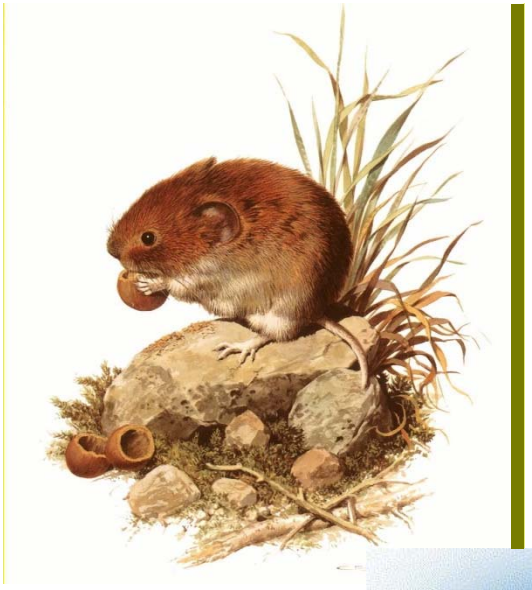
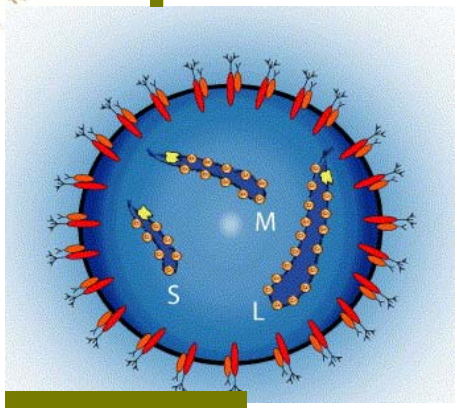




Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Muis en mast in de lage landen……

onderdiagnostiek van hantavirus infecties in Nederland

Chantal Reusken
Marco Goeijenbier

3 december 2013

Discovery of hantaviruses

- 1976: identification of causative agent of Korean hemorraghic fever:
  virus detected in Asian striped field mice (*Apodemus agrarius*)

- location of circulation: Hantan river -> Hantaan virus

- Discovery of other related viruses causing hemorrhagic fever with kidney damage originating from rodents.

- 1985: formal definition of genus hantavirus
  within family *Bunyaviridae*

Nairovirus	Crimean-Congo hemorraghic fever
Phlebovirus	Rift Valley fever, sandfly fever
Bunyavirus	La Crosse encephalitis
Hantavirus	Hantavirus pulmonary syndrome (HPS), Haemorrhagic fever w. renal syndrome (HFRS)
Tospovirus	-

Lee *et al*., 1976,78

Human disease - hantavirus

Etiologic agent of :

Hantavirus pulmonary syndrome (HPS) ► New World
target = lungs

Haemorrhagic fever w. renal syndrome (HFRS) ► Old World
Nephropathia epidemica (NE) ► N-W Europe
target = kidneys

HFRS: <u>Frequent</u>

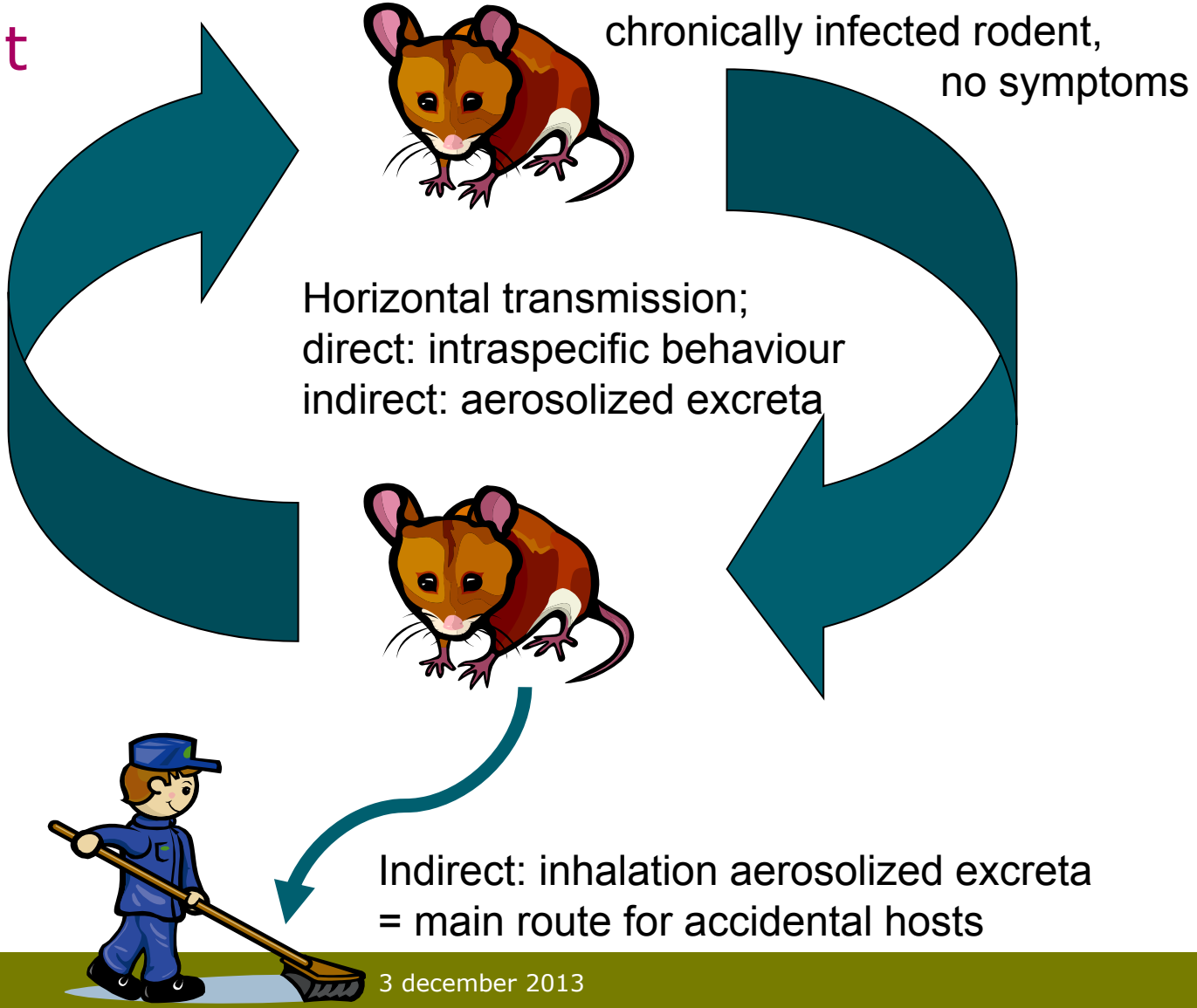
- ► fever
- ► headache, backache
- ► nausea, vomiting
- ► flank, abdominal pain
- ► myalgias
- ► diarrhea

