Observations, sensitivity and Bayesian inference in QMRA

- **Background of the problem: dealing with uncertainty and probabilistic inference in RA.**
- **Two example problems where overall sensitivity of surveillance matters.**
- **Discussion.**

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Engineering example: Falcon HTV-2 hypersonic aircraft

- First tested in *wind tunnel conditions* and *computer simulations*
  - **"It's time to conduct another flight test to validate our assumptions and gain further insight into extremely high Mach regimes that we cannot fully replicate on the ground."**
  - **”We wouldn't know exactly what to expect based solely on the snapshots provided in ground testing. Only flight testing reveals the harsh and uncertain reality."**

Air Force Maj. Chris Schulz / CBSNEWS 11.Aug.2011.

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Remarks from Falcon HTV-2:

- **Experimental conditions do not match real situation.**
- **Simulations may largely rely on assumptions.**
- **Data from actual flight conditions needed!**

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Compare with QMRA on food production chains:

- **Experimental conditions do not match real situation.**

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Compare with QMRA on food production chains:

- **Experimental conditions do not match real situation.**
- **Simulations may largely rely on assumptions.**
- **Data from actual *production chain* needed!**

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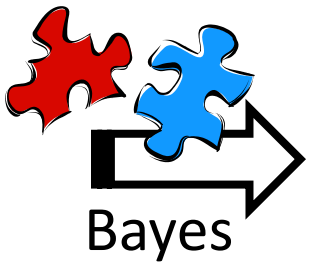
Idea (*not new, but still…*) of probabilistic evidence synthesis:

- **Experimental conditions** can provide prior information.
- **Assumptions** can describe other prior information.

$P(\theta)$

- **Data from actual *production chain*** is direct evidence.

$P(X \mid \theta)$



$$P(\theta \mid X) = \frac{P(X \mid \theta)P(\theta)}{\int_{\Theta} P(X \mid \theta)P(\theta)d\theta}$$

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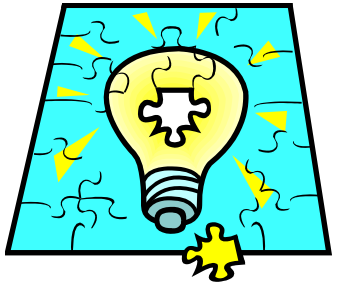
Another example: controlling FMD outbreak

- **”The models’ veterinary assumptions did not fit with either field or experimental reality and represented a different (wholly theoretical) virus”.**
- **”The use of non-validated models as predictive tools to guide policy during an epidemic of FMD remains highly questionable, especially given the imprecision of the available data and the complex nature of the biology of FMD virus”**
  - Mansley LM, Donaldson AI, Thrusfield MV, Honhold N: Destructive tension: mathematics versus experience – the progress and control of the 2001 foot and mouth disease epidemic in Great Britain. Rev. sci. tech. Off. int. Epiz., 2011, 30 (2), 483-498.

Underestimating uncertainty?
Can these problems be avoided ?



- **Experiments are difficult, or impossible, with a real production chain.**
  - Costs are much too high, consequences irreversible.
  - Can be forbidden by law.

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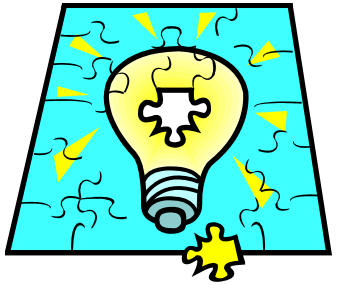

- **Experiments are difficult, or impossible, with a real production chain.**
- **Purely experimental conditions are simplified versions of reality – can we extrapolate?**
  - Infection experiments possible with some inoculated animals under test conditions. E.g. hens in cages.
  - Other contamination experiments under 'similar' conditions.
  - Only limited number of factors can be controlled.

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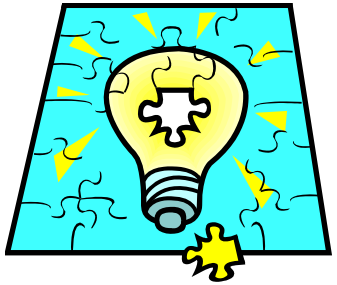

- **Experiments are difficult, or impossible, with a real production chain.**
- **Purely experimental conditions are simplified versions of reality – can we extrapolate?**
- **Real life data from other production systems usually context dependent, systems not identical – can we borrow estimates?**
  - Can data from one slaughterhouse describe those in all EU MSs?
  - Is any study from one country informative of others?
  - Meta analysis methods?

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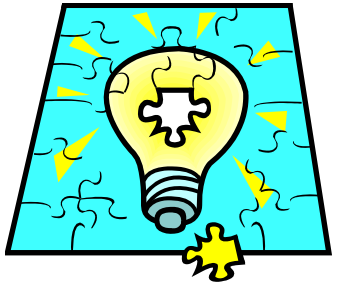

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- **Purely experimental conditions are simplified versions of reality – can we extrapolate?**
- **Real life data from other production systems usually context dependent, systems not identical – can we borrow estimates?**
- **Computer simulations with Monte Carlo methods based on assumptions – not (only) estimates from actual field data.**
  - **Assuming e.g. that all practices over the production chain are done according to adopted quidelines, protocols and laws.**

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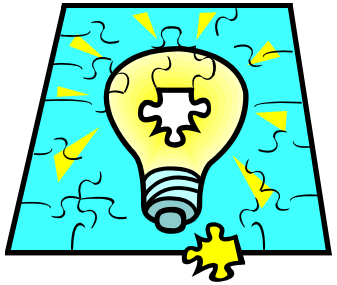

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- **Mechanistic modelling aims to replicate reality in detail but will introduce lots of uncertain parameters.**
  - **Is every detail needed?**
  - **Criteria for relevant scope of the model in relation to what is known?**
    → model uncertainty! Model assessment.

