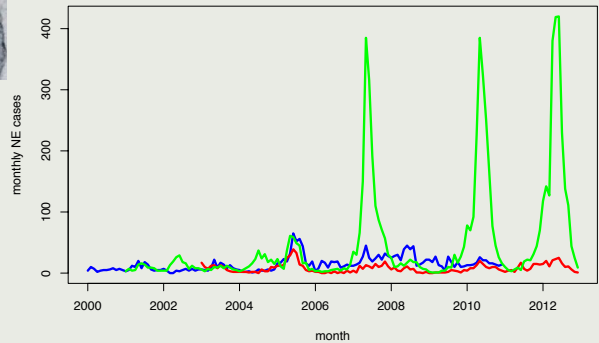


Forecasting *Puumala* virus outbreaks in Western Europe through space and time.

Tersago K, Sedda L, Wint W, Quoilin S, Reynes JM, Faber M, Reusken C, Wint W, Alexander N, Metz M, Ducheyne E, Leirs H



© Vilda_Rollin Verlinde



Introduction

Environmental drivers \sim infectious disease dynamics



Many potential mechanisms have been described for various disease systems

Need for early warning mechanisms for effective disease management

(Mills et.al., 2010, Altizer et al., 2013)



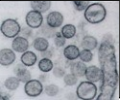
Vector-borne and Zoonotic diseases:

Complexity \rightarrow applied use of models?

What about predicting infection outbreaks in a space-time matrix?

Vector-borne diseases: Nice examples from Malaria , Dengue (Löwe et al., 2013)

Other zoonotic infections?



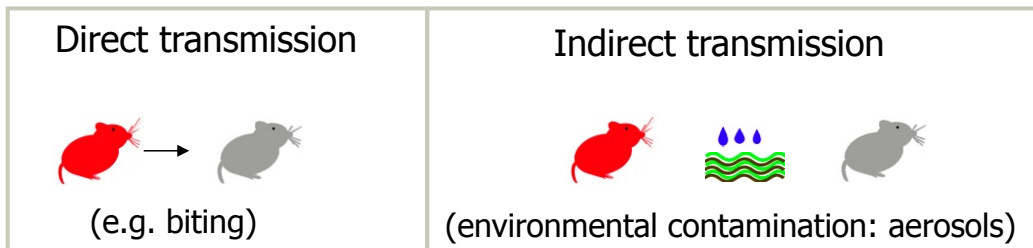
Hantaviruses

Prime example of zoonotic infections affected by climate change

Hantaviruses (Family Bunyaviridae, genus *Hantavirus*)

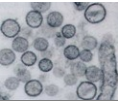
Single strand, negative sense RNA-viruses

- Infected reservoir hosts remain chronically infected
- Shed virus through their excretions (urine, saliva, faeces)



 Non-infected reservoir host

 Infected reservoir host



Hantaviruses

Indirect transmission



↓ Most likely transmission route towards human hantavirus infection



Dead-end Host



Potential disease symptoms:

HFRS: Hemorrhagic fever with Renal Syndrome

HPS or HCPS: Hantavirus CardioPulmonary Syndrome

Study system: Puumala virus

Puumala virus (PUUV)



Reservoir host: bank vole (*Myodes glareolus*)



Potential human disease:
nephropathia epidemica (NE)

(Mild form of hemorrhagic fever with renal syndrome)



NE incidence in Europe:

Explicit heterogeneity through space and time

Can we build a space-time prediction tool?