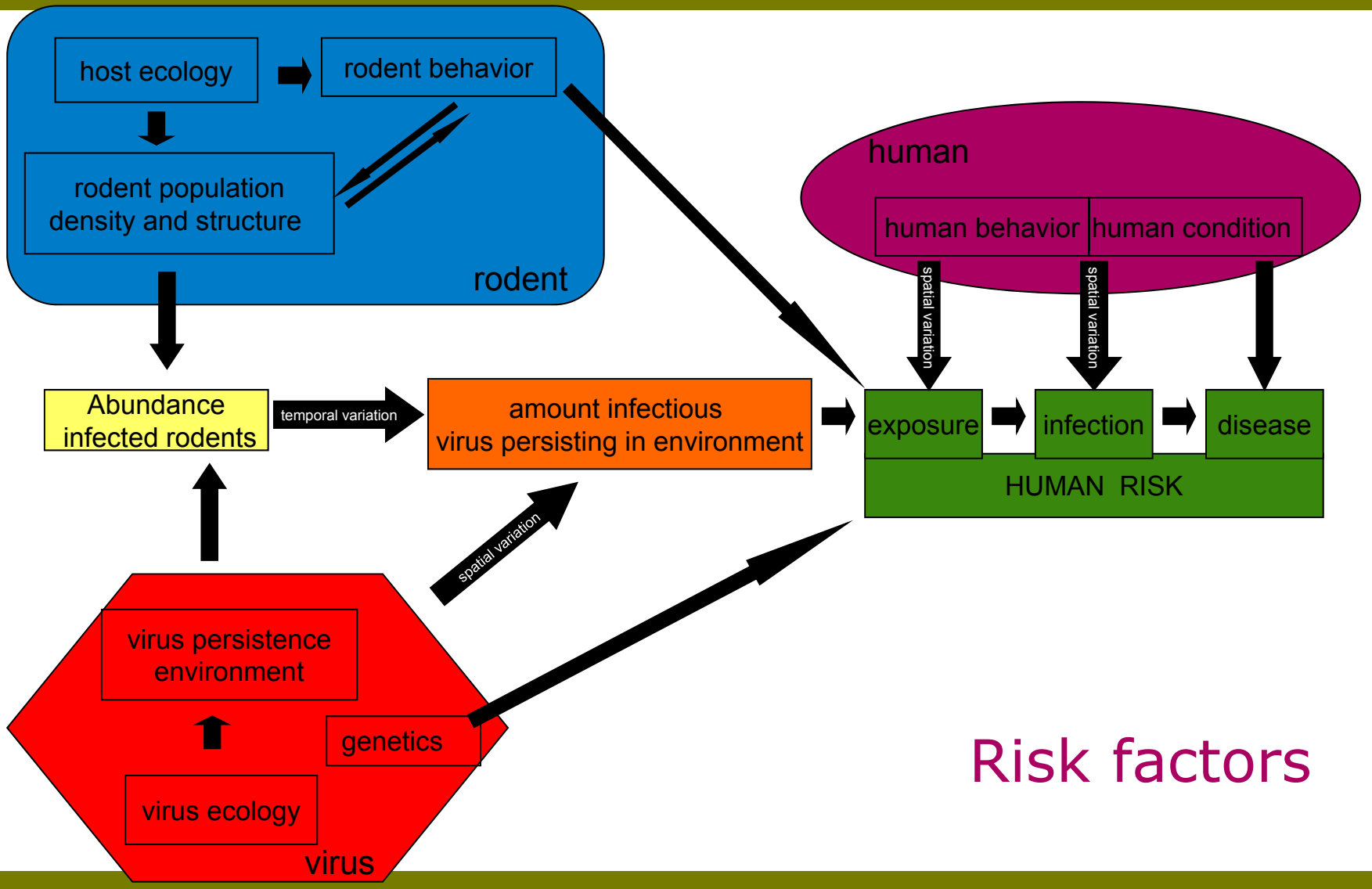
<u>Occasional</u>

- ► acute myopia
- ► renal disfunctioning
- ► haemorrhagic manifestations

mortality HFRS upto 12%; NE ~0.1%
(HPS 30-40%)