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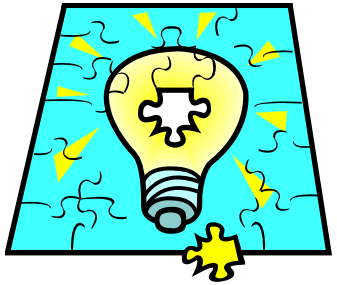

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- **Simple statistical models do not utilize relevant prior knowledge.**
  - **'Modeling the data' vs. 'modeling the problem'?**

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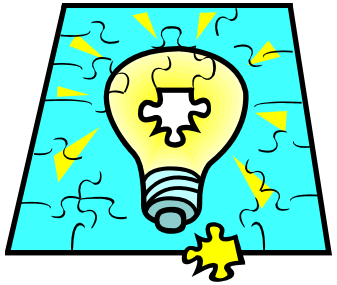
Underestimating uncertainty?
Can these problems be avoided ?



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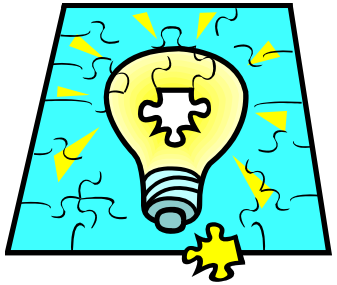

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- **Simple statistical models do not utilize relevant prior knowledge.**
- **Models may not be valid, but do we have valid data either?**
  - **Good quality does not mean it's valid for RA-question.**

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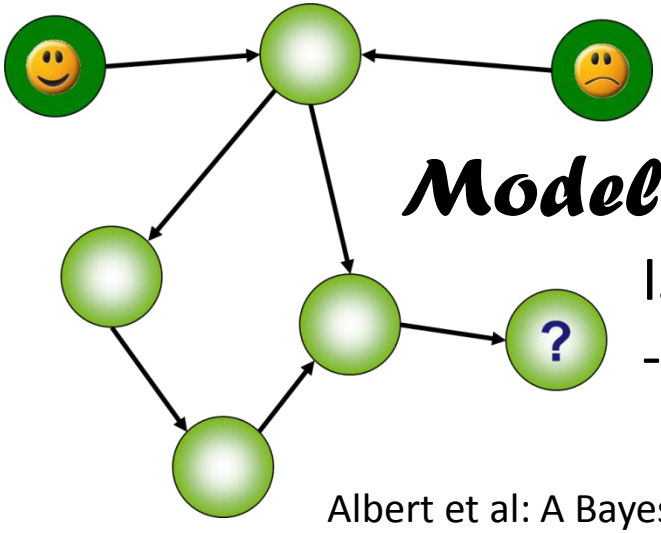
The Quest for More Unifying Treatment of Uncertainty

Need to find a link between different uncertainties (aleatory / epistemic)

- **Directed Acyclic Graph (DAG) of the whole model clarifies a bit**
- **Information on one part of the model is connected to others (Bayes)**



Modeling evidence synthesis

Is it feasible?

- Some examples exist

→ More examples needed.

Albert et al: A Bayesian evidence synthesis for estimating campylobacteriosis prevalence, Risk Analysis, 31(7), 1141-55. 2011.

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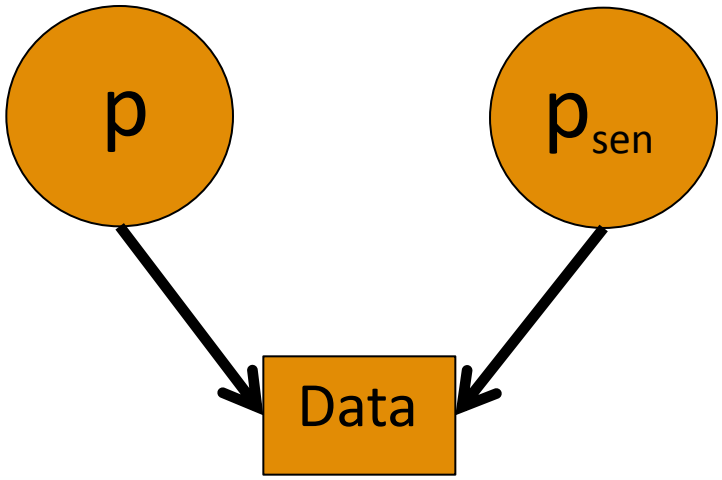
Surveillance data from food production chain

- **Data will *constrain* what can be inferred…**
- **Sensitivity of the surveillance method is part of the problem.**

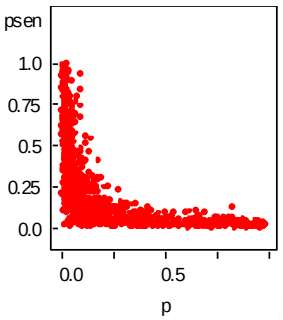


- **We may need to model both p & p_{sen}.**
- **Identifiability?**

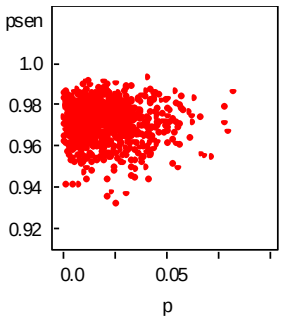
Assume N=100 tested, X=1 positive:

Two Priors:

P(psen) = U(0,1)



E(psen)=0.97, SD(psen)=0.01



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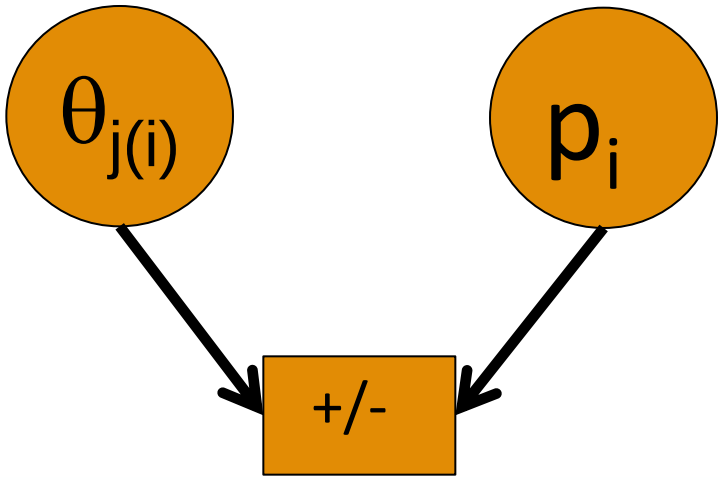
Salmonella surveillance: detection of infected cattle herds

- In each geographical area A_i
  - True infection prevalence $\theta_{j(i)}$
  - p_i = overall sensitivity of detection, for the year.