Complex? nature of PUUV transmission

PUUV infection risk to humans

$$C \approx N \cdot P \cdot \beta_{a,b} \cdot H_s$$

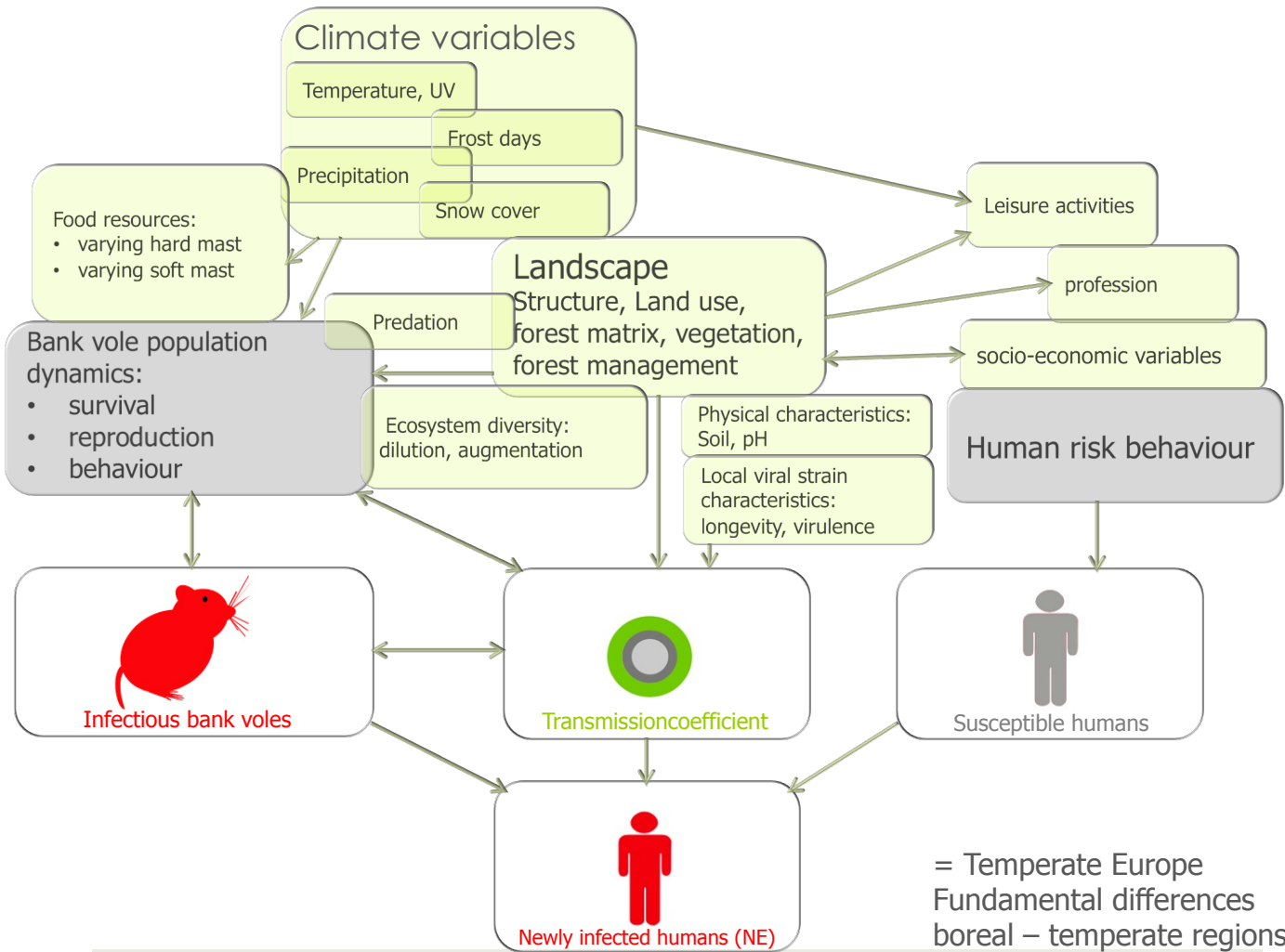
Newly infected humans (NE)

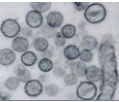
Infectious reservoir hosts

Transmission coefficient

Susceptible humans

(Davis et al., 2005)



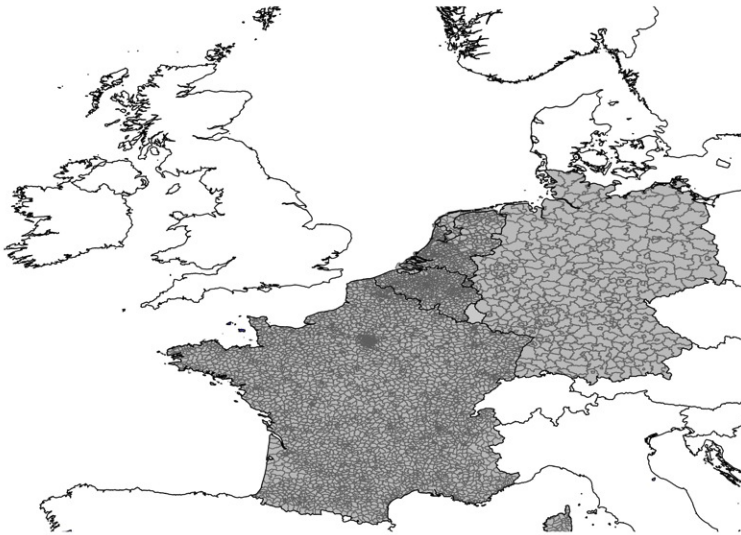


Methodology: NE data collection



New PUUV infections

(NE case data georeferenced by place of infection or residence)