Zoonotic agent





Risk factors

Reusken and Heyman, Curr. Opin.Virol. 2013

Human- associated risk factors

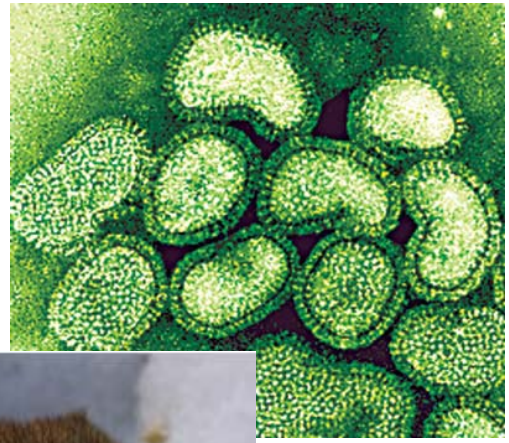
- Farming
- Camping/outdoor recreation
- Forestry
- (Cleaning) summer residences
- Living < 50 m from forest
- Male 35-45 yrs
- smoking

- military

Virus - associated risk factors

- Virus ecology

Environmental factors influencing virus survival;
Humidity, low temp. increase survival rate of virus;
UV leads to decrease



- Virus genetics

Serotype-dependent severeness of human disease

Dobrava virus -> severe HFRS
Seoul virus -> moderate HFRS
Puumala virus-> mild HFRS (NE)
Sin Nombre virus-> HPS

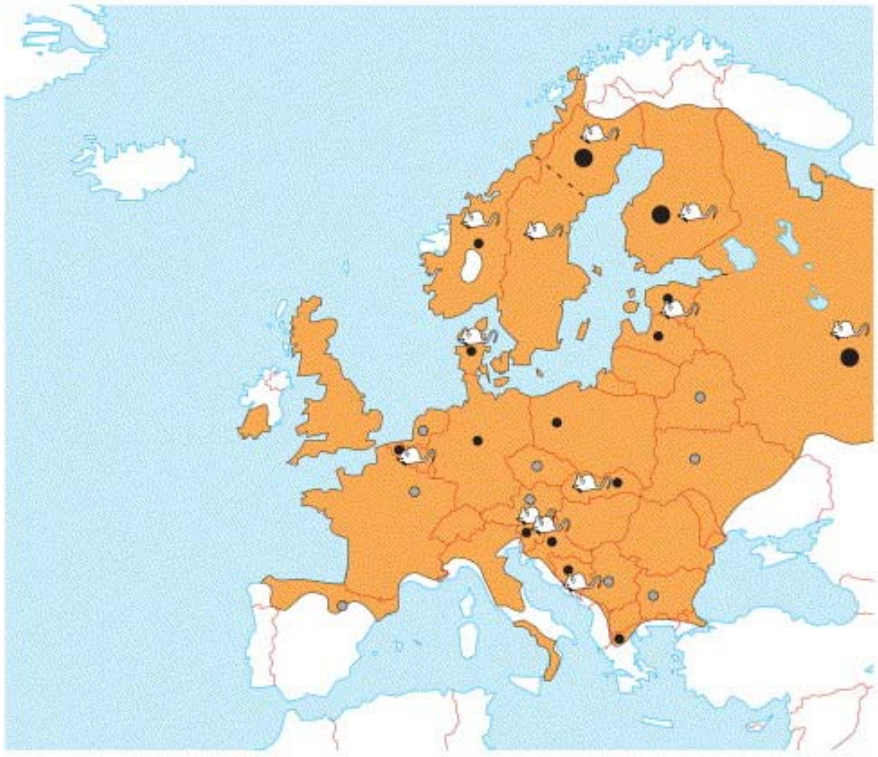
Rodent- associated risk factors

- Each hantavirus serotype is associated with a specific rodent species. (millions of years of co-evolution)
- Hantavirus – rodent reservoir combinations known in Europe:

Virus type	**Host**
<u>Murinae-associated</u>	
Dobrava virus	*Apodemus flavicollis*
Saaremaa virus	*Apodemus agrarius agrarius*
Seoul virus	*Rattus norvegicus/ rattus*
<u>Arvicolinae-associated</u>	
Puumala virus	*Myodes glareolus*
Tula virus	*Microtus arvalis*

Geographic distribution host limits distribution virus

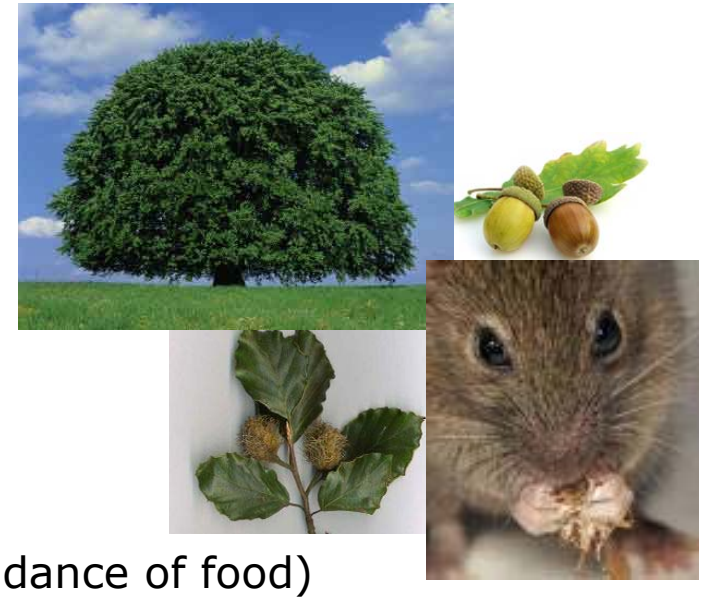
Myodes glareolus -> PUUV



(Vapalahti et al;., 2003)

hantavirus epidemiology = rodent host ecology

Of mice and mast.....