  - #positives detected =Y_i & # cattle herds =N_i known.
    # tested herds = Z_i is unknown in 'small' areas (regionally known).



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- p_i = overall sensitivity, depends on
  - α =P(tested | clinical symptoms)
  - β_i =P(tested | no clinical symptoms)
  - k = Number of animals pooled (if pooled)
  - p_w = Within herd prevalence
  - p_f = Laboratory sensitivity of faecal test

Global parameter

Regional parameter

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- $Y_i \sim$ Binomial(N_i,P(detection))

$$P(\text{detection}) = \theta_{j(i)}(\alpha + \beta_i - \alpha\beta_i)\, p_i$$

$$p_i = P(CS \setminus NCS \mid \text{tested})\, p_f$$

$$+ P(NCS \setminus CS \mid \text{tested}) \sum_{k=1}^{K} (1-(1-p_w)^k)\, p_f\, P(k)$$

$$+ P(CS \cap NCS \mid \text{tested}) \left[1-(1-p_f)(1-\sum_{k=1}^{K} (1-(1-p_w)^k)\, p_f\, P(k)) \right]$$

Laboratory sensitivity p_f is only one small part of this!

Information about each parameter exploited, WinBUGS model → posterior distribution.

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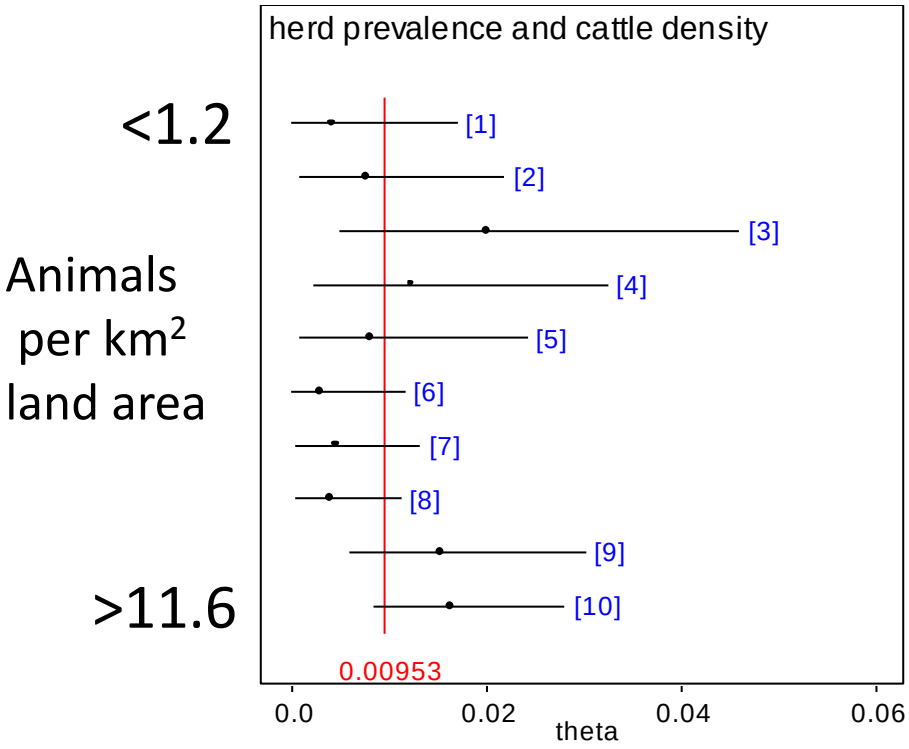
After some MCMC simulations