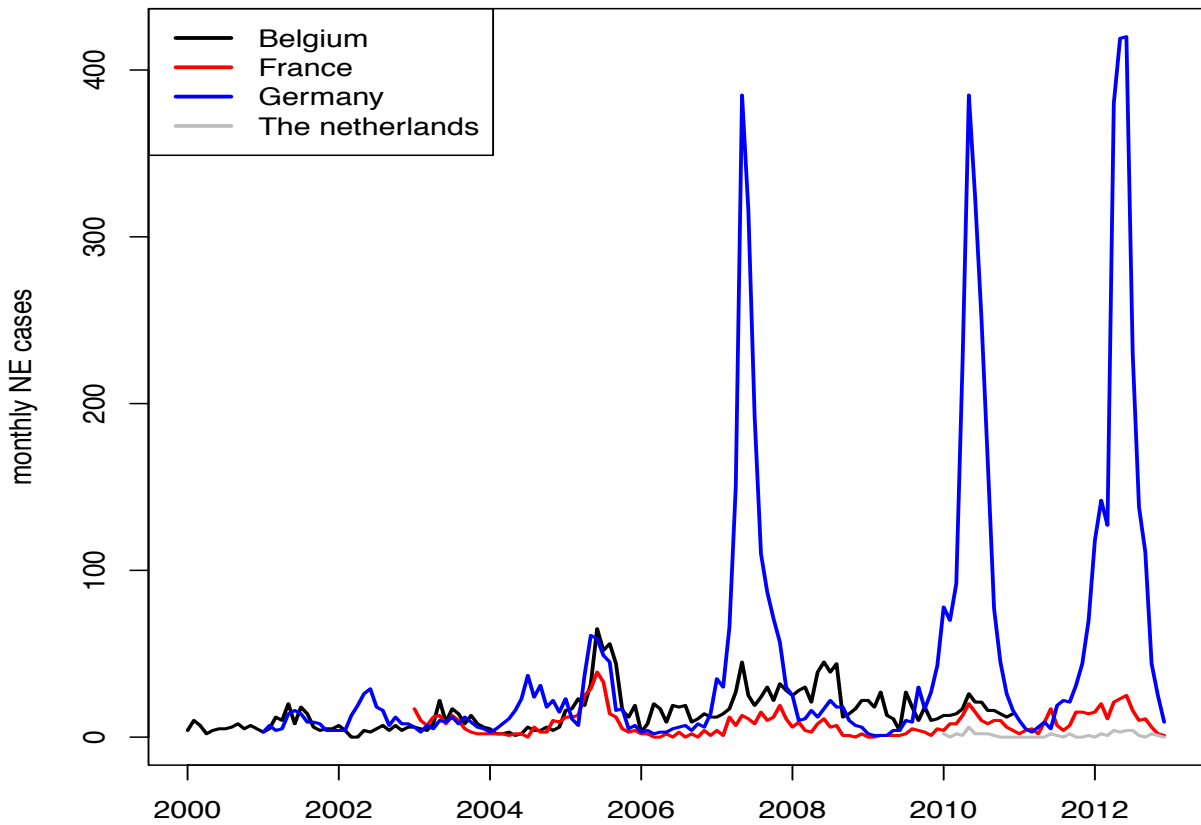


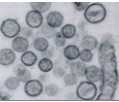
- Belgium: 2000-2010 (WIV)
- France: 2003-2012 (Institut Pasteur)
- Germany: 2002-2012 (RKI)
- The Netherlands: 2008-2012 (RIVM)