High seed production of oak and beech:
(mast production, t= -1)

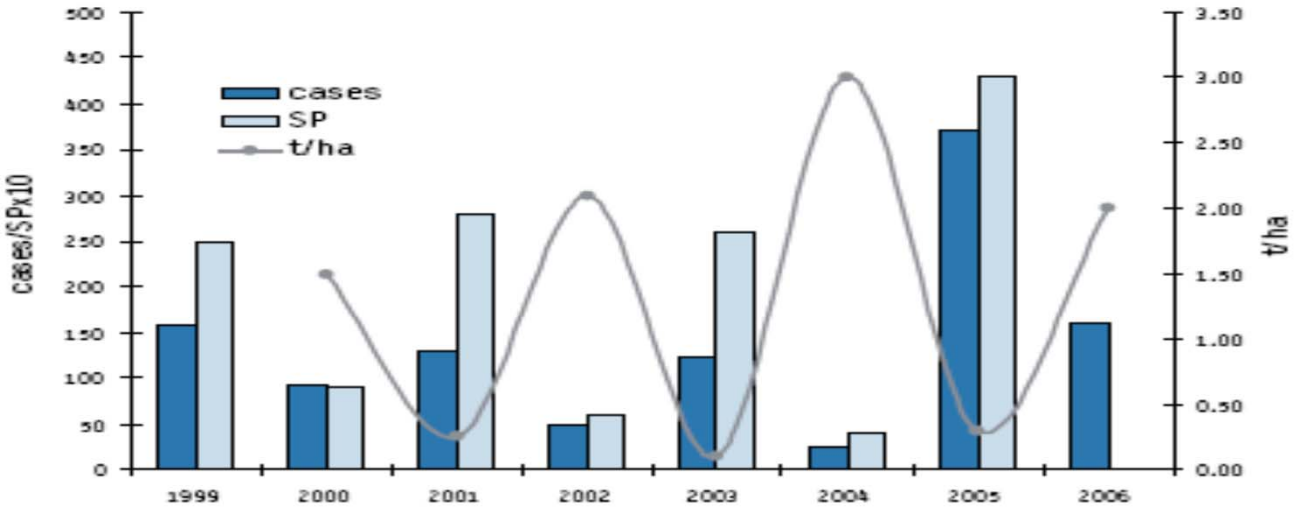
- Improved winter survival
- Elongation of breedingperiod
- Induction of winterbreeding
- Higher proportion of breeding females

(smaller breeding territories due to abundance of food)

→ High rodent population densities until next spring

→ Increase incidence NE (t=0)

Mast production vs
NE incidence and PUUV seroprevalence in rodents Belgium



Cases: yearly numbers of cases 1999-2006 (dark blue bars)
SP: mean PUUV seroprevalence in rodents on ten sites in Belgium (light blue bars)
t/ha: tons of acorns per hectare (grey line).

P. Heyman et al., 2008

Climate and NE incidence

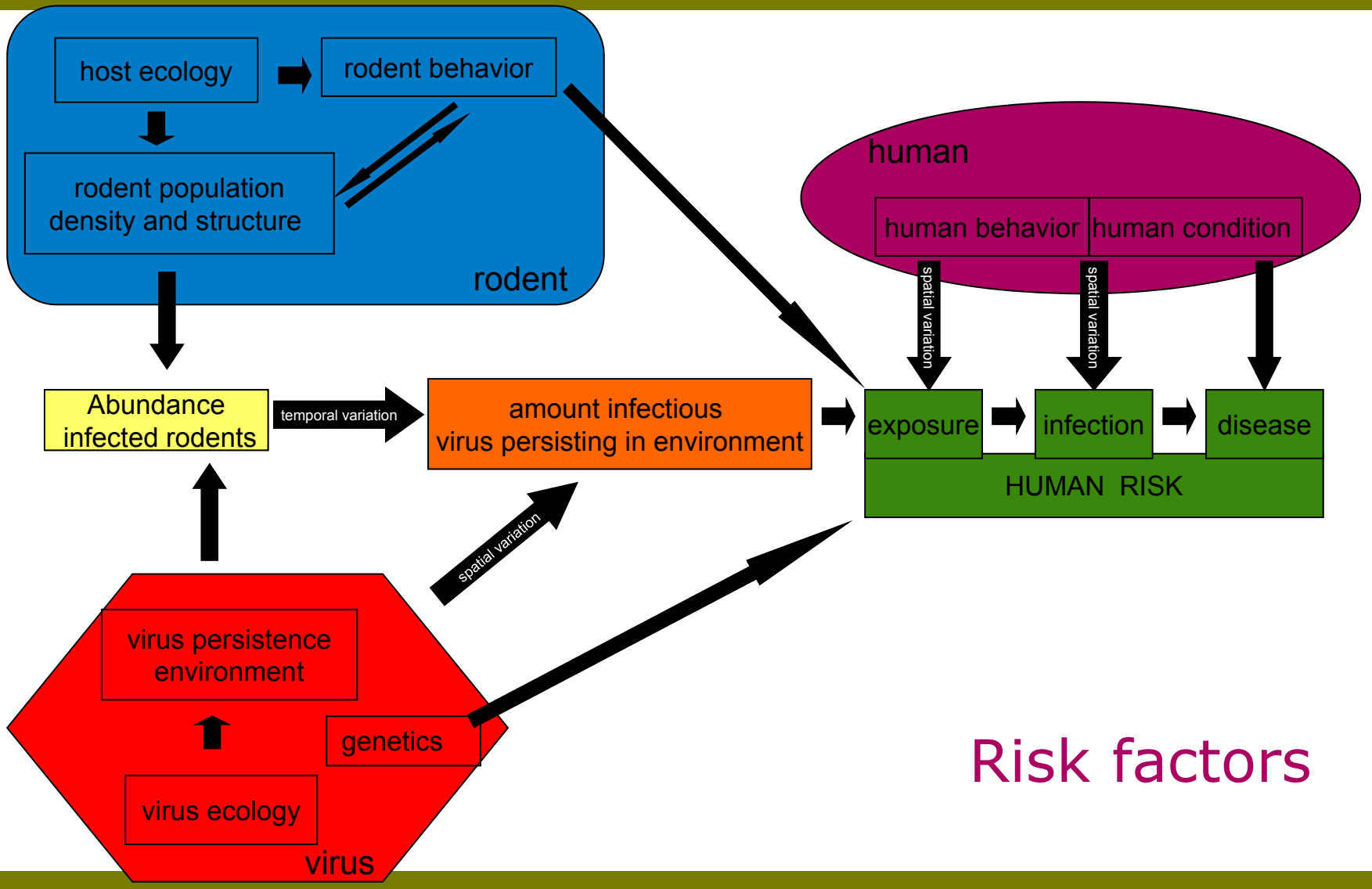
Hantavirus infections in NW-Europe are very sensitive to climate variabilities due to mast connection