(10% of municipalities in each class [1]-[10])

```
model{
for(iin 1:437){    # foreach municipality in 1999 in Finland
 cattledens[i]<-cattle[i]/area[i]      # cattle density
 herdsinf[i]~dbin(pinf[i],herds[i])  # number of infectedherds
 pinf[i]<- expression1[i]+expression2[i]
 expression1[i]<- p[1]*step(1.18739-cattledens[i])+p[2]*step(1.89658-cattledens[i])*(1-step(1.18739-
cattledens[i]))+
p[3]*step(2.52852-cattledens[i])*(1-step(1.89658-cattledens[i]))+p[4]*step(3.37003-cattledens[i])*(1-step(2.5285
cattledens[i]))+p[5]*step(4.40459-cattledens[i])*(1-step(3.37003-cattledens[i]))
 expression2[i] <-p[6]*step(5.41454-cattledens[i])*(1-step(4.40459-cattledens[i]))+p[7]*step(6.59755-
cattledens[i])*(1-step(5.41454-cattledens[i]))+p[8]*step(8.29316-cattledens[i])*(1-step(6.59755-
cattledens[i]))+p[9]*step(11.6191-cattledens[i])*(1-step(8.29316-cattledens[i]))+p[10]*step(cattledens[i]-11.6191
 hprev a[i]<- herdsinf[i]/herds[i]                # herd prev alence
 herdsinf sel[i] ~ dbin(pselinf[i],herdsinf[i])   # selected inf ectedherds
 pselinf[i] <- pncs[i] +alpha -pncs[i]*alpha    # chance of selection fortesting
 herdspos[i] ~ dbin(hsens[i],herdsinf sel[i])  # detected positiv e herds (giv en as data)

 denom[i]<- alpha-alpha*pncs[i]+pncs[i]
 hsens[i] <- ((alpha-alpha*pncs[i])/denom[i])*labsens +
             ((pncs[i]-alpha*pncs[i])/denom[i])*ncssens+
             ((alpha*pncs[i])/denom[i])*(1-(1-labsens)*(1-ncssens))  # herd lev eltest sensitiv ity
 riskcattle[i]<-  meancattle[i]*herdsinf[i]     # estimated number of cattlein inf ectedherds.
 # probability of being tested (independent of salmonella status):
 pncs[i] <- equals(prov ince[i],1)*beta[5]+equals(prov ince[i],2)*beta[6]+
            equals(prov ince[i],3)*beta1+equals(prov ince[i],4)*beta[11]+
            equals(prov ince[i],5)*beta[3]+equals(prov ince[i],6)*beta[2]+
            equals(prov ince[i],7)*beta[7]+equals(prov ince[i],8)*beta[10]+
            equals(prov ince[i],9)*beta[4]+equals(prov ince[i],10)*beta[9]+
            equals(prov ince[i],11)*beta[12]+equals(prov ince[i],12)*beta[8]
 }
#### s e n s i t i v i t y  o f  p o o l e d  s a m p l e s: ################################
 ncssens<-sum(A[])  # NCS sensitiv ity
for(iii in 1:10){  # equal probabilities forselecting 1-10 animals in a joint sample
 A[iii]<-(0.01)*((1-pow(1-pwithin,iii)))*labsens
}
for(iiii in 11:15){  # equal probabilities forselecting 11-15 animals in a joint sample
 A[iiii]<-(0.03)*((1-pow(1-pwithin,iiii)))*labsens
}
for(iiiii in 16:20){  # equal probabilities forselecting 16-20 animals in a joint sample
 A[iiiii] <-(0.15)*((1-pow(1-pwithin,iiiii)))*labsens
}
hinfsel<-sum(herdsinf sel[])    # total number of inf ectedherds that become selected fortesting
meanhsens<-mean(hsens[])  # mean herd sensitiv ity(ov erall herd sensitiv ity)
###### p r i o r  d i s t r i b u t i o n s: ########################################
ly mphsens ~ dbeta(279.7,652.6333)      #mean=0.3, std=0.015
labsens ~ dbeta(74.31556,6.462222)      #  prior forlaboratory sensitiv ity
pwithin ~ dunif(0,1)  # prior forexpectedwithin herd prev alence
# prior forchance to become CS tested while inf ected:
alpha ~ dbeta(3.057145, 6.86865)
# prior forchance to become NCS tested while inf ected:
beta[12] ~ dunif(beta[11],ncs[12])
beta[11] ~ dunif(beta[10],ncs[11])
beta[10] ~ dunif(beta[9],ncs[10])
beta[9]  ~ dunif(beta[8],ncs[9])
beta[8]  ~ dunif(beta[7],ncs[8])
beta[7]  ~ dunif(beta[6],ncs[7])
beta[6]  ~ dunif(beta[5],ncs[6])
beta[5]  ~ dunif(beta[4],ncs[5])
beta[4]  ~ dunif(beta[3],ncs[4])
beta[3]  ~ dunif(beta[2],ncs[3])
beta[2]  ~ dunif(0,ncs[2])
beta[1]  ~ dunif(0,1) # dummy v ariable, not used.
beta1<-0 # this is beta forÅland
    ncs[1] <- 0.00001  # dummy v ariable, not used.
    for(ein 2:12){
      ncs[e] <- ncstests[e]/herdsprov ince[e]
    }
```

…and continues

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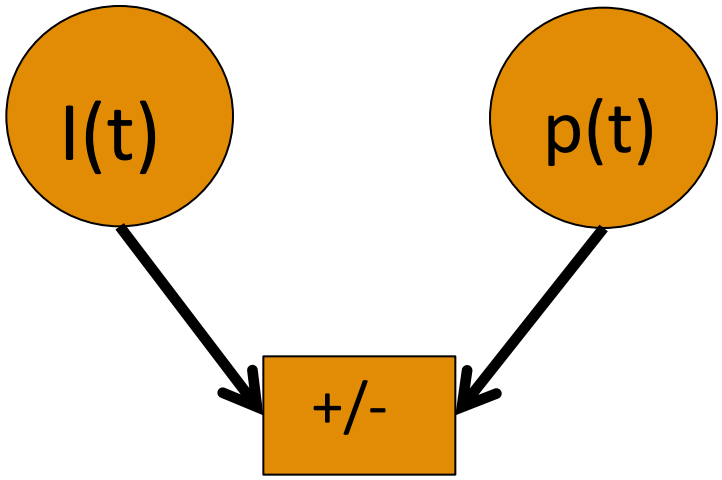
Salmonella surveillance: detection of infected laying flocks

- I(t) = true infection status at time t: I(t) = 1 or 0.
- t = time since beginning of laying period.
- p(t) = overall sensitivity of testing at time t.
- Testing results $D_1, D_2, D_3, \ldots$ at times $t_1, t_2, t_3, \ldots$



I(t) = hidden Markov process,
Intensities λ and μ.

p(t) can change due to within flock epidemic .

First approach had assumed p(t) = p for all times t.

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Hidden Markov process:

Transition probabilities for a flock: 0→1, and 1→0

$$p_{01} = P(I_t = 1 \mid I_0 = 0, \lambda, \mu) = \frac{\lambda}{\lambda+\mu} - \frac{\lambda}{\lambda+\mu}\exp(-(\lambda+\mu)t)$$

$$p_{10} = P(I_t = 1 \mid I_0 = 0, \lambda, \mu) = \frac{\lambda}{\lambda+\mu} + \frac{\mu}{\lambda+\mu}\exp(-(\lambda+\mu)t)$$

Solve the probability of hidden positive, at age t.

