Conclusions

- Data Analysis:
  - Poisson-Gamma method can handle different types of data better than the Changepoint analysis
  - Tendency to overestimate number of outbreaks in data like *Infantis* (ie. long stretches of zeros and then high counts)
- Simulation:
  - Frequency of outbreaks (p)
  - Upper bound probability (alpha)
  - Bias

Questions?

Appendix: Poisson-Gamma Distribution

Here, one assumes independently and identically (iid) Poisson distributed reference values with parameter λ. A gamma distribution is used as prior distribution for λ. The reference values are defined to be $R_{\text{Bayes}} = R(w, w_0, b) = \{y_1, \ldots, y_n\}$ and $y_{0:t}$ is the value to predict. Thus, $\lambda \sim \text{Ga}(\alpha, \beta)$ and $y_i|\lambda \sim \text{Po}(\lambda)$, $i = 1, \ldots, n$. Standard derivations show that the posterior distribution is

$$\lambda|y_1, \ldots, y_n \sim \text{Ga}\left(\alpha + \sum_{i=1}^{n} y_i, \beta + n\right).$$

Computing the predictive posterior distribution for the next observation

$$f(y_{n+1}||y_1, \ldots, y_n) = \int_0^\infty f(y_{n+1}|\lambda)\, f(\lambda|y_1, \ldots, y_n)\, d\lambda,$$

one gets the Poisson-gamma distribution, which is a generalisation of the negative binomial distribution. Altogether,

$$y_{n+1}|y_1, \ldots, y_n \sim \text{NegBin}\left(\alpha + \sum_{i=1}^{n} y_i, \frac{\beta + n}{\beta + n + 1}\right).$$

Using Jeffrey's prior $\text{Ga}(\frac{1}{2}, 0)$ as non-informative prior distribution for λ, the parameters of the negative binomial distribution are

$$\alpha + \sum_{i=1}^{n} y_i = \frac{1}{2} + \sum_{y_{i:j} \in R_{\text{Bayes}}} y_{i:j} \quad \text{and} \quad \frac{\beta + n}{\beta + n + 1} = \frac{|R_{\text{Bayes}}|}{|R_{\text{Bayes}}| + 1}.$$

surveillance: An R package for the surveillance of infectious diseases (2007), M. Hoehle, Computational Statistics, 22(4), pp.571--582.