- **Positive correlation between average summer temp. at t= -2 and NE incidence at t=0.**
  Warm/dry summer during flower bud formation = high seed production t= -1.

- **Positive correlation between average autumn temp. at t= -1 and NE incidence at t=0**
  Increased bank vole reproduction; extended presence of green biomass = elongation breedingperiod and positive effect on bodycondition

- **Influence on indirect transmission routes.**
  f.i. humidity and cold/snow increase survival rate of virus; UV leads to decrease.

(Tersago *et al.*, 2008)



Risk factors

Reusken and Heyman, Curr. Opin.Virol. 2013

Hanta virus trends in Europe

Table 1

Hantaviruses circulating in Europe.

Virus	CFR[a]	Carrier (scientific name)	Carrier (common name)	Disease[b]
Seoul virus (SEOV)	1–2%	*Rattus rattus* *R. norvegicus*	Roof rat, black rat, ship rat Brown rat, Norway rat	HFRS
Tula virus (TULV)	?	*Microtus arvalis* *M. rossiaemeridionalis* *M. agrestis*	Common vole Russian Common Vole Field vole, short-tailed vole	HFRS, mild
Puumala virus (PUUV)	<0.1%	*Myodes glareolus*	Bank vole	HFRS, mild
Dobrava-Belgrade virus (DOBV)	12%	*Apodemus flavicollis*	Yellow-necked field mouse	HFRS, severe
Saaremaa virus[c]	?	*A. agrarius agrarius*	Striped field mouse, western subspecies	HFRS, mild
Kurkino virus[c]	?	*A. agrarius agrarius*	Striped field mouse, western subspecies	HFRS, mild
Sochi virus[c]	10%	*A. ponticus*	Black Sea field mouse	HFRS, severe
Viruses carried by insectivores				
Seewis virus (SWSV)	?	*Sorex araneus*	Eurasian common shrew	?
Nova virus (NVAV)	?	*Talpa europeae*	European mole	?

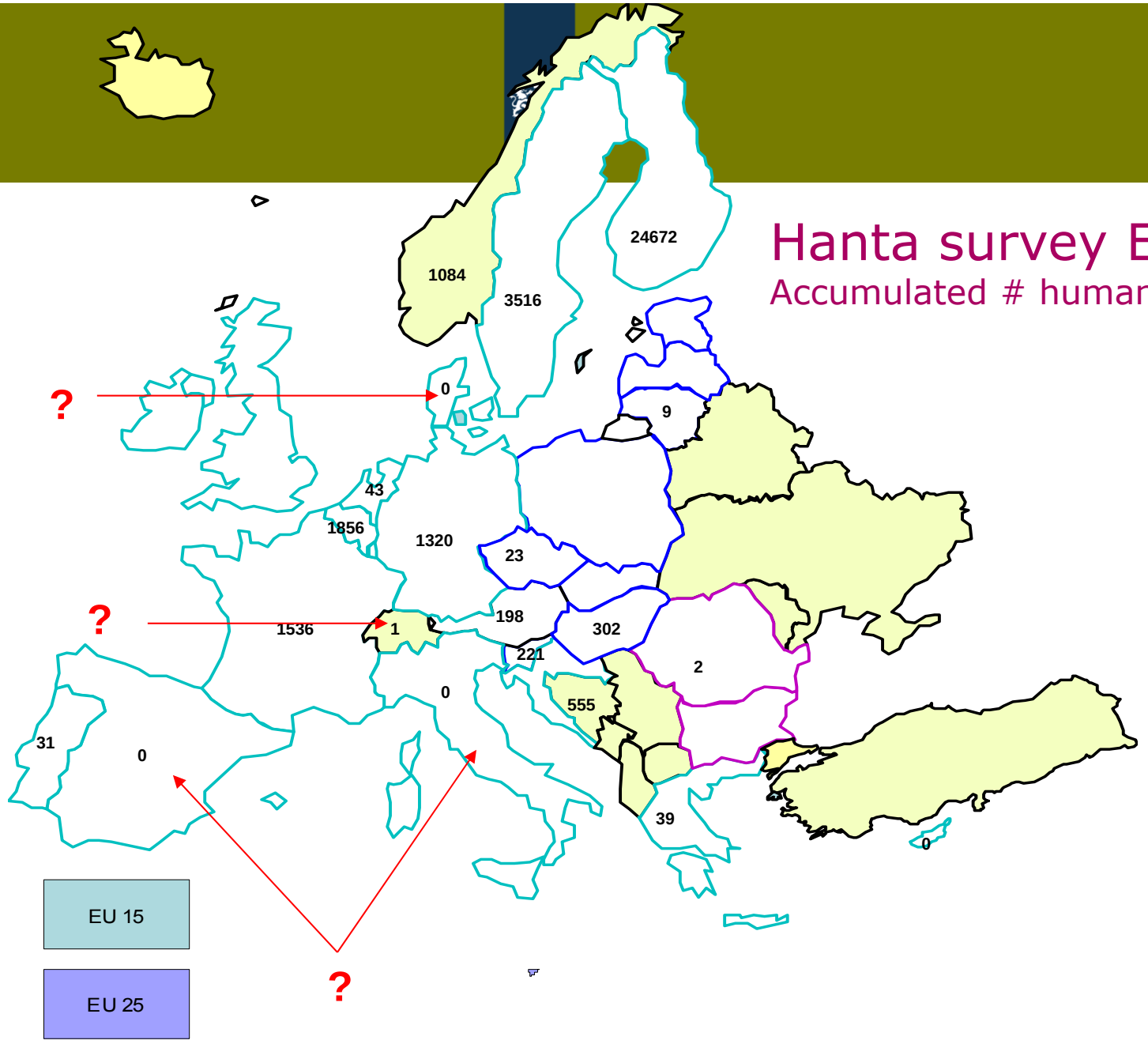
[a] Case fatality rate.
[b] HFRS: hemorrhagic fever with renal syndrome. Adapted from [1•].
[c] DOBV genotypes [76].