This can be written recursively (Nagelkerke *et al*., 1990):

$$\rho_t = \begin{cases} \dfrac{(1-p)[(1-p_{01}-p_{10})\rho_{t-1}+p_{01}]}{1-p[(1-p_{01}-p_{10})\rho_{t-1}+p_{01}]}, t>1 \\ \dfrac{(1-p)P(I_1=1)}{(1-p)P(I_1=1)+P(I_1=0)}, t=1 \end{cases}$$

Here: $\rho_t = P(I_t = 1 \mid D_1,\ldots,D_t)$, depends on the history.

If $D_t=1$, then we know $I_t=1$, but typically $D_1=0,\ldots,D_t=0$

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- **Since salmonella is a rare thing (in Finland):**
  λ is likely to be small

- **Since salmonella is hard to clear out from a flock:**
  μ is likely to be small

What is known of sensitivity p(t)?

- EFSA report: *”the rate of transmission of Salmonella within a flock determines the change in within-flock prevalence, which, in turn determines when a colonised flock can be detected”.*

- If flock is very recently infected, detection not likely.
- After 2-4 weeks since infection, detection almost sure. (Within flock prevalence gets > 5%).
- After some longer time, detection may be less optimal, (intermittent shedding, immunity, adaptation, other effects?)

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What is known of sensitivity p(t)?

- EFSA report: ”*most hens stop shedding the bacteria after approximately three weeks*”.
  - AND: ”*over time the number of organisms excreted by infected birds, and as a consequence, the within-flock prevalence, may decrease*”.

- To simplify, this could be described **by a function of duration** of infection in the flock.
  - Duration depends on time of infection. This is unknown parameter τ_0.

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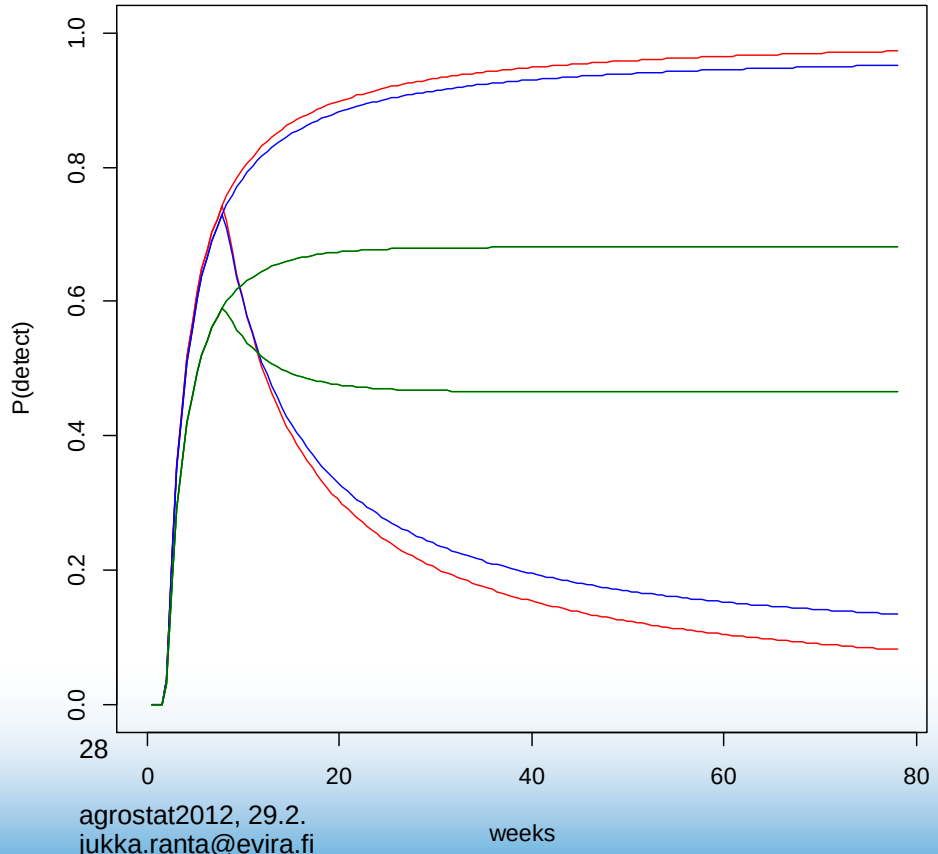
- Sensitivity as a function of duration **$d = t-\tau_0$** ?
  - E.g. simple function:

$$P(\oplus_t \mid \tau_0, I_t = 1) = p(d) = \begin{cases} 0 & , \text{if} \quad d < d_1 \\ p^* & , \text{if} \quad d_1 < d < d_2 \\ 0 & , \text{if} \quad d > d_2 \end{cases}$$

  - To get sensitivity at time t (age of flock), we need to integrate over unknown τ_0.

$$P(\oplus_t \mid I_t = 1) = \int_0^t P(\oplus_t \mid \tau_0, I_t = 1)\pi(\tau_0 \mid I_t = 1)d\tau_0$$

$$\Rightarrow \frac{p^* e^{-\mu t}}{1 - e^{-\mu t}}\left(e^{\mu \max\{t-d_1,0\}} - e^{\mu \max\{t-d_2,0\}}\right)$$



$p^* = 1$, $\mu = 0.1, 1, 10$,
$d_1 = 2/52$, $d_2 = 8/52$, $d_2 = \infty$

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- Sensitivity as a function of duration **$d = t-\tau_0$** ?
  - But which function?

$$P(\oplus_t \mid \tau_0, I_t = 1) = p(d) = \begin{cases} 0 & , \text{if} \quad d < d_1 \\ p^* & , \text{if} \quad d_1 < d < d_2 \\ 0 & , \text{if} \quad d > d_2 \end{cases}$$