Population data:
national institutes of statistics

Spatial resolution and extent of NE data provided by collaborators

Methodology: NE data description





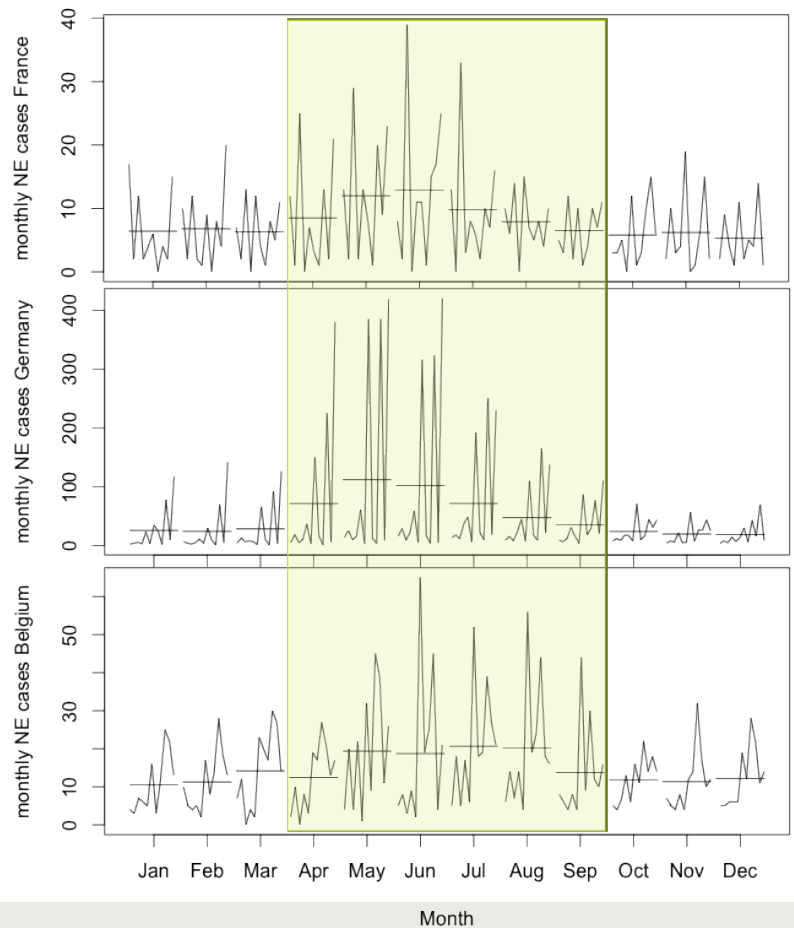
Methodology: NE data description

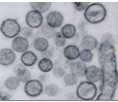
Using yearly NE incidence for
computational reasons:

Seasonal patterning?

Time lag: date of disease onset
versus date of reporting...

monthly deviation and mean plot





Methodology: environmental data collection



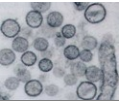
Space-time environmental variables and proxies

Yearly values extracted per polygon (with time lags)

Proxies:	Space-time variable	Proxy (source)
	Length of bank vole reproductive season	Length of the greening period (MODIS v5)
	Overall resource availability	Primary production (MODIS v5)

Variables:	Space-time variable	Source
	Temperature (monthly, seasonal)	MODIS LST and ENSEMBLE
	Precipitation (seasonal)	ENSEMBLE
	Snow cover	MODIS v5
	Frost days (monthly,seasonal)	MODIS v5





Methodology: environmental data collection



Spatial environmental variables

Single value extracted per polygon

Spatial variable (random)	Source
Bank vole habitat	Globcover 2009 based categorisation
Tree species occurrence (beech and native oak species)	EFDAC 2000
Bank vole – human interaction	Globcover 2009: bank vole habitat within 400m of artificial area



Methodology: model selection & validation

Geostatistical Poisson mixed model:

$$Y | \beta, W, Z \sim \text{Poisson}(\eta \beta \exp(W + Z(\gamma)))$$

- Y is a vector of NE cases (at point s and time t)
- $\eta \beta$ is the fixed effect
- W non-spatial random effect
- Z and spatially structured random effect.

Double spherical model correlation structure added

- Model fitted to data from 2004-2010 (= training set): Belgium, France, Germany, The Netherlands
- Out-of sample validation 2011-2012 (=validation set): France, Germany, The Netherlands

Methodology: model selection

- 1st step: Selection of most important variables for space-time NE trend
Bootstrapped stepwise selection (AIC) with randomized order
- 2^d step: Variables that appear in 2/3 of the model repetition: selection

Selected space-time variables

Max temperature winter Year NE occurrence -2

max temperature summer Year NE occurrence -2

Frost days autumn Year NE occurrence -1

Rainfall spring Year NE occurrence -1

Snowdays spring Year NE occurrence -1

max temperature summer Year NE occurrence -1

max temperature spring Year NE occurrence

Population

- 3^d step: select spatial variable ~ spatially structured random component

Selected spatial (random) variable

Proportion of beech (*Fagus sylvatica*)