Reusken and Heyman, *Curr. Opin. Vir.*, 2013

Hanta survey EU

Accumulated # human cases

PUUV
DOBV
SAAV

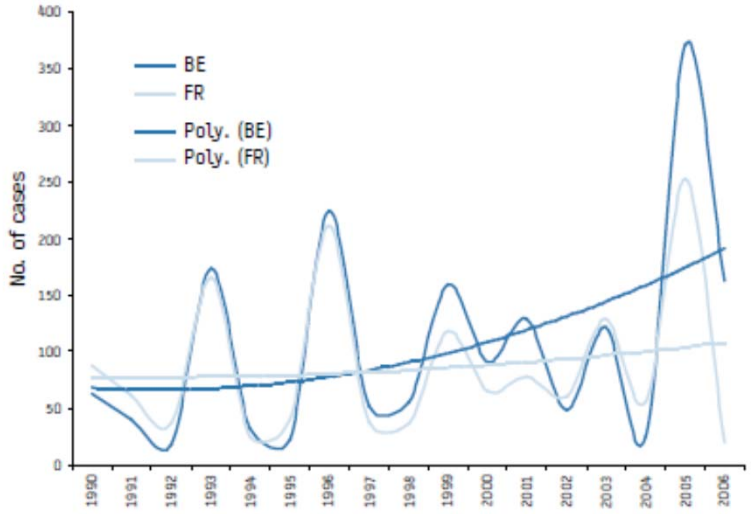


19 april 2011

P. Heyman & A.Vaheri,
on behalf of ENIVD members

Trends Belgium, Germany, France.

Trends of hantavirus infections in Belgium and France, 1990-2006, ENIVD study 2007



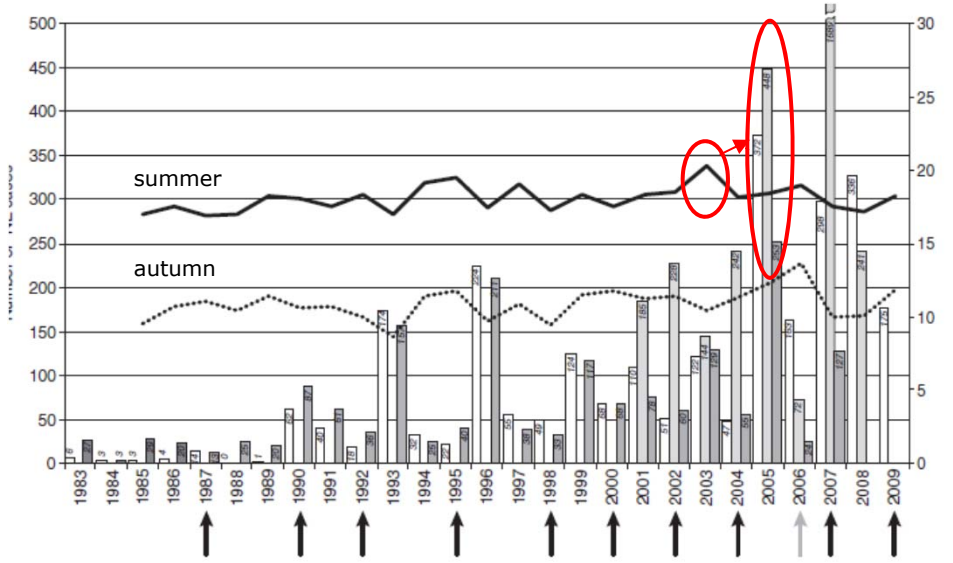
Dark blue: yearly number of cases in Belgium
Light blue: yearly number of cases in France

Poly : Polynomial trendline: Calculates the least squares fit through points by using the following equation:
y = b + c1x + c2x2 + c3x3 + ... c6x6 , where b and c1... c6 are constants.