Step function

$$P(\oplus_t \mid \tau_0, I_t = 1) = p(d) = p^* e^{-0.5(d-a)^2/\sigma^2}$$

Gaussian curve

$$P(\oplus_t \mid \tau_0, I_t = 1) = p(d) = p^*(1-e^{-ad})$$

Exponential increasing

$$P(\oplus_t \mid \tau_0, I_t = 1) = p(d) = p^*(1-e^{-ad})e^{-a\max\{d-d^{**}\}}$$

Exponential increasing, & decreasing

Desideratum:

- Should reflect assumptions
- Should be simple (for ease of integration)
- As few parameters as possible
- Parameters with meaningful interpretation (to be elicited)
- To be fitted to experimental data, if ever available

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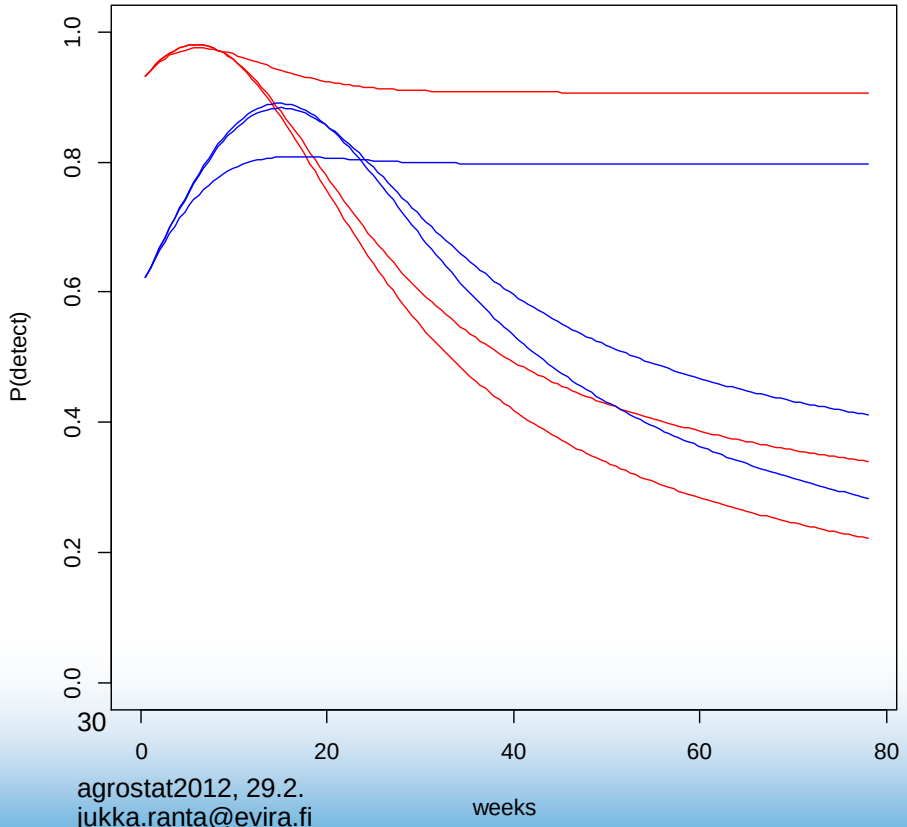
- Sensitivity as a function of duration **d = t-τ_0** ?
  - For example, Gaussian function gives:

$$P(\oplus_t \mid I_t = 1) =$$

$$\frac{p^* \mu}{1 - e^{-\mu t}} e^{-0.5(a^2 - (a - \mu\sigma^2)^2)/\sigma^2} \sqrt{2\pi}\sigma[\Phi((t - a + \mu\sigma^2)/\sigma) - \Phi((-a + \mu\sigma^2)/\sigma)]$$



p* = 1, a=4/52, a=10/52
σ=10/52,
μ = 0.1, 1, 10

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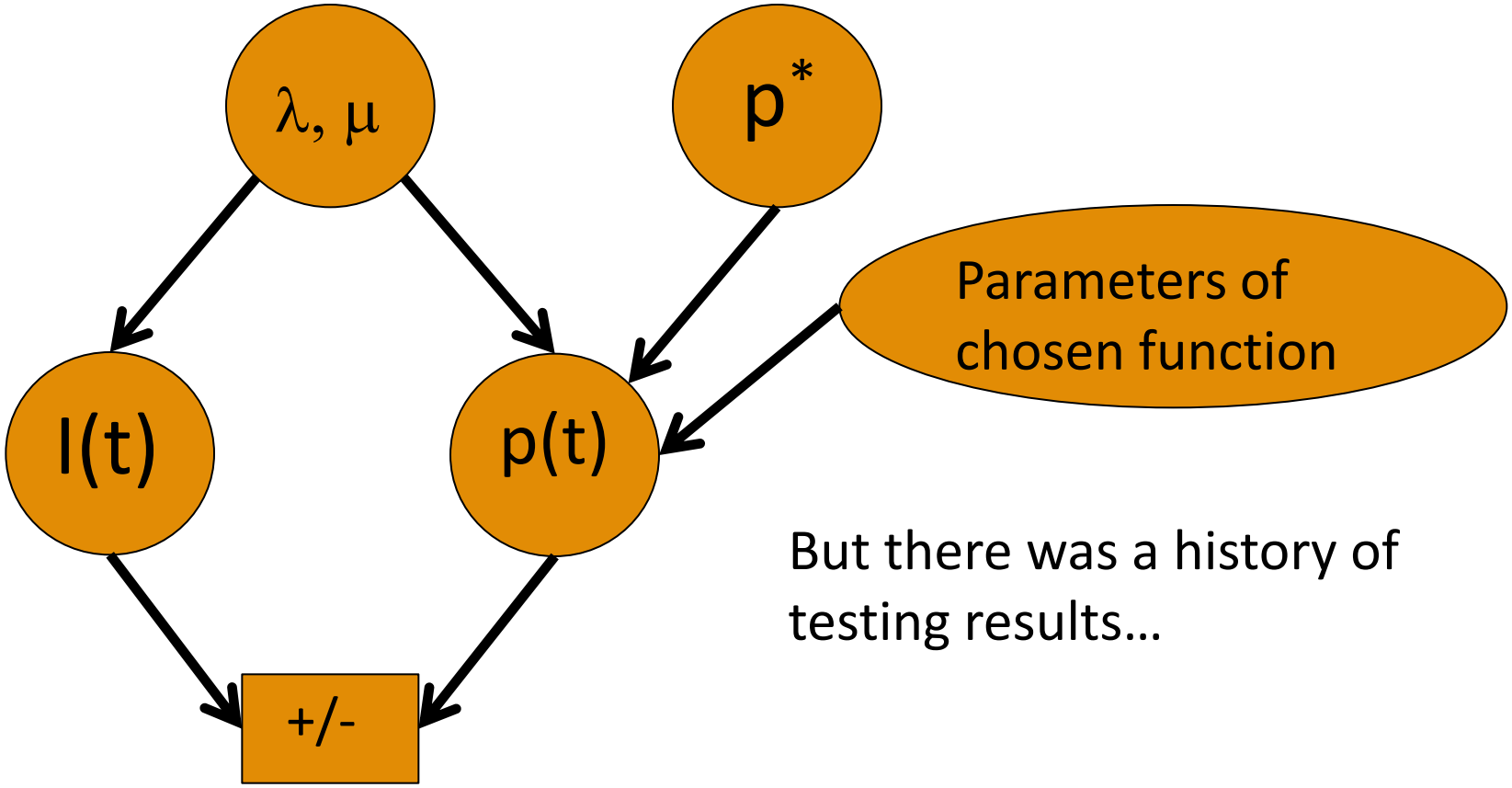
- DAG of previous models for hidden process and sensitivity, with one testing result only:



But there was a history of testing results…

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- Past testing results provide evidence about where τ_0 probably was, given that I(t)=1.

- The history is necessarily a series of negatives *(positive flocks are eliminated).*
- To compute p(t) at a time point t between 1st and 2nd testing times t_1 and t_2, e.g. with Gaussian function:

$$P(\tau_0 \mid I_t = 1) \propto \begin{cases} e^{-(t-\tau_0)\mu}(1 - p^* e^{-0.5(t_1-\tau_0-a)^2/\sigma^2}) & , \text{if } \tau_0 \in [0, t_1] \\ e^{-(t-\tau_0)\mu} & , \text{if } \tau_0 \in [t_1, t], t < t_2 \end{cases}$$

- More testing times → more steps!
- Normalizing constant by numerical integration.

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- Finally, solving again:

$$P(\oplus_t \mid I_t = 1) = \int_0^t P(\oplus_t \mid \tau_0, I_t = 1)\pi(\tau_0 \mid I_t = 1)d\tau_0$$

- But this also becomes numerical, because of a more complicated $\pi(\tau_0 \mid I_t=1)$.

- But OpenBUGS has a procedure for this:

  result <- integral(F(),start,end,accuracy)

- Becomes eventually slow, but better than simulating τ_0 for every flock.

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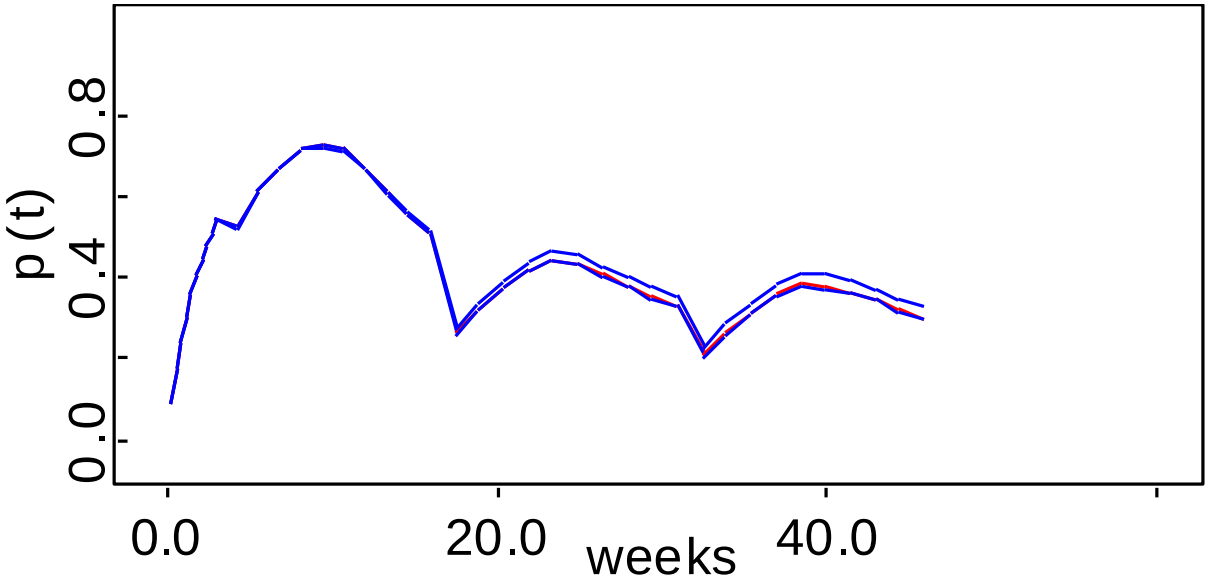
- **Test results**: compute posterior, for example with p^*=0.9, and with exponential increase & decrease with a=-log(0.05)/(4/52), d**=8/52



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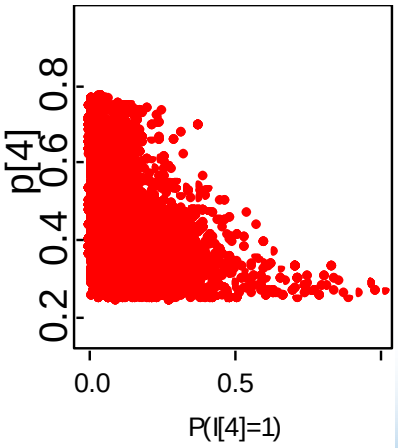
- **Test results**: posterior probability of true prevalence at 4 testing times:

	mean	sd	val2.5pc	median	val97.5pc
p(I[1]=1)	0.1579 %	0.143	0.01861	0.1146	0.6258
p(I[2]=1)	0.1312 %	0.08776	0.02076	0.1098	0.353
p(I[3]=1)	0.1332 %	0.1013	0.01676	0.1079	0.3773
p(I[4]=1)	0.1559 %	0.1313	0.01395	0.1174	0.486

- Finally, estimate true prevalence over laying period to quantify risk of production → further used in RA.