Variable*	Coefficient	Std. Error	DF	t-value	p-value	Error %
2 year time lag						
LST winter	-0.105	0.008	21230	-12.884	< 0.001	153
LST summer	0.071	0.011	21230	6.786	< 0.001	62
1 year time lag						
Frost days autumn	-0.172	0.014	21230	-12.079	< 0.001	83
Rainfall spring	0.002	0.027x10 ⁻²	21230	8.070	0.018	100
Snowdays spring	-0.044	0.014	21230	-3.117	< 0.001	96
LSTsummer	-0.037	0.010	21230	-3.769	0.006	134
No time lag						
txspring	-0.025	0.009	21230	-2.754	< 0.001	102
population	0.036x10 ⁻⁴	0.033x10 ⁻⁴	21230	10.767	< 0.001	122

Error % represents the error increase when parameter is removed from the model.

Results: validation

Cross-validation results validation set (2011-2012):

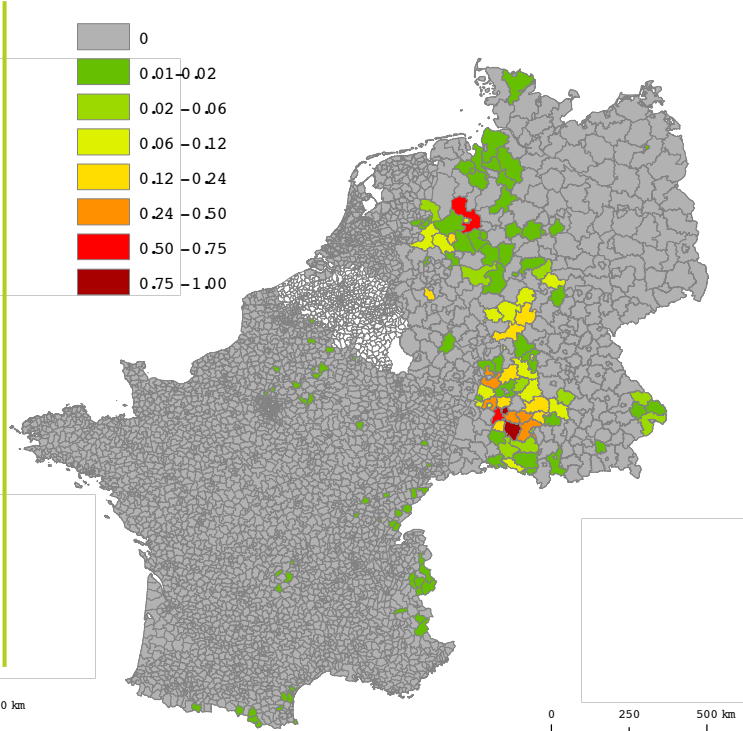
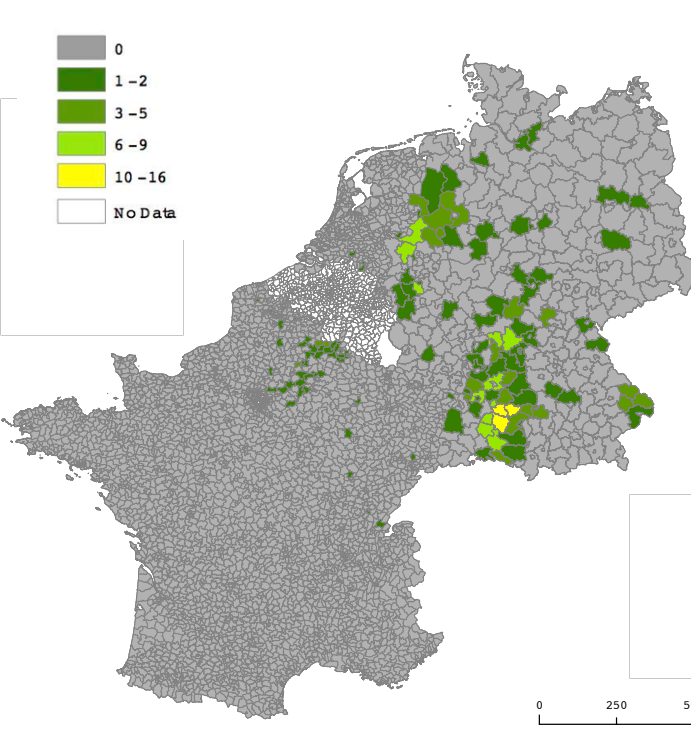
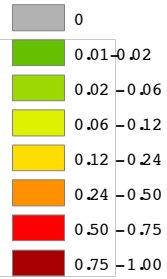
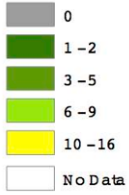
- Sensitivity: 60%
- Specificity: 96%
- Mean error of full model: 10%
- Mean error of model (without spring temp in prediction year): 20%