Trendlines in corresponding colour.

P. Heyman et al., 2008

-Gradual increase # NE
-Higher frequency of mast years; 3-year -> 2-year
-Expansion endemic areas in Be, Fr, Ger;
Ger even into urban areas.



Clement et al., 2010

SEOV in pet rats

RAPID COMMUNICATIONS

The continued emergence of hantaviruses: isolation of a Seoul virus implicated in human disease, United Kingdom, October 2012

L J Jameson (lisa.jameson@hpa.org.uk)[1,2], C H Logue[1], B Atkinson[1], N Baker[3], S E Galbraith[2], M W Carroll[1], T Brooks[4], R Hewson[1]
1. Virology and Pathogenesis, Microbiology Services, Health Protection Agency, Porton Down, Wiltshire, United Kingdom

RAPID COMMUNICATIONS

Pet rats as a source of hantavirus in England and Wales, 2013

L J Jameson (lisa.jameson@hpa.org.uk)[1,2], S K Taori[3], B Atkinson[1], P Levick[4], C A Featherstone[5], G van der Burgt[6], N McCarthy[7], J Hart[8], J C Osborne[3], A L Walsh[9], T J Brooks[3], R Hewson[1]
1. Virology and Pathogenesis, Microbiology Services, Health Protection Agency, Porton Down, Wiltshire, United Kingdom

RAPID COMMUNICATIONS

Pet rat harbouring Seoul hantavirus in Sweden, June 2013

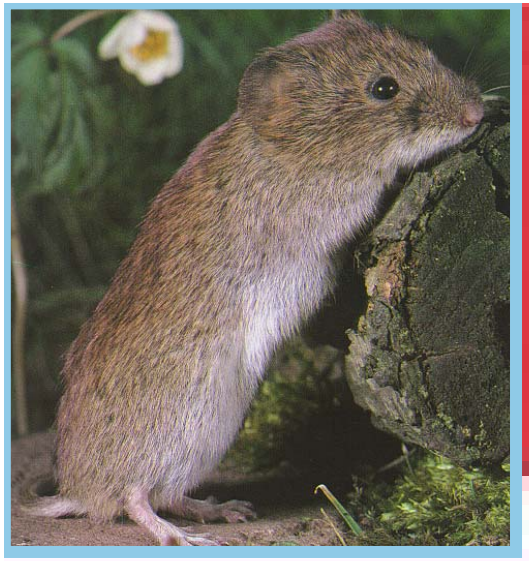
Å Lundkvist (ake.lundkvist@smi.se)[1,2,3], J Verner-Carlsson[1,2], A Plyusnina[4], L Forslund[5], R Feinstein[5], A Plyusnin[4]
1. Swedish Institute for Communicable Diseases, Solna, Sweden

Case Report

UK hantavirus, renal failure, and pet rats

Surabhi K Taori, Lisa J Jameson, Andrew Campbell, Peter J Drew, Noel D McCarthy, Judy Hart, Jane C Osborne, Malur Sudhanva, Timothy J G Brooks

Hanta virus in the Netherlands: what do we know?



Myodes glareolus = PUUV

Microtus arvalis = TULV

Apodemus flavicollis = DOBV

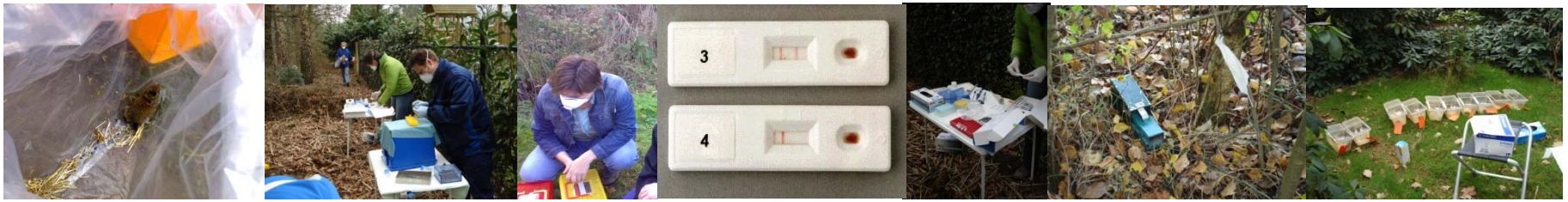
Rattus rattus/

Rattus norvegicus = SEOV

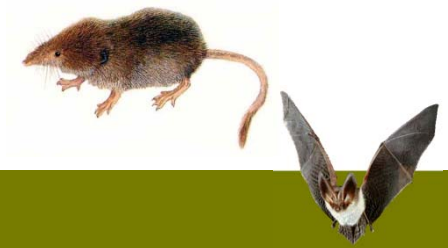
Apodemus sylvaticus ????

Reservoir studies

- PUUV in *Myodes glareolus*. Serology, Molecular.
- TULV in *Microtus arvalis.* Serology, Molecular. Human cases?
- SEOV in *Rattus norvegicus* and *Rattus rattus*. Serology. -> debate
- No active studies in *Apodemus flavicollis* for DOBV.
- PUUV seropositivity in *Apodemus sylvaticus*, known spill-over host



- Currently*:* insectivoren, *Rattus* sp. other wildlife.



