NBVCG Riga 4-10-2018

Viral infections emerging from wildlife

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Emerging infections

- **scale**: *global - regional - local*
- **significance**: *human /animal health - food supply - economy*
- **current megatrends favoring emergence**:

globalisation - travel - urbanization - environmental changes - industrial animal husbandry

- but also: modern diagnostic tools

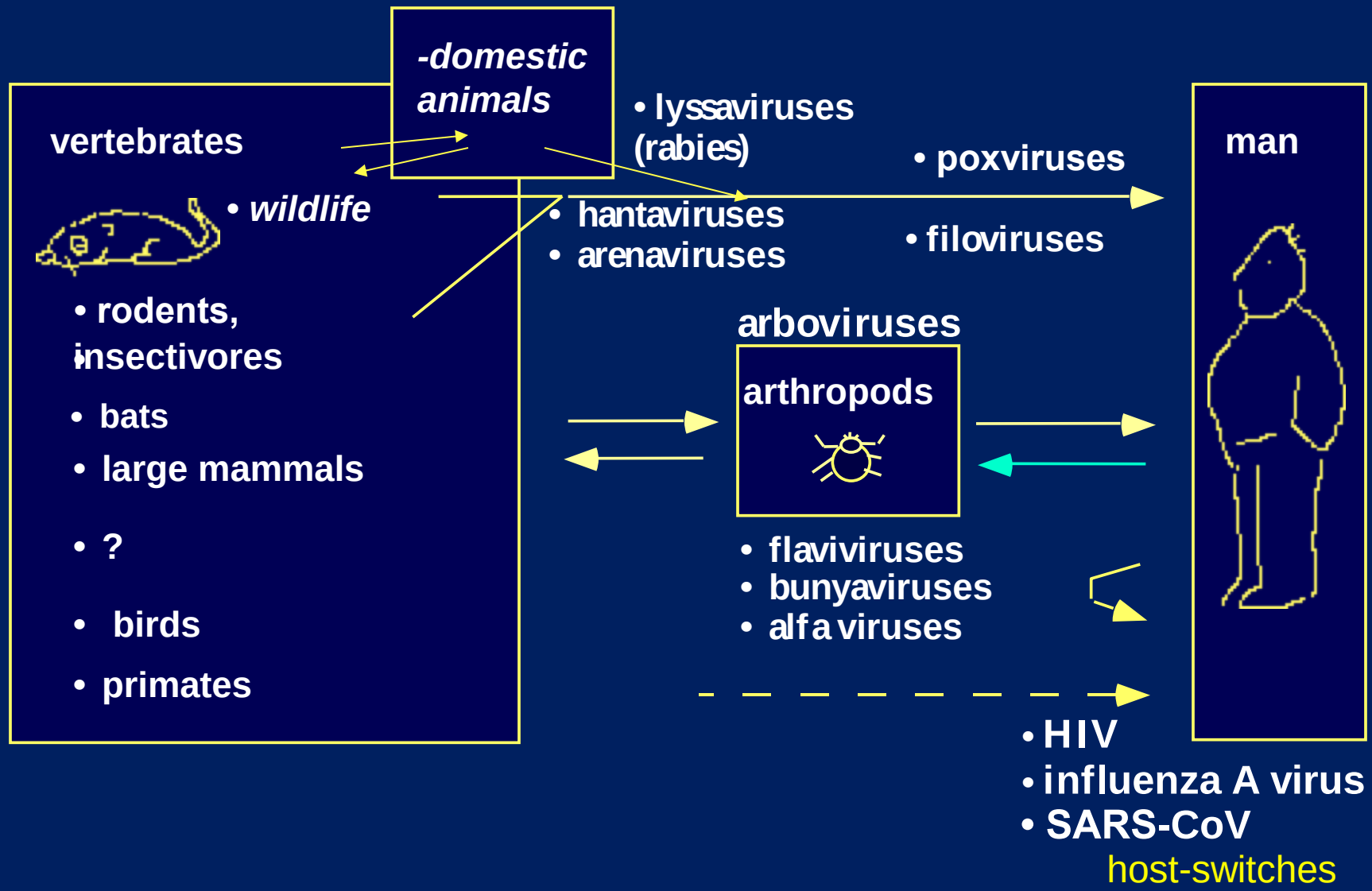
Agenda today

- general aspects of viral *zoonoses* emerging from wildlife
- viruses/diseases from wildlife (on stage today)

- rodent/insectivore-borne
  - hantaviruses
  - arenaviruses
  - bornaviruses
  - orthopoxviruses
- bird-borne – influenza A virus -arboviruses -TBEV
- bat-borne: lyssaviruses, (filoviruses),
- • Surveillance in Europe, Protective measures, Potential treatments

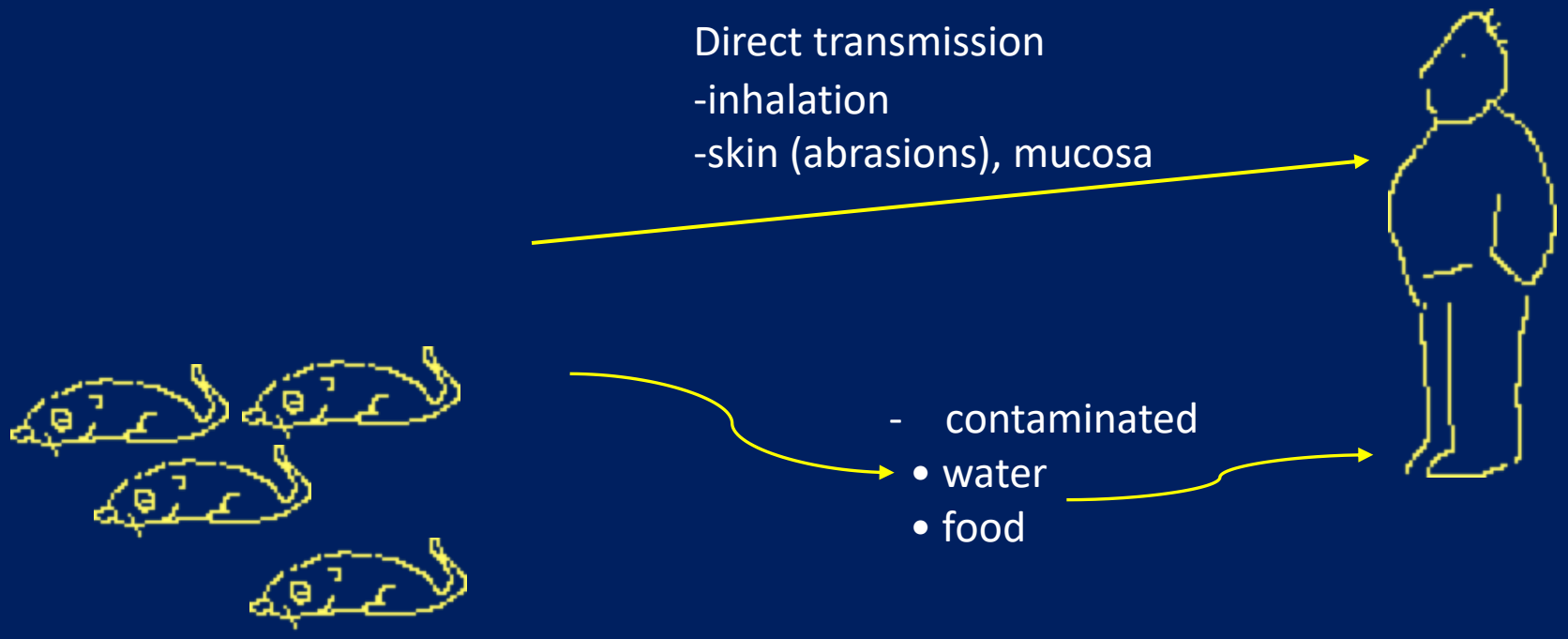
- metagenomics approaches to study viral diversity, molecular epdiemiology,evolution

ZOONOTIC VIRUSES AND HOST-SWITHCES



Rodent-borne

Rodent-borne zoonotic infections



Rodent-borne zoonotic infections

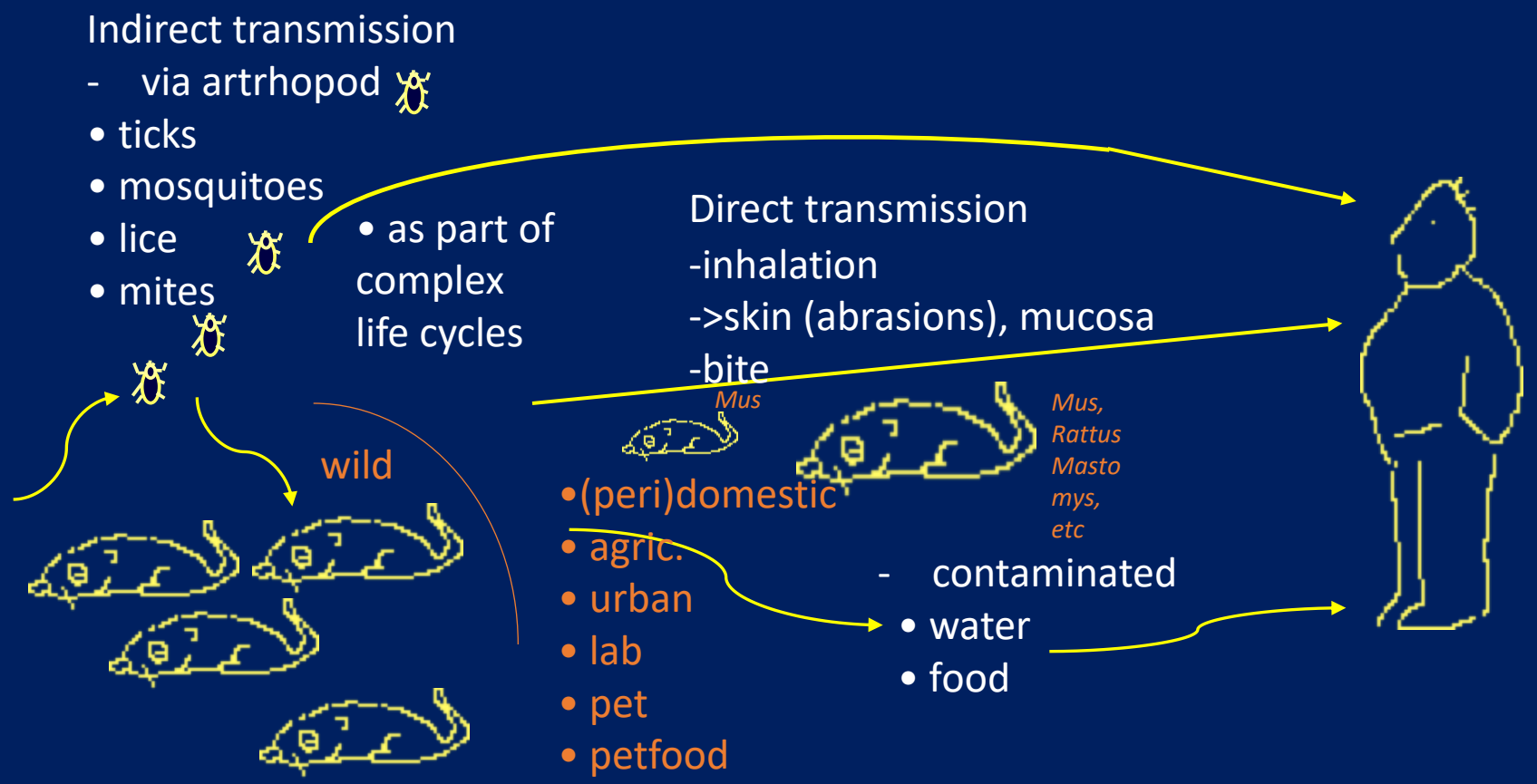
Indirect transmission
- via artrhopod
• ticks
• mosquitoes
• lice
• mites