Results: validation

Observed NE cases

2011

predicted relative risk

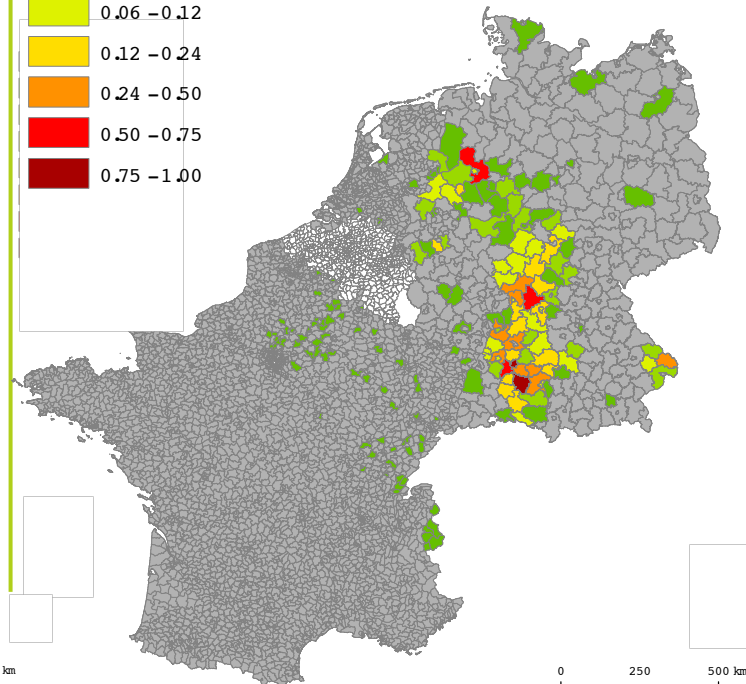
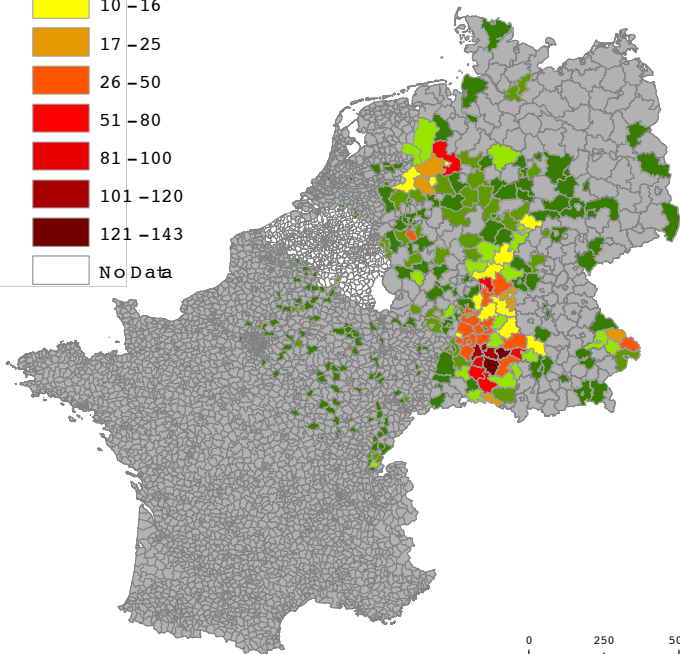
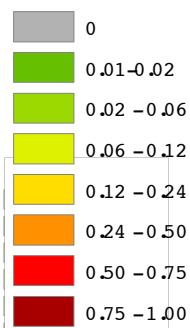
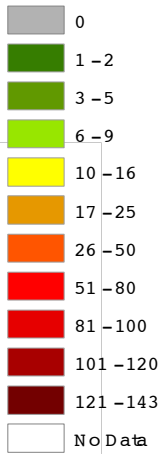