Predictions based on European beech mast connection

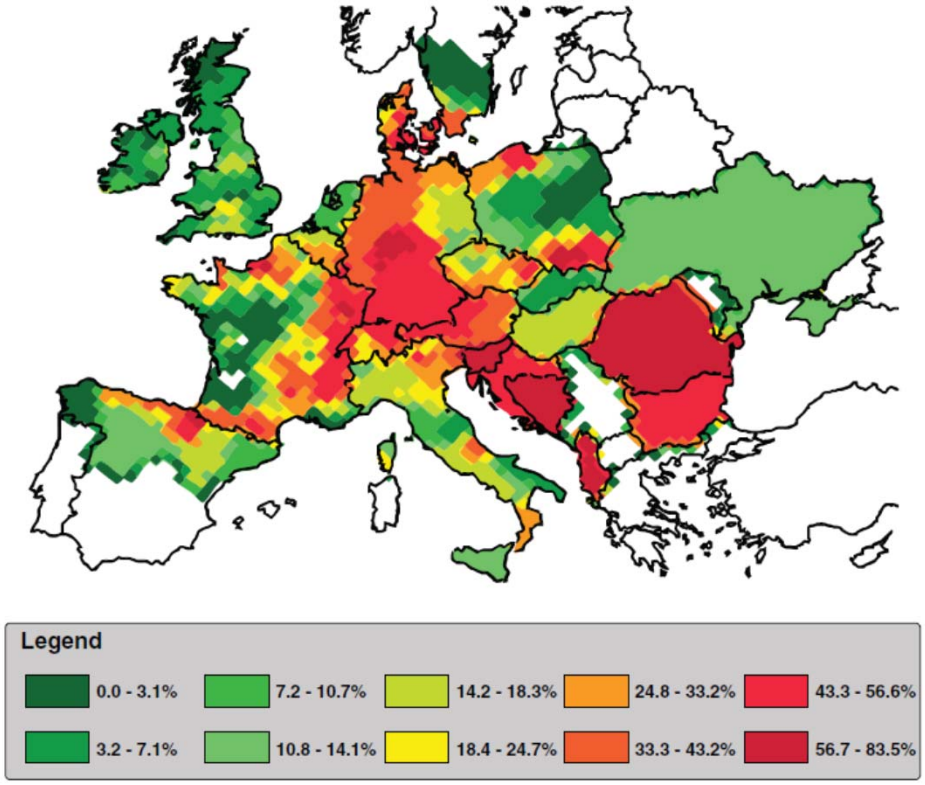


Fig. 3. Density of the European beech (*F. sylvatica*) in percentage of broadleaf forests; adapted from [35]. The spread of the beech tree mirrors almost exactly the spread of NE in Europe: absence in the UK and in Southern Europe, and heavy presence in Southern Germany, Northeast France, Southern Belgium and most of the Balkans. The tiny eastern peak in the Netherlands with somewhat denser beech cover (around Enschede near the German border) is also the first and only region wherein a dense NE outbreak was documented [47]. In contrast to these countries, Romania and Bulgaria are only thinly populated with bank voles, despite their dense beech cover. Moreover, lower medical awareness and diagnostic possibilities can contribute to lower reporting of NE from these countries.

Clement et al., 2010

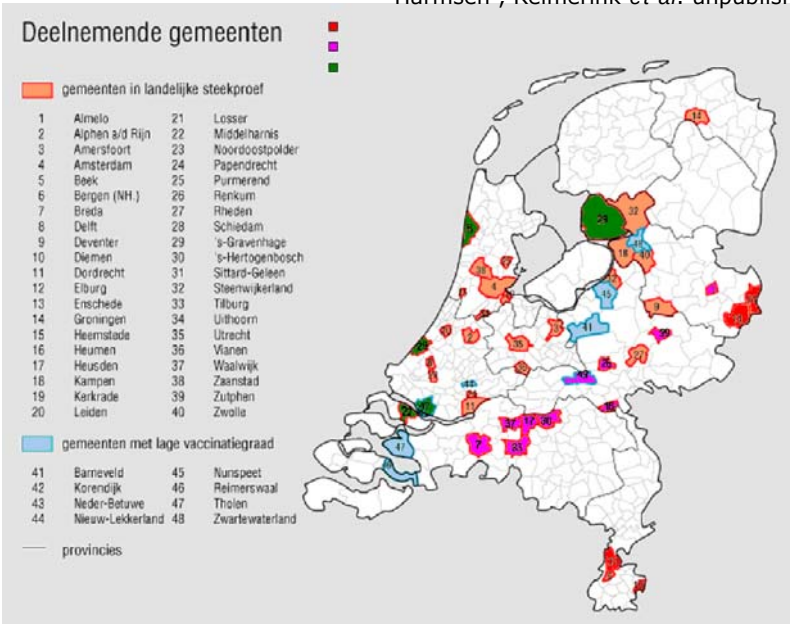
Human cases in the Netherlands.

- Only notifyable since december 2008.
- All typed based on serology as PUUV, but crossreactivity with TULV !
- Registered cases:

2003: 0
2004: 1
2005: 7
2006: 8
2007:27
2008:17
2009:7*
2010: 19*
2011: 7*
2012: 23*
---
116 cases

Seroprevalence study the Netherlands.

Harmsen , Reimerink *et al*. unpublished



Method
- Tested 2929 sera Pienter 2 (2006-2007)
- IgG ELISA + confirm. IFA

Results
- Seroprevalence 1.7% (95%BI 1.29-2.28%)
- Risk factors:
  - dog (OR 5.02, BI 2.85-8.85)
  - livestock (OR 4.59, BI 2.81-7.49)
  - netto income < €1150,00 (OR 4.72, BI 2.07-10.77)
  - female (0R 1.81, BI 1.17-2.82)
  - living in Twente (OR 5.24, BI 3.73-7.38)

Conclusion based on notification vs seroprevalences:
- Hantavirus infections are underdiagnosed in the Netherlands -> Marco Goeijenbier