← **Vague prior distribution for function parameters instead of point values – identifiability?**

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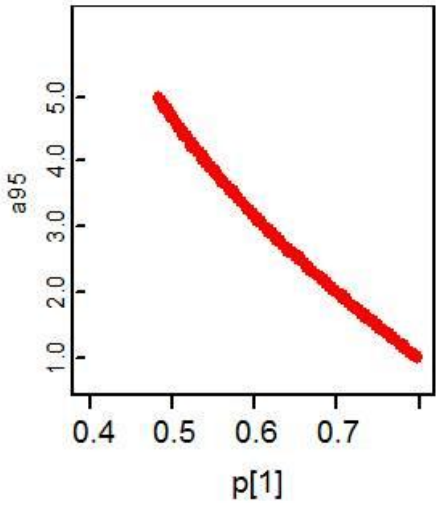
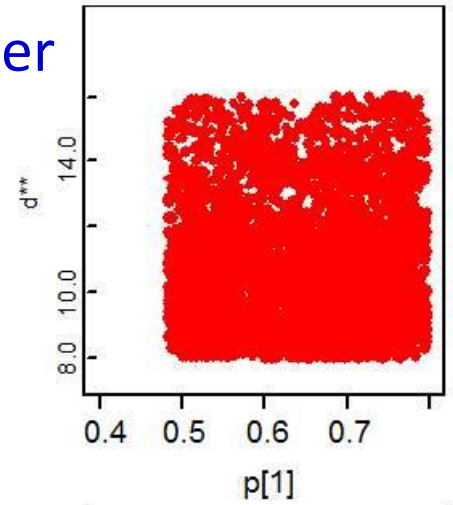
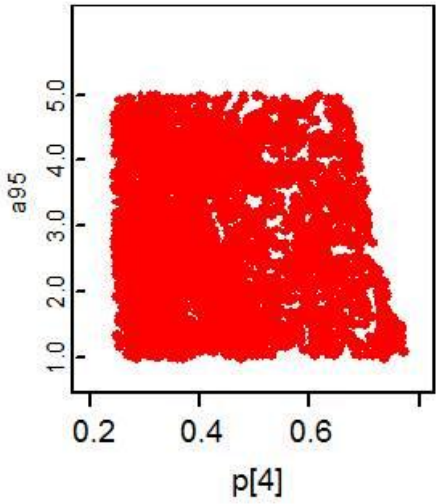
Sensitivity to parameter assumptions

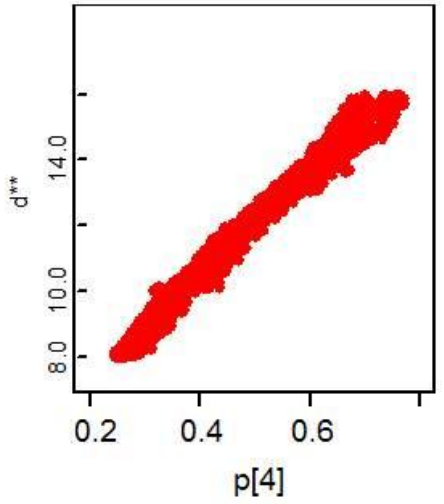




Test sensitivity p[i] at 1st and 4th testing time: how they depend on parameters of the function.

$$p(d) = p^{*}(1-e^{-ad})e^{-a\max\{d-d^{**}\}}$$





95% of max sensitivity (p*=0.9) achieved in a_w ~ U(1,5) weeks.
a95 = -log(0.05)/(a_w/52)

Decrease begins after d** ~ U(8,16) weeks.

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- To conclude:

- **Observed data represent the only direct evidence we have about a current situation in a food production chain, e.g. egg production, under risk of e.g. salmonella.**

- **However, information in surveillance data depends on sensitivity of the whole testing scheme which can be variable over time or geographical areas.**

- **This is challenging for inference, because the underlying process state and the sensitivity need to be jointly modeled.**

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- To conclude:

- **Bayesian inference deals with unknown parameters jointly, instead of an independent analysis for each, which would not represent the combined uncertainty.**

- **Computationally intensive, so try not to make it more complicated than necessary – ”models should be kept as simple as possible, but not more”.**

– *Merci beaucoup pour votre attention!*

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A biased selection of some papers:

–Karlin, S., Taylor, H.M. (1975). A First Course in Stochastic Processes. Second Edition. Academic Press, San Diego.

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–Maijala R, Ranta J, Seuna E, Pelkonen S, Johansson T. (2005). A quantitative risk assessment of the public health impact of the Finnish Salmonella control program for broilers. Int. J. Food Microbiology. 102 (1), 21-35.

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–Albert I, Espié E, de Valk H, Denis J-B. (2011). A Bayesian evidence synthesis for estimating campylobacteriosis prevalence. Risk Analysis, 31(7), 1141-55. 2011.

–Ranta J, Matjushin D, Virtanen T, Kuusi M, Viljugrein H, Hofshagen M, Hakkinen M. (2011). Bayesian Temporal Source Attribution of Foodborne Zoonoses: *Campylobacter* in Finland and Norway. Risk Analysis, 31(7), 1156-1171.

–Manuscript under preparation of the hidden Markov model of this talk.