• as part of complex life cycles

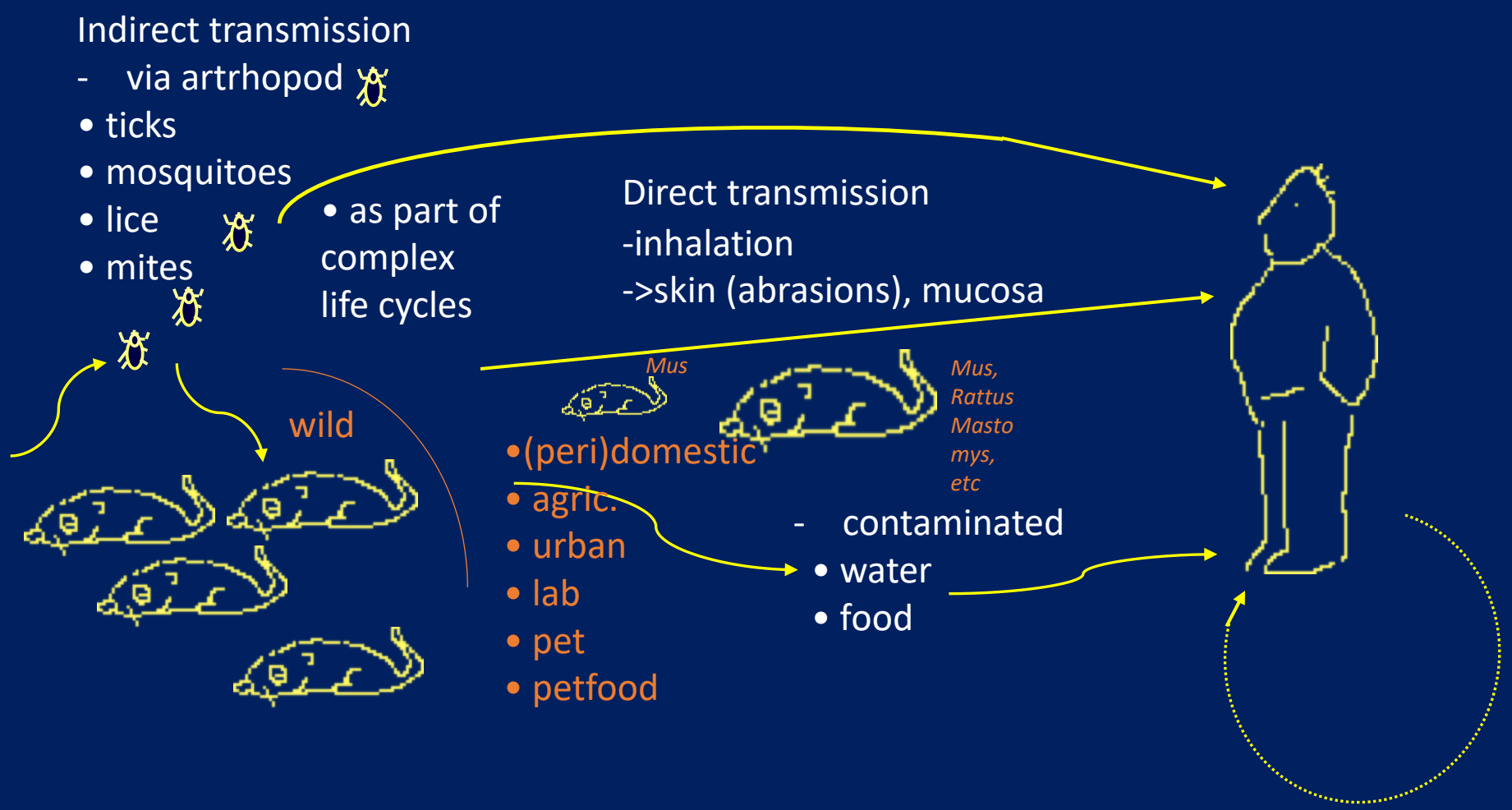
Direct transmission
-inhalation
->skin (abrasions), mucosa

- contaminated
• water
• food

Rodent-borne zoonotic infections

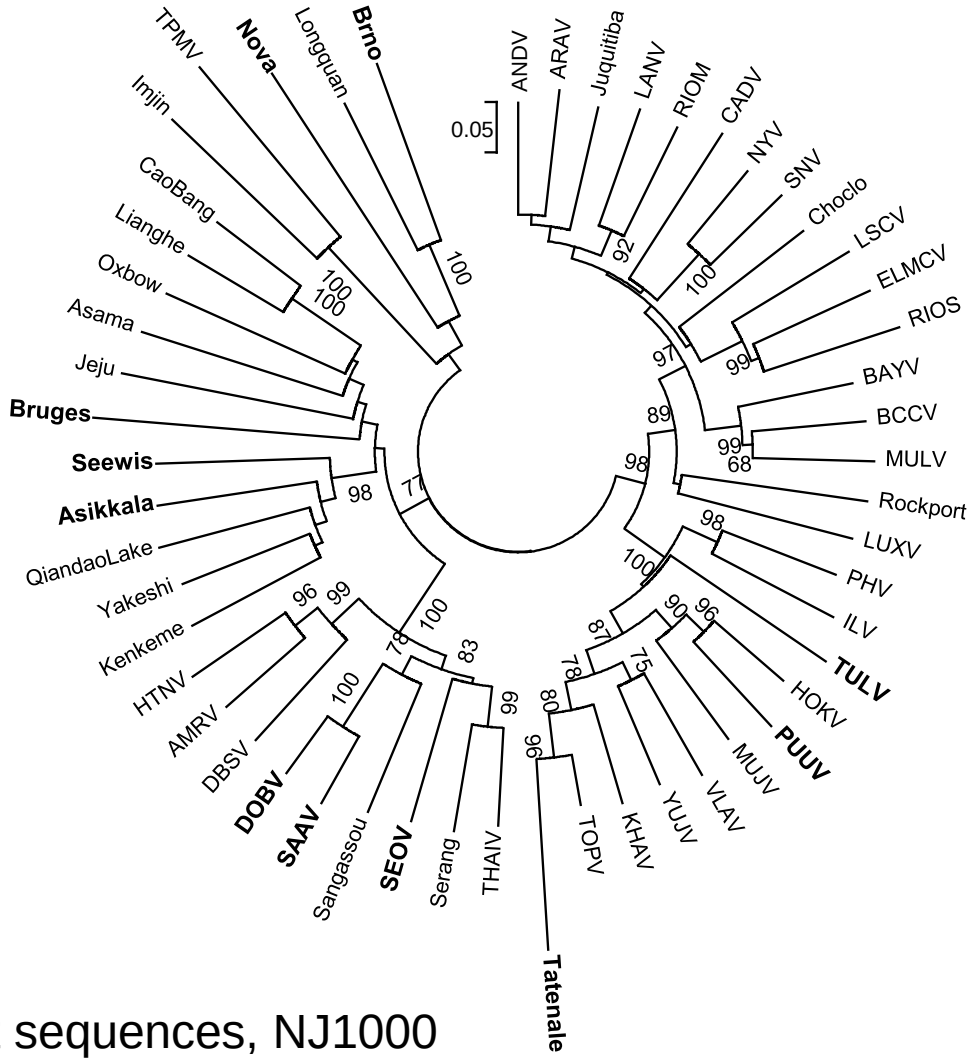


Rodent-borne zoonotic infections



Hantavirus species

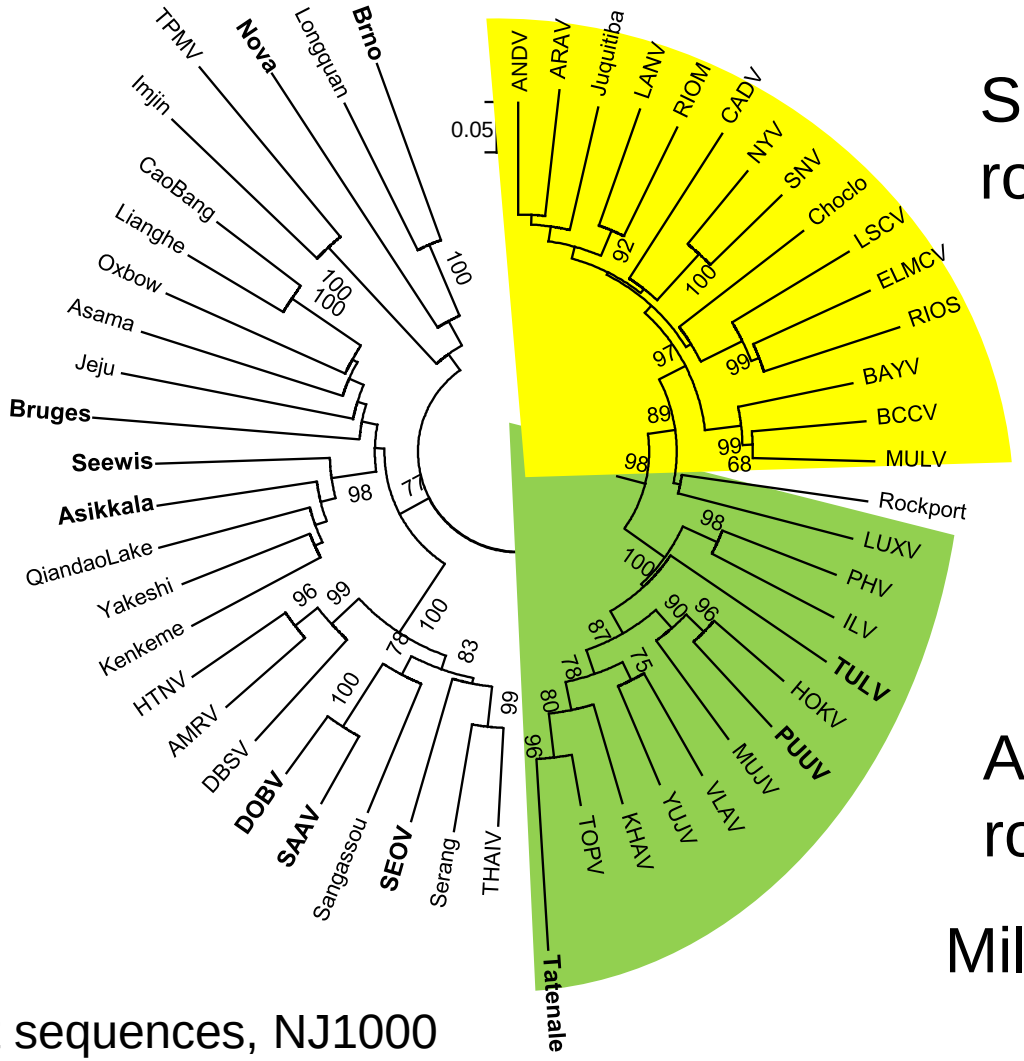
(Europeans **in bold**)



Partial S segment sequences, NJ1000

Hantavirus species

(Europeans **in bold**)



Sigmodontine rodents

HPS

Arvicoline rodents

Mild HFRS/NE

Partial S segment sequences, NJ1000

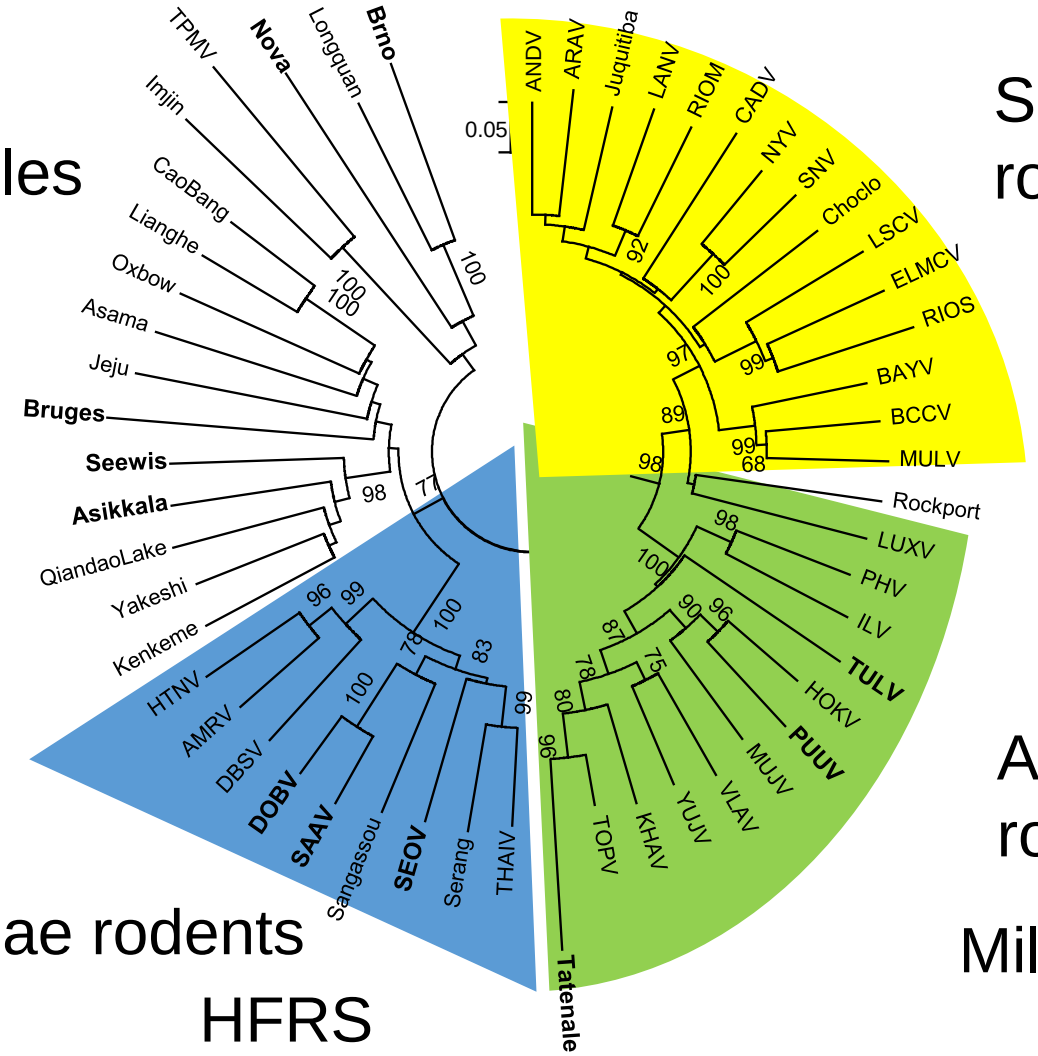
Hantavirus species

(Europeans **in bold**)

Bats

Insectivores

-Shrews, -Moles



Sigmodontine rodents

HPS

Arvicoline rodents

Mild HFRS/NE

Muridae rodents

HFRS

Partial S segment sequences, NJ1000

Carrier of PUUV MILD HFRS

Bank vole *Myodes glareolus*

Carrier of DOBV SEVERE HFRS

-Dobrava lineage

Yellow-necked mouse *Apodemus flavicollis*

Carrier of DOBV MILD HFRS

- Kurkino and Saaremaa lineages

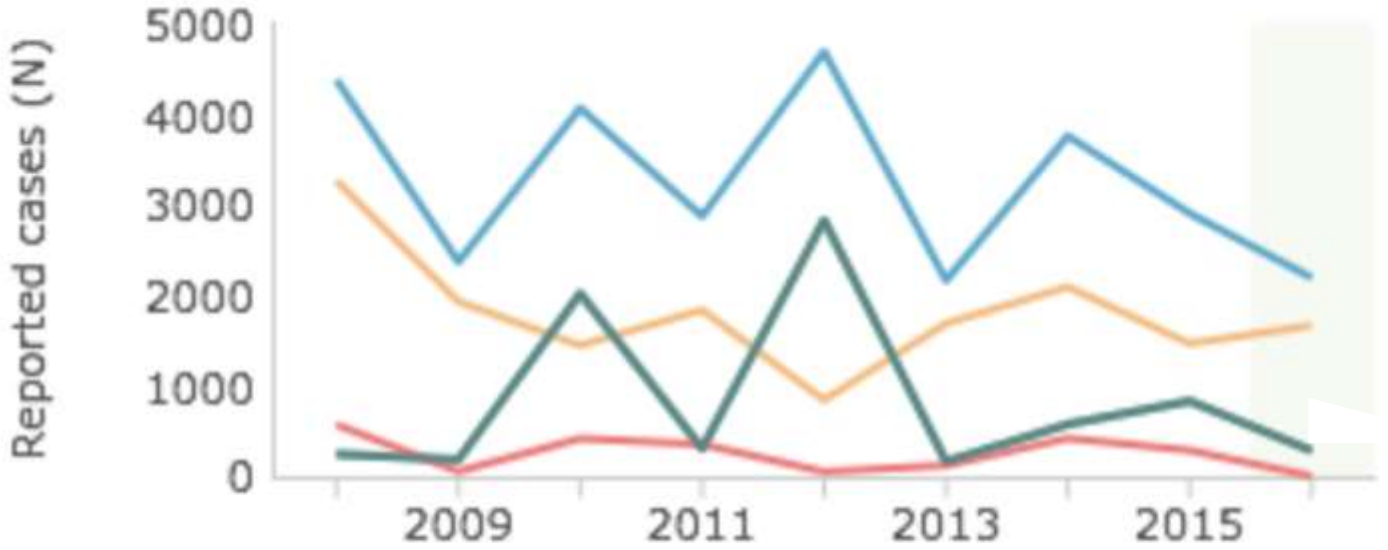
Striped field mouse *Apodemus agrarius*

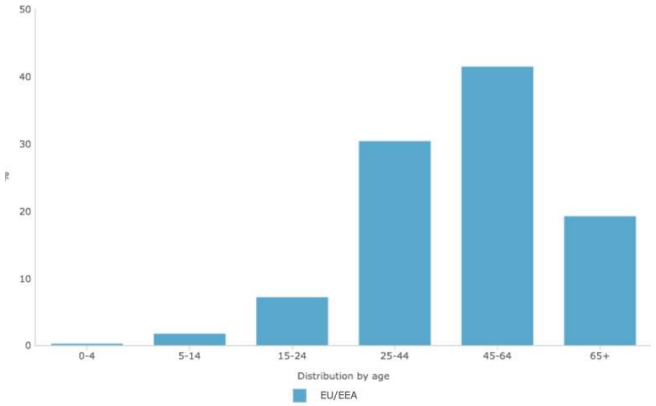
Carrier of DOBV MODERATE-SEVERE HFRS

Sochi lineage

Black sea field mouse *Apodemus ponticus*

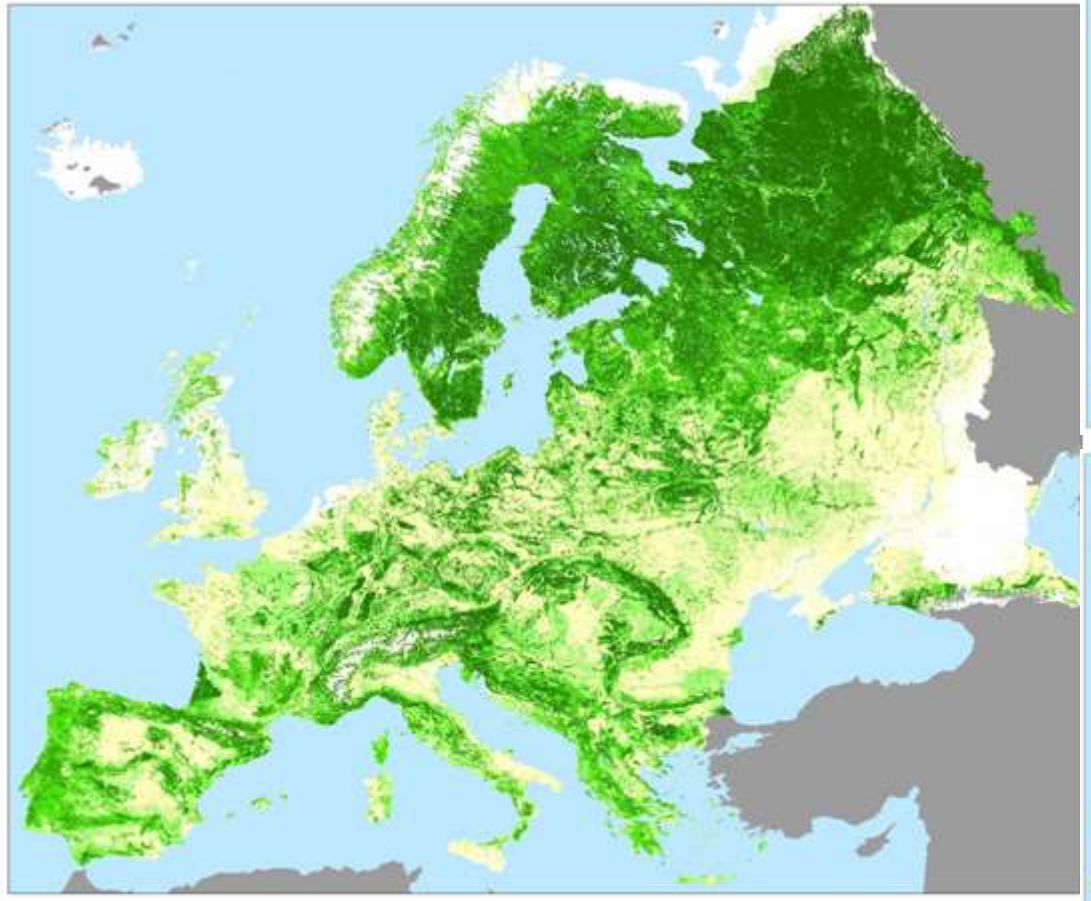
Hantavirus infections in Europe (EU/EEA) 2008-16 and Germany, Finland and Sweden





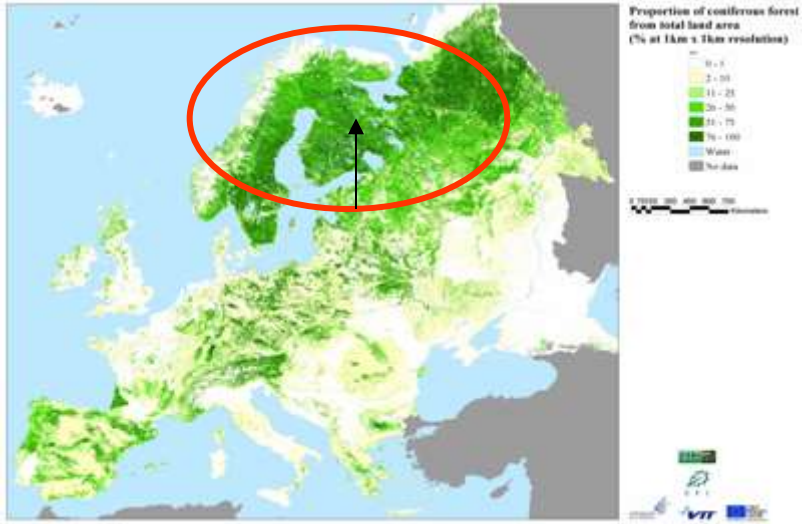
Forest coverage in Europe (by EFI) and rodent patterns

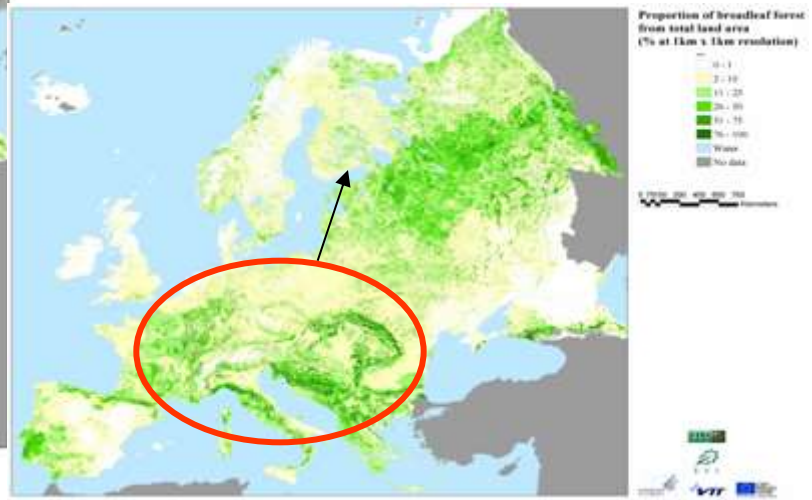
Total



Forest landscape
homo/ heterogeneity

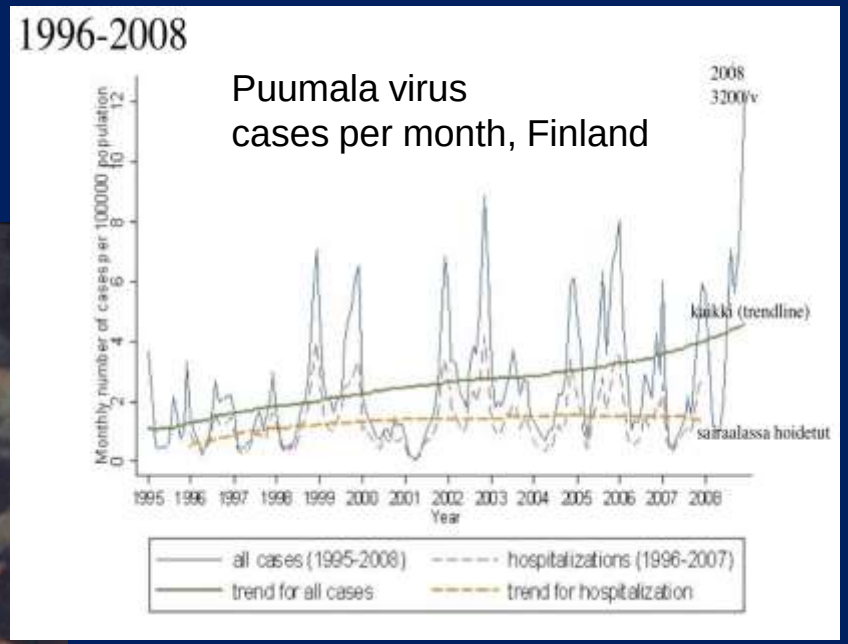
conif., cyclic snowy world





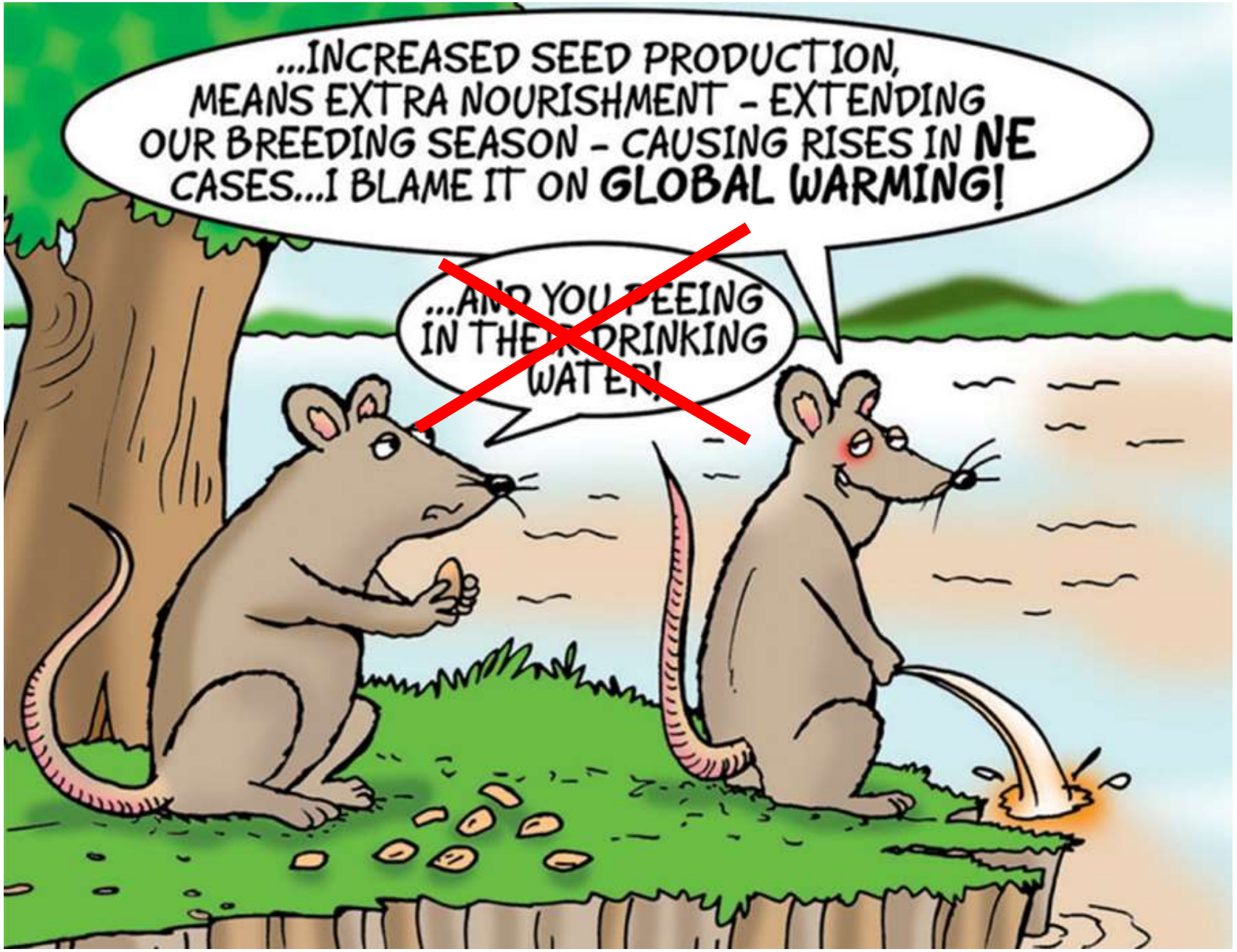
decid., mast driven dynamics

Bank vole
(Myodes glareolus)



Excreta are infectious 2 weeks in RT, Kaliio J Gen Virol 06

Spring Autumn Spring Autumn Spring Autumn



Dixon, Lancet Infectious Diseases, March 2009

Main risk factors for Puumala virus:
- smoking
- house has openings allowing rodents to enter

→ transmission indoors inhalation

Seoul virus:
increasing threat

- Pet rats
- Wild/urban population
- Rats raised for ”reptile food”
- Experimental animals

• **United Kingdom:** Jameson L et al: Pet rats as a source of hantavirus in England and Wales, 2013. Euro Surveill. 2013

• **Sweden:** Lundkvist Å, et al: Pet rat harbouring Seoul hantavirus in Sweden, Euro Surveill. 2013

• **France:** • Reynes J, et al. Seoul Virus Infection in Humans, France, 2014–2016. Emerg Infect Dis. 2017 (3 cases, construction worker, pet rat owner, person raising rats as a food source for snakes)

• **Belgium:** Plyusnina A, Genetic characterization of seoul hantavirus originated from norway rats (Rattus norvegicus) captured in Belgium. J Med Virol, 2012.

• **The Netherlands:** Verner-Carlsson J, First evidence of Seoul hantavirus in the wild rat population in the Netherlands. Infect Ecol Epidemiol. 2015

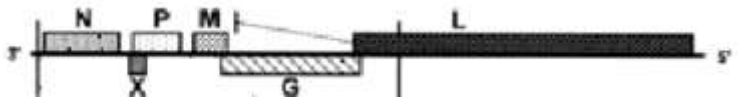
Most common pet rodent species (Finland)

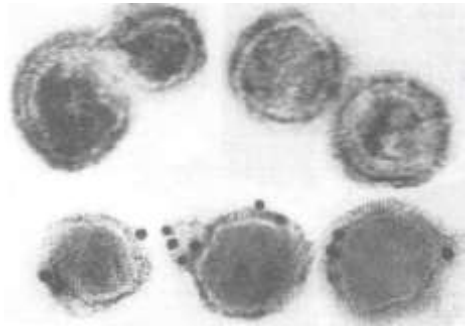
Family	Genus	Species	English name	Natural distribution
Caviidae	Cavia	porcellus	guinea pig, cavy	S America
Chinchillidae	Chinchilla	lanigera	chinchilla	S America (Andes)
Cricetidae	Cricetulus	barabensis (griseus)	Chinese hamster	China, Mongolia
	Mesocricetus	auratus	Golden/ Syrian hamster	SE Europe Middle East
	Phodopus	campbelli	Campbell's Dwarf hamster	Mongolia, China, C Asia
		roborovskii	Roborovski hamster	Mongolia, N China
		sungorus	Djungarian / Winter-white Russian hamster	Kazakstan, Mongolia, Siberia
Muridae	Acomys	cahirinus	Cairo Spiny mouse	N Africa, Middle East
	Lemniscomys	barbarus	Barbary striped grass mouse	N, C Africa
	Mastomys	natalensis	Natal multimammate mouse	Africa
	Meriones	unguiculatus	Mongolian gerbil	Mongolia
	Mus	musculus	Mouse, Fancy mouse	Global
	Rattus	norvegicus	Fancy rat	Global
Octodontidae	Octodon	degus	degu, brush-tailed rat	S America (Andes)
Sciuridae	Cynomus	ludovicianus	Prairie dog	N America
	Tamias	sibricus	Siberian chipmunk	Siberia

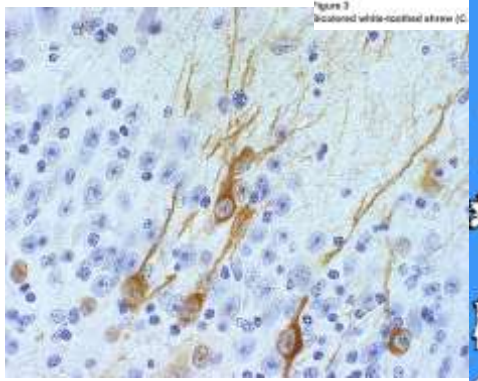
Milla Mertaoja, licenciate thesis, Faculty of Veterinary Medicine, Univ. of Helsinki, 2012

Borna disease virus (BDV)

- *Mononegavirales:*
- genome 8.9 kb RNA; replikaatio ja transcription in the nucleus
- neurotropic
- infect many vertebrates, also human, lethal CNS disease found in horse, sheep, cat(?)
- reservoir: shrew (Crocidura leucodon)
- BoDV gene sequences integrated to mammalian genomes







titz, Tübingen

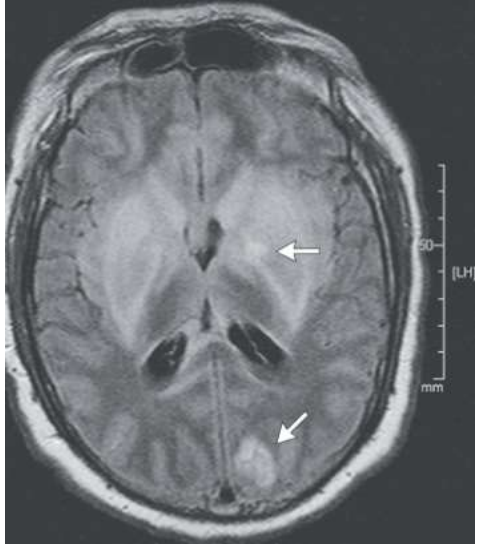
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2015;373:154-62.

BRIEF REPORT

A Variegated Squirrel Bornavirus Associated with Fatal Human Encephalitis

Bernd Hoffmann, D.V.M., Dennis Tappe, M.D., Dirk Höper, M.Sc., Christiane Herden, D.V.M., Annemarie Boldt, M.D., Christian Mawrin, M.D., Olaf Niederstraßer, M.D., Tobias Müller, M.D., Maria Jenckel, M.Sc., Elisabeth van der Grinten, D.V.M., Christian Lutter, D.V.M., Björn Abendroth, M.Sc., Jens P. Teifke, D.V.M., Daniel Cadar, D.V.M., Ph.D., Jonas Schmidt-Chanasit, M.D., Rainer G. Ulrich, Ph.D., and Martin Beer, D.V.M.



Variagated squirrel

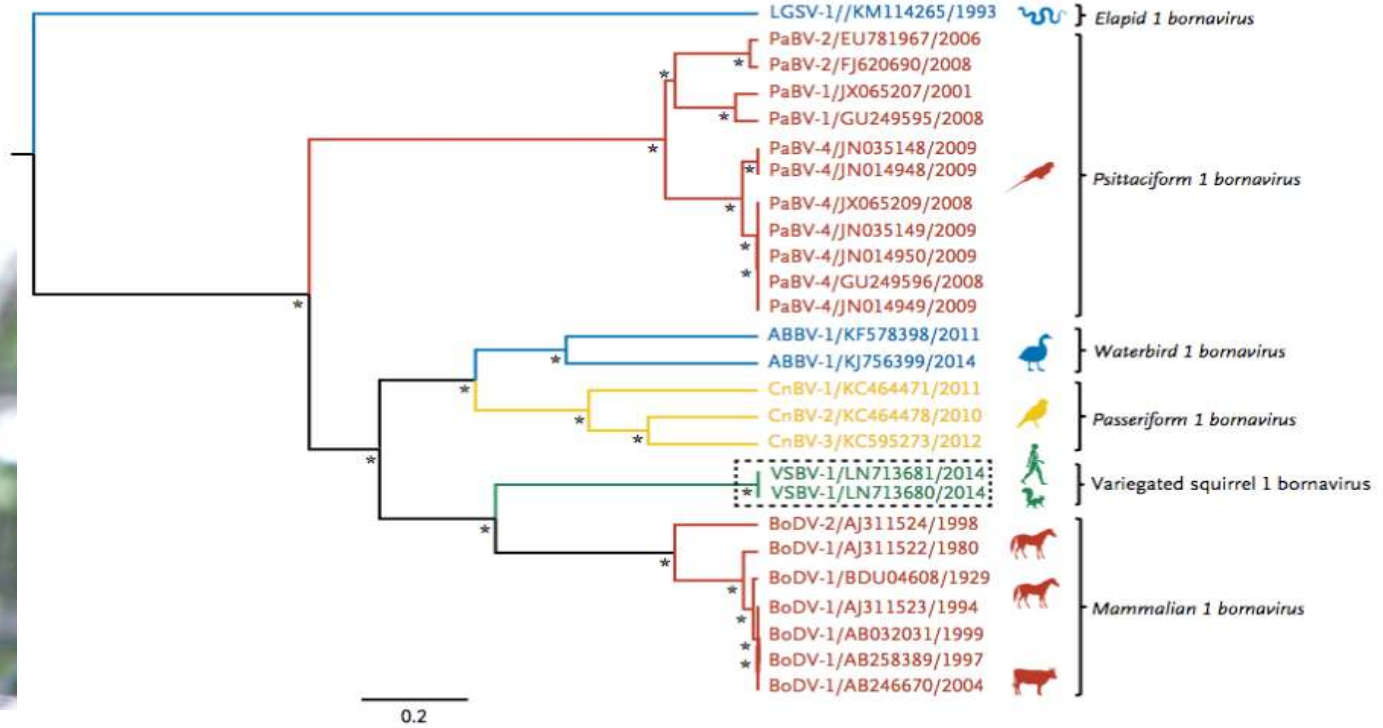


Figure 2. Phylogenetic Analysis of the Members of the Bornavirus Genus, Including the Putative Variegated Squirrel 1 Bornavirus (VSBV-1)

Lethal encephalitis of ”classical” BoDV, via transplantation, Germany (RKI/FLI reported 3/2018)

- cluster of 3 solid organ recipients from a single donor from southern Germany, 2 died.
- Organ donor died of unrelated reasons/ not of neurological disease.
- 100 d after receiving transplants (2 kidney, 1 liver transplant) → severe encephalitis/encephalopathy while being on standard immunosuppression therapy. Both kidney recipients fell into a coma and died. Liverrecipient survived with residual degenerative optic nerve atrophy.
- Diagnostics/ FLI:
  - BoDV-1 genome in both kidney transplant recipients by RT-qPCR and NGS
  - BoDV-1-specific seroconversion in all patients.
  - IHC, ISH : presence of BoDV-1 antigens and RNA.
- additional lethal case of encephalitis due to BoDV-1 found in southern Germany during the investigation of this transmission cluster with no epidemiological link, another patient with encephalitis is currently under investigation; these patients have not received any organ transplantation .

Poxviridae

Genus/species	reservoir	geographic distr	other hosts infected
Orthopoxvirus			
Variola virus	Humans (labs?)	Worldwide (extinct)	None
Vaccinia virus	?	Worldwide	Humans, cows, buffaloes, rodents
Cowpox virus	Rodents	Europe, W Asia	Cats, humans, cows, zoo animals
Ectromelia virus	(Lab) rodents	Europe, Japan, China	Fox, mink
Monkeypox virus	Squirrels	W and Central Africa	Monkeys, humans, prairie dogs
Camelpox virus	Camels	Africa, Asia	None
Raccoon poxvirus	Raccoons	E USA	None
Parapoxvirus			
Pseudocowpox virus	Cattle	Worldwide	Humans
Orf virus	Sheep	Worldwide	Reindeer, Humans

Cowpox in humans – more after cessation of smallpox vaccinations

Becker & al. 2009

Paula Kinnunen

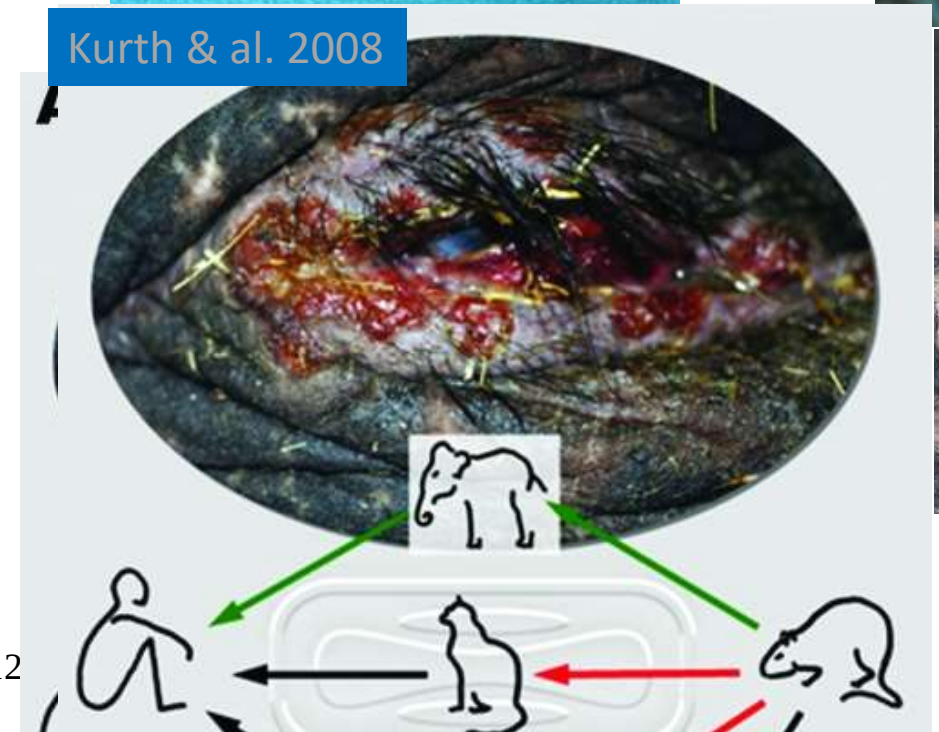
Cowpox in animals

Courtesy of Aiden Foster

Courtesy of Malcolm Bennett

Circulation in wild rodent populations of Eurasia

Kurth & al. 2008



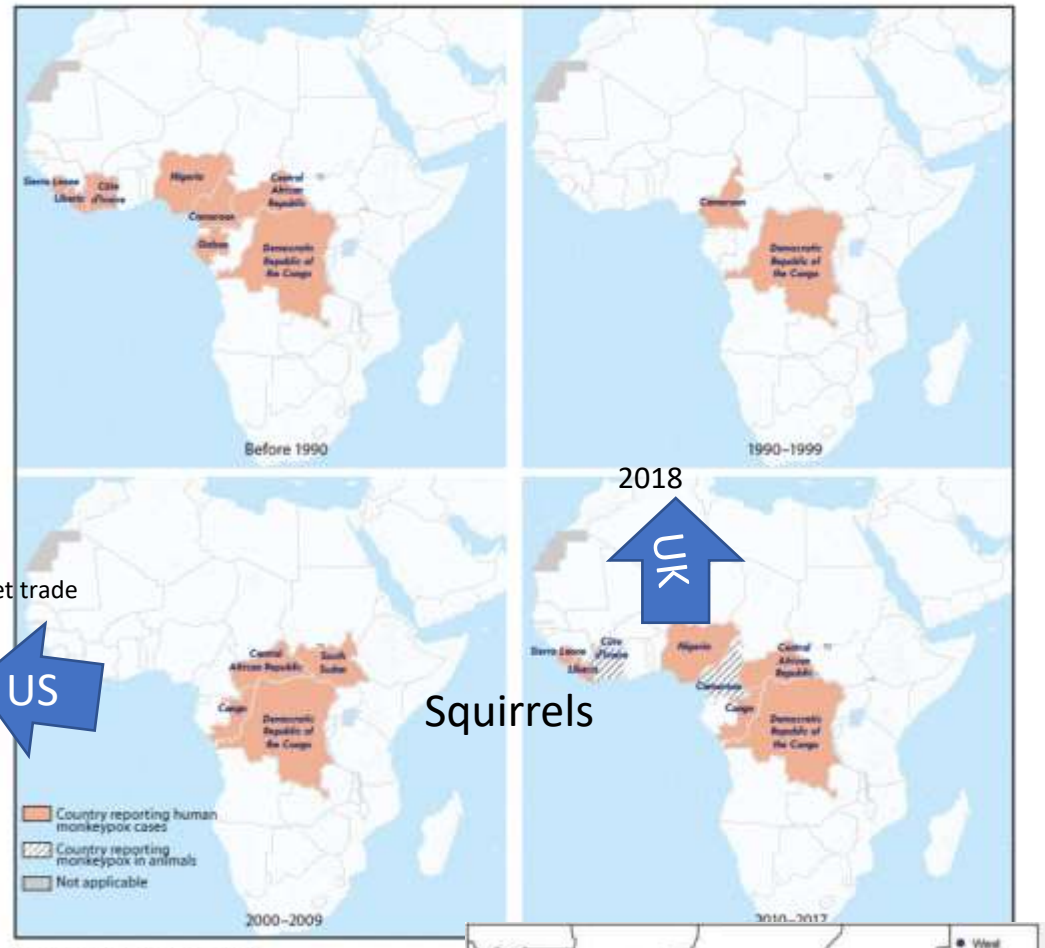
Monkeypox

Prairie dogs et al, 2003

Pet trade

US

FIGURE. Countries reporting monkeypox cases in humans and animals — West and Central Africa, 1970–2017*



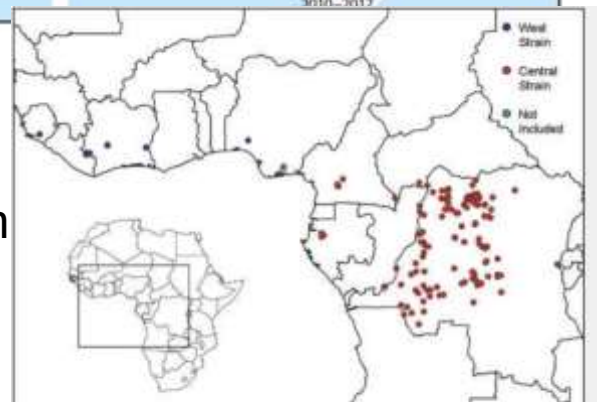
* Current as of February 25, 2018.

2018

UK

Squirrels

African Rodent Importation Ban



LCMV (lymphocytic coriomeningitis) infections - arenavirus

- ✓ Asymptomatic infection (most common)
- ✓ Influenza-like disease (common)
- ✓ Aseptic meningitis (most common complication)
- ✓ Meningoencefalomyelitis (rare)
- ✓ Severe infecion of immunosupressed (transplantation)
- ✓ Congenital-infections can be manifested by:
  - ✓ Hydrocefalus, mikrocefalus
  - ✓ Chorioretinitis
  - ✓ Mental or psychomotor retardation

Dg: RT-PCR, serology (IFA; EIA, WB), isolation from: wild mice, pet mice and hamsters

LCMV-IF: Mammalogists and Veterinarians

Mammalogists				
Place	Year	NO TOT	NO POS	% POS
Southampton	1995	155	6	3,9
Jyväskylä	1999	152	10	6,6
Praha	2003	69	2	2,9
	TOT	376	18	4,8

Veterinarians			
Year	NO TOT	NO POS	% POS
2001	150	15	10

BIRD-BORNE

Influenza A virus hosts

H3N8, (H7N7)

All subtypes in wild waterfowl ducks, gull H1-16, N1-9

LPAI → HPAI

H5,H7

H1-3, N1,2

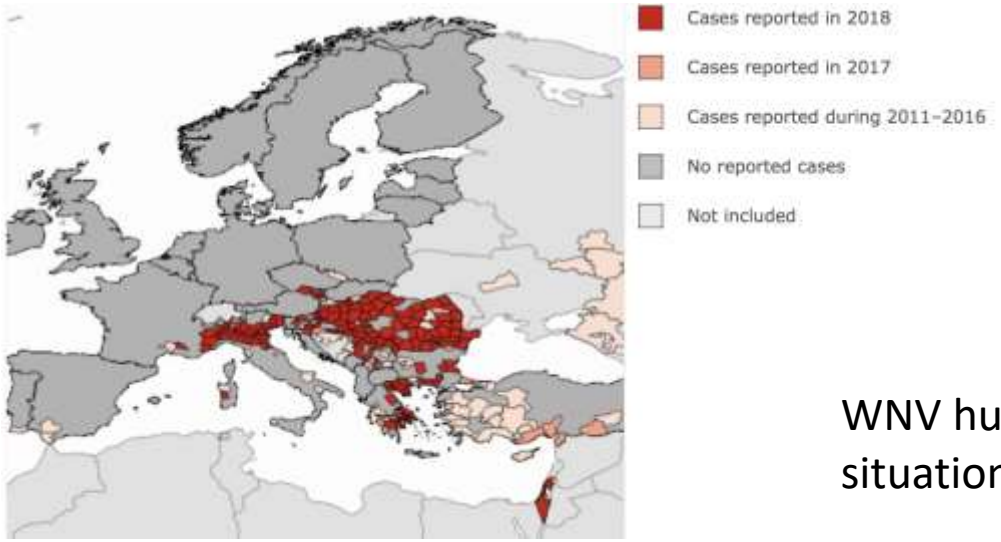
H1N1, H3N2

wet market chicks

MIGRATORY BIRDS AS (ArBo)VIRUS DISTRIBUTORS

mosquito-bonre:

- West Nile virus
- Usutu virus
- Sindbis-virus
- Tick-borne encephalitis virus



WNV human infections situation 28 Sept 2018

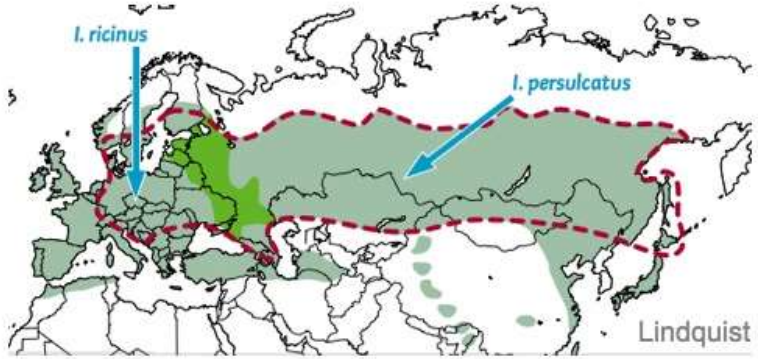
Tick-borne encephalitis virus

Genus Flavivirus, *Family Flaviviridae*

- **TBEV VECTORS**

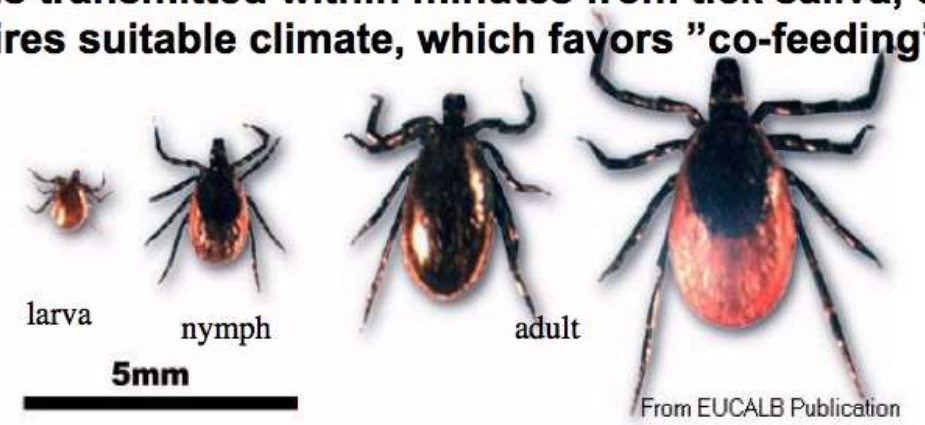
***Ixodes ricinus* - sheep tick** — **(TBEV European subtype)**

***Ixodes persulcatus* - taiga tick** — **(TBEV - Siberian and Far Eastern subtypes)**



Lindquist & Vapalahti, Lancet 2008

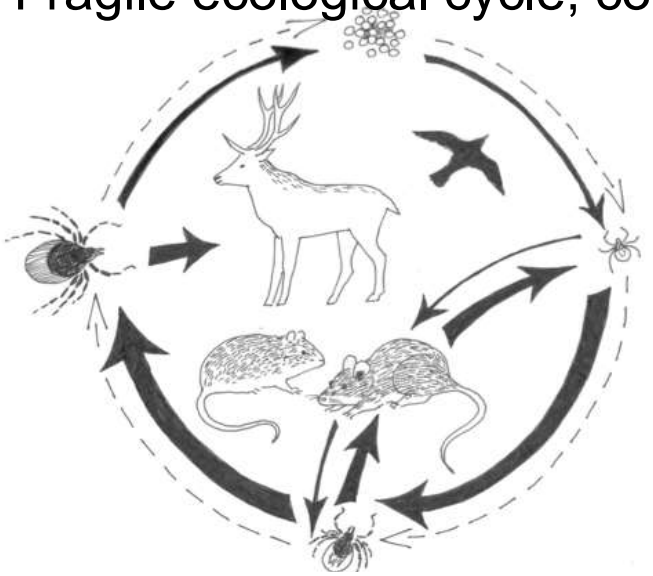
- virus transmitted within minutes from tick saliva, cycle in nature requires suitable climate, which favors "co-feeding"



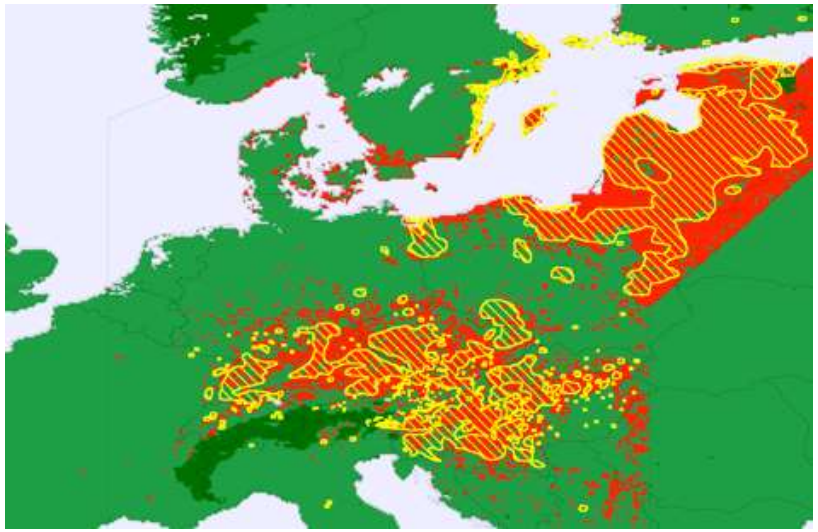
(also milk transmission)

TBE - sensitive to climate

- Fragile ecological cycle, cofeeding

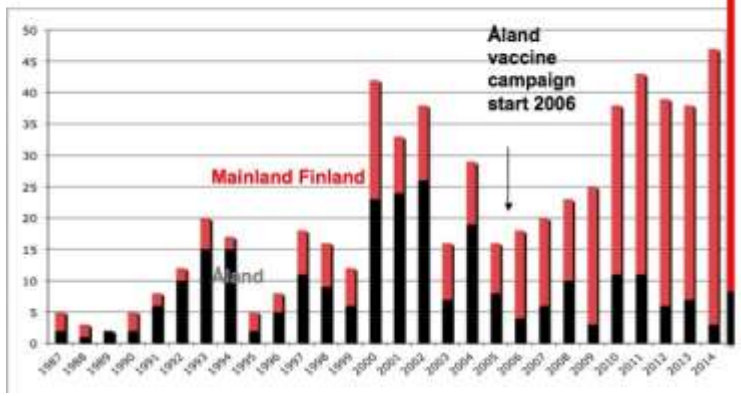


- “Focal” occurence -climate influences

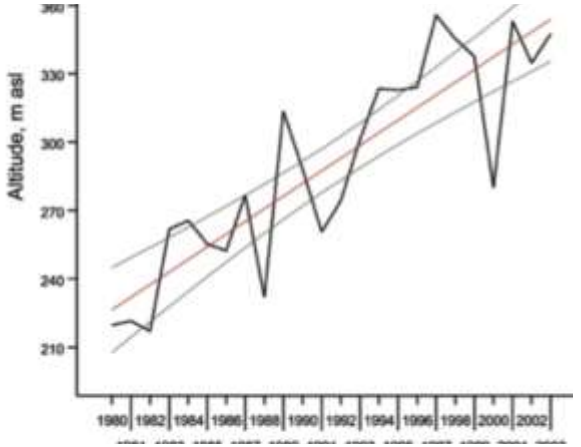


Randolph SE (2000), *Advances in Parasitology* 47, 217-243

- Case numers rising in Finland and elsewhere in N Europe



- TBE risk areas are rising on the mountains in C Europe

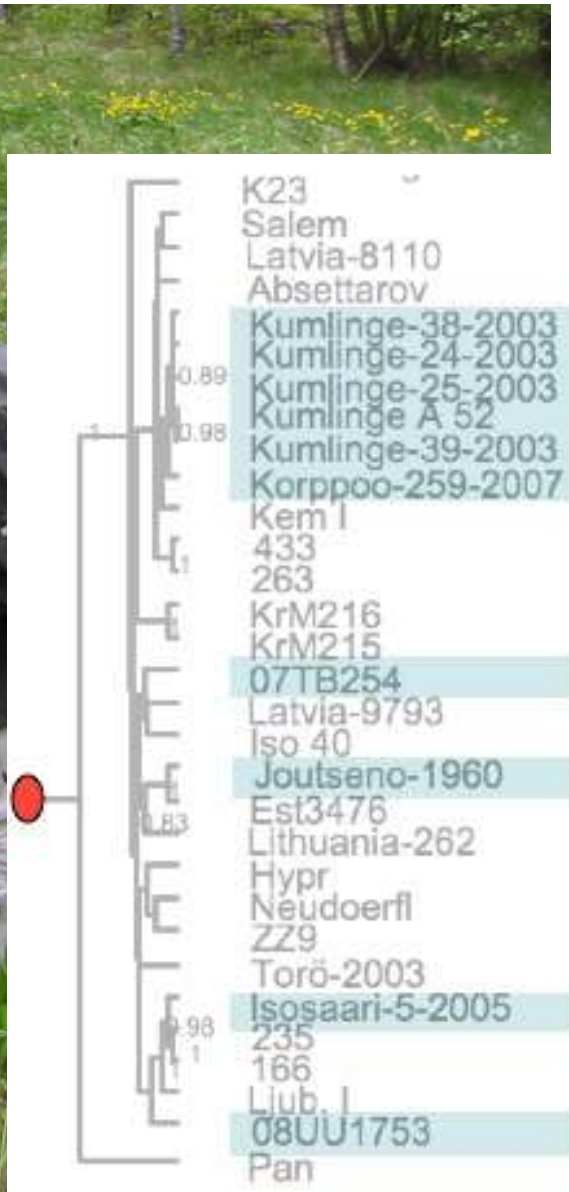


CLIMATE WARMING and TICK-BORNE ENCPALITIS, SLOVAKIA
Lukan et al, Emerg Infect Dis, 2010

TBE focus investigations

(--> molecular epidemiology)

1% of ticks, up to several % of rodent pos for TBEV-RNA

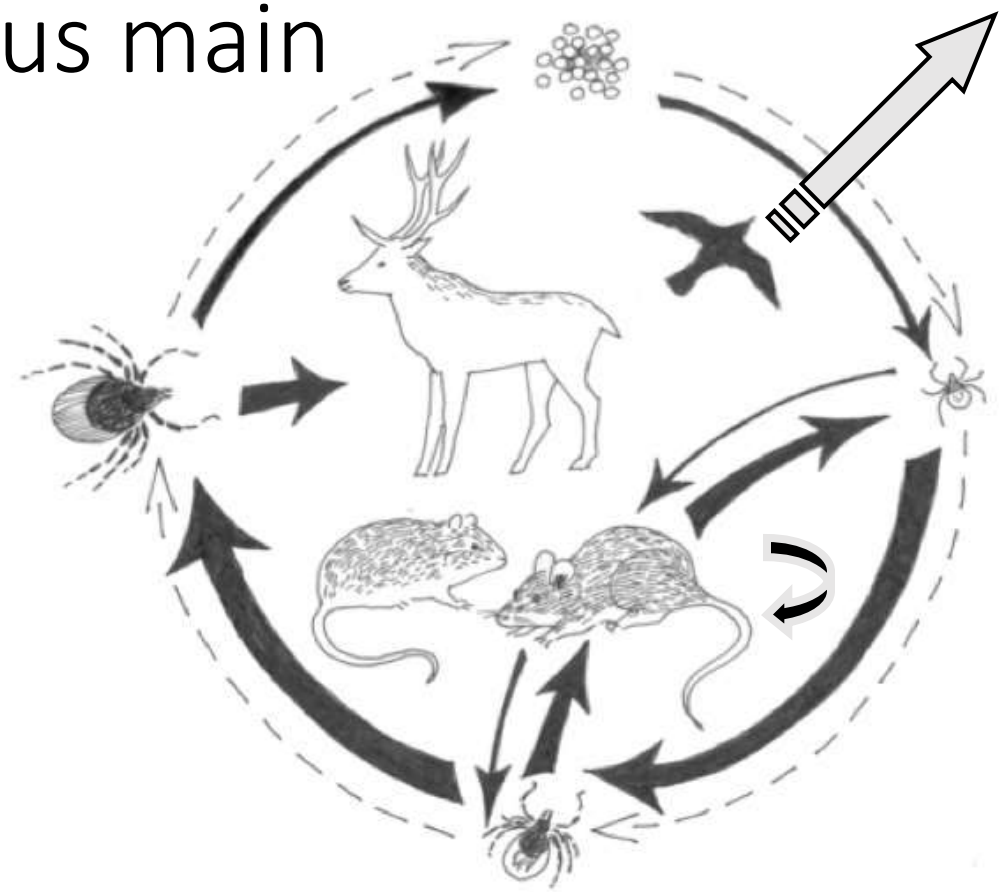


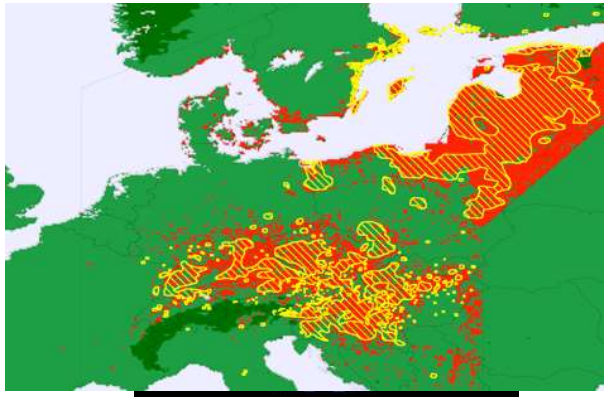
Suomalaise
kannat

photo: Ola Nordsteien. Jomfruland bird observatory Sept 2003

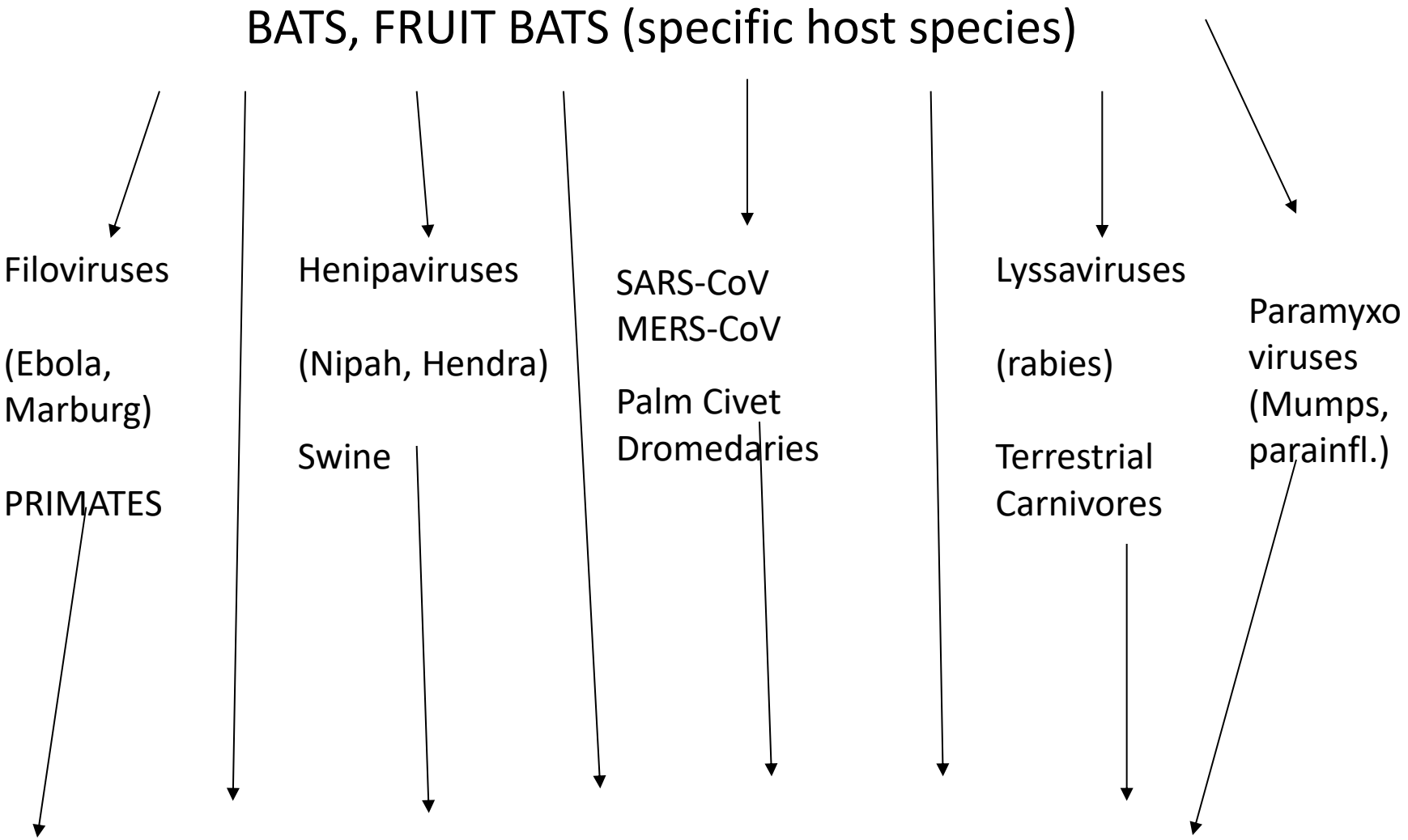
Greenfinch, *Carduelis chloris*,

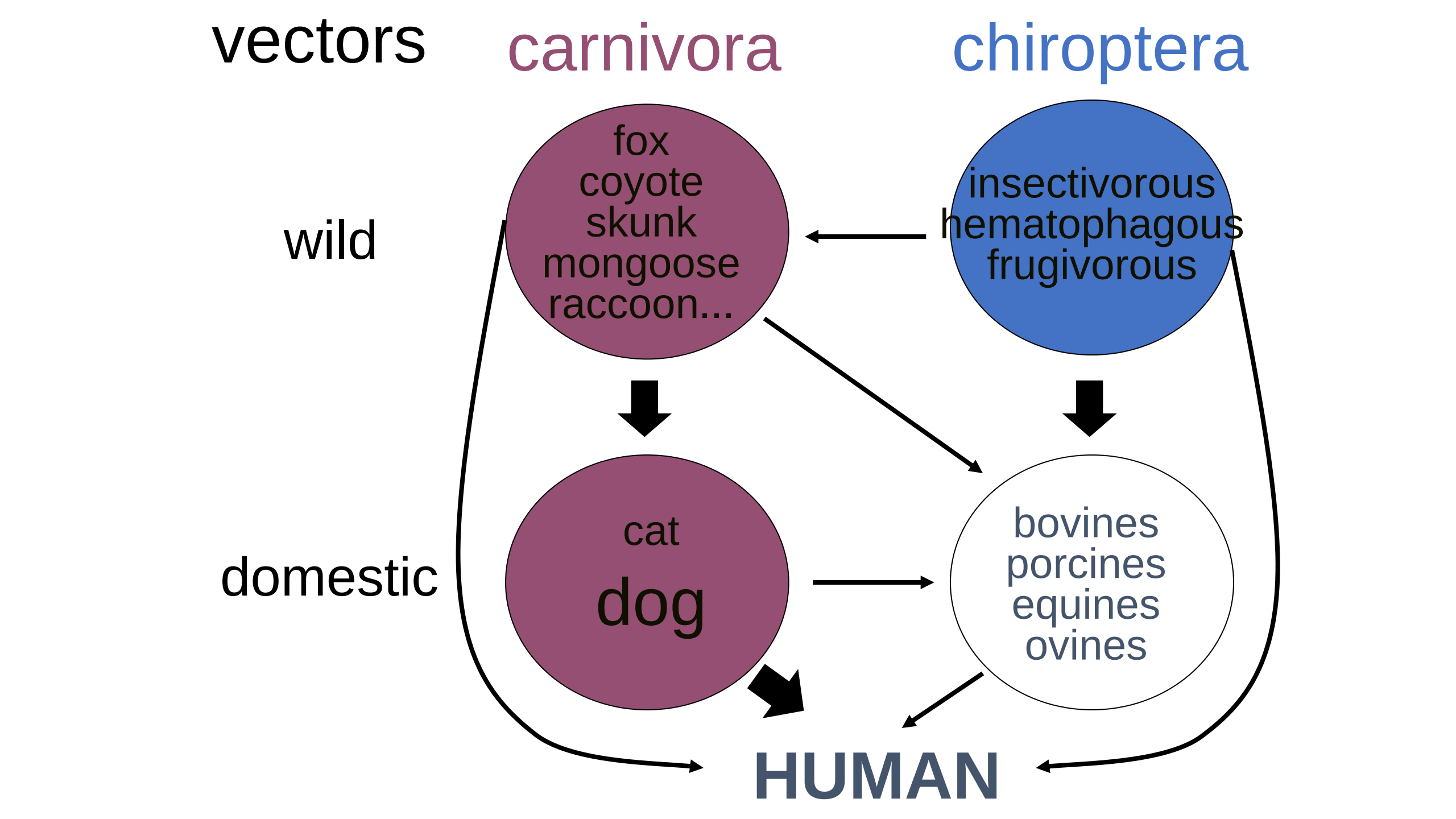
TBE focus main players



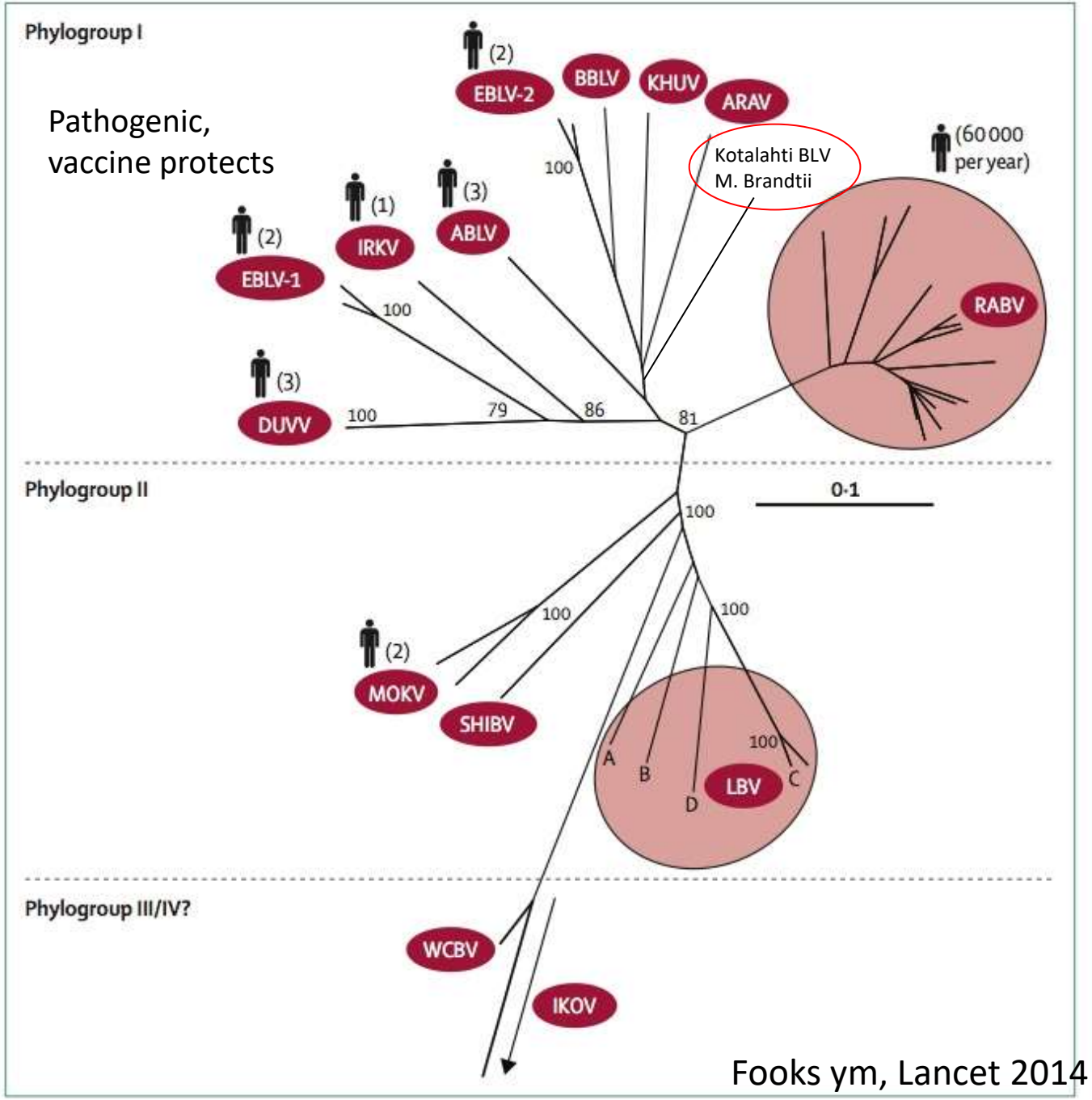


BAT-BORNE


BATS, FRUIT BATS (specific host species)
Filoviruses
(Ebola, Marburg)
PRIMATES
Henipaviruses
(Nipah, Hendra)
Swine
SARS-CoV
MERS-CoV
Palm Civet
Dromedaries
Lyssaviruses
(rabies)
Terrestrial Carnivores
Paramyxo viruses (Mumps, parainfl.)
HUMAN


vectors
carnivora
chiroptera
wild
domestic
fox
coyote
skunk
mongoose
raccoon...
insectivorous
hematophagous
frugivorous
cat
dog
bovines
porcines
equines
ovines
HUMAN

Lyssavirus Phylogenetic tree