Results: validation

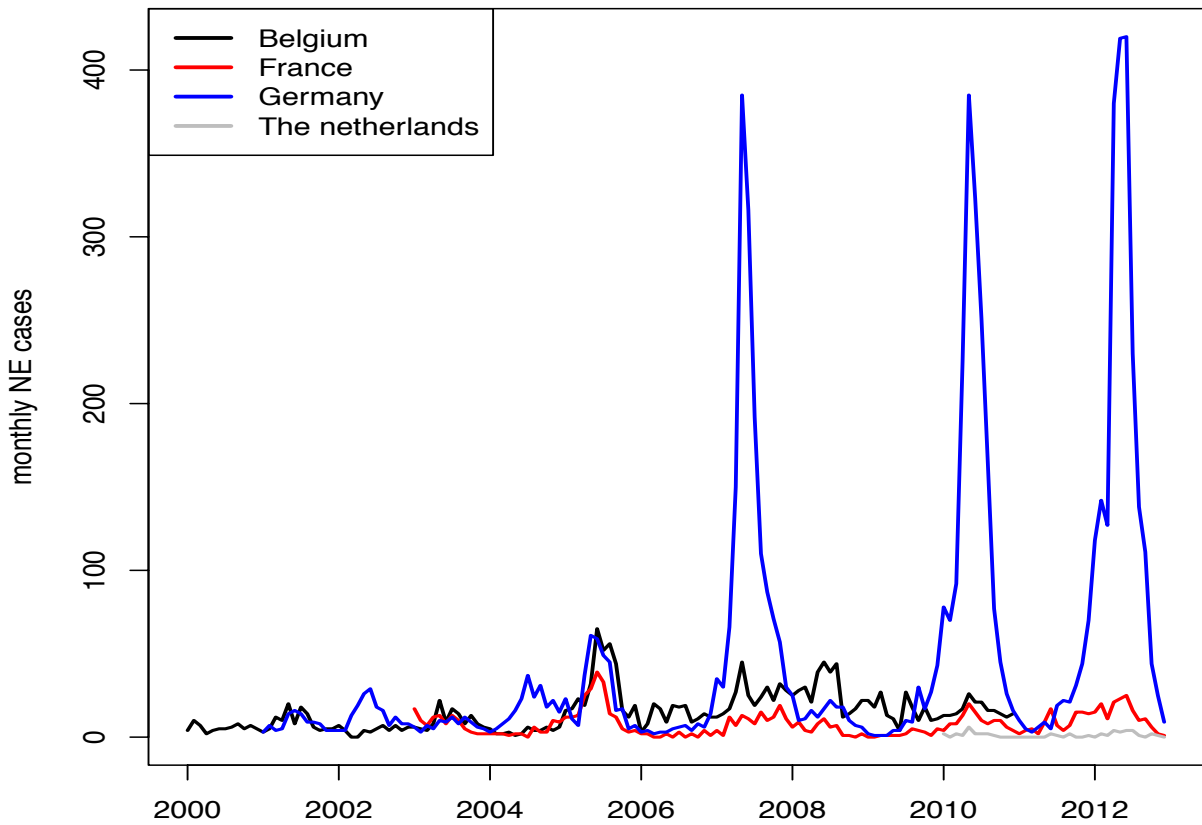
Observed NE cases

2012

predicted relative risk

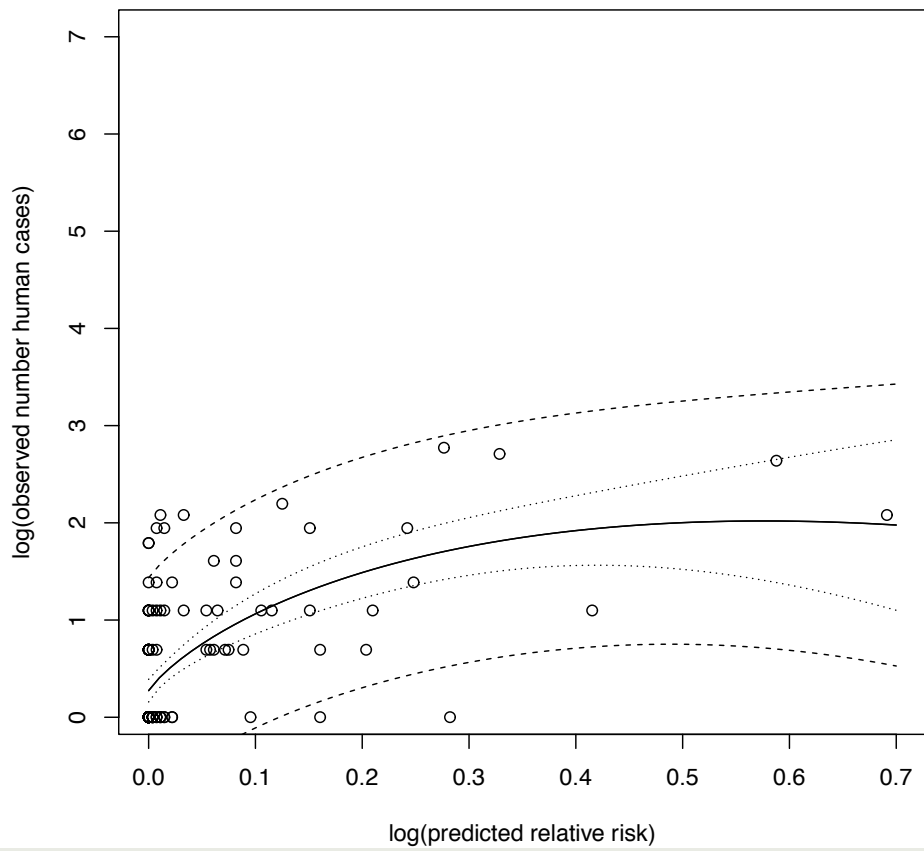


Results: validation



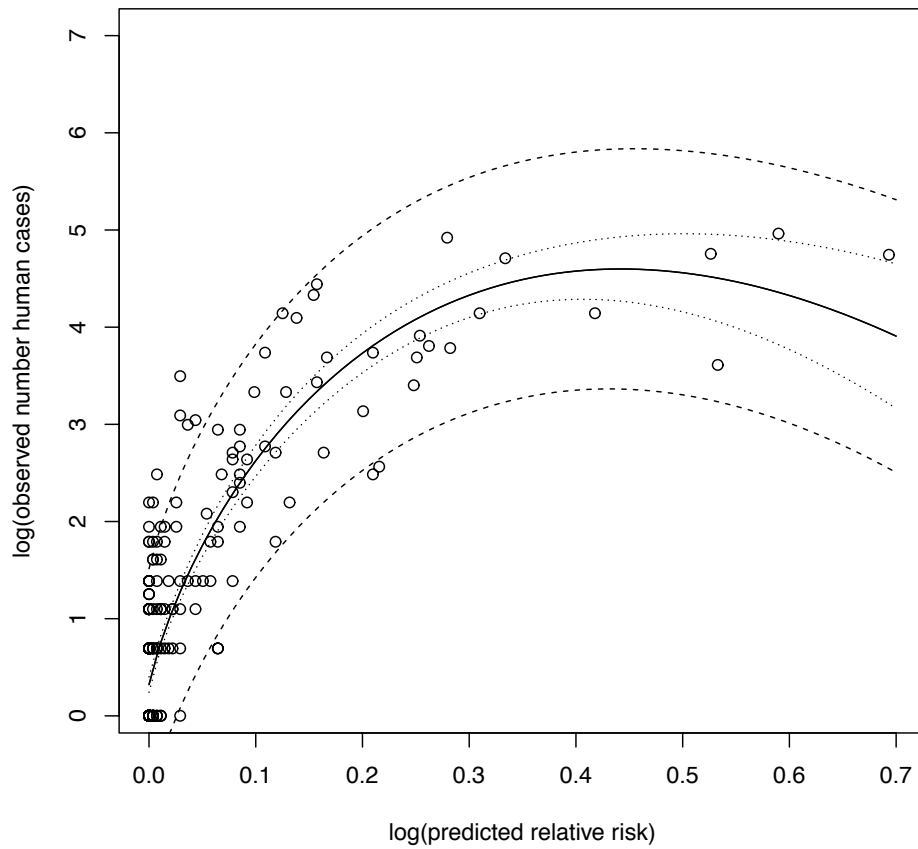
Results: validation

2011



Methodology: validation

2012



Discussion/conclusion

- Climate based model frame allows production of NE relative risk maps with acceptable accuracy.
- Model confirms the importance of temperature, precipitation indices and local beech occurrence for NE epidemiology.
- Results show that the potential exists to make meaningful space-time predictions over western Europe based on a single model frame.

Rather low sensitivity?

- Training set and validation set differ in proportional outbreak intensity (see Germany)
- Some error is inherent to NE data (place of residence is not always place of exposure!)
- Consecutive high epidemic peak years are unlikely to happen in a single location (biological constraints) -> needs to be added to model frame or as a correction factor in the presentation of the risk maps?

Longer time series for validation will be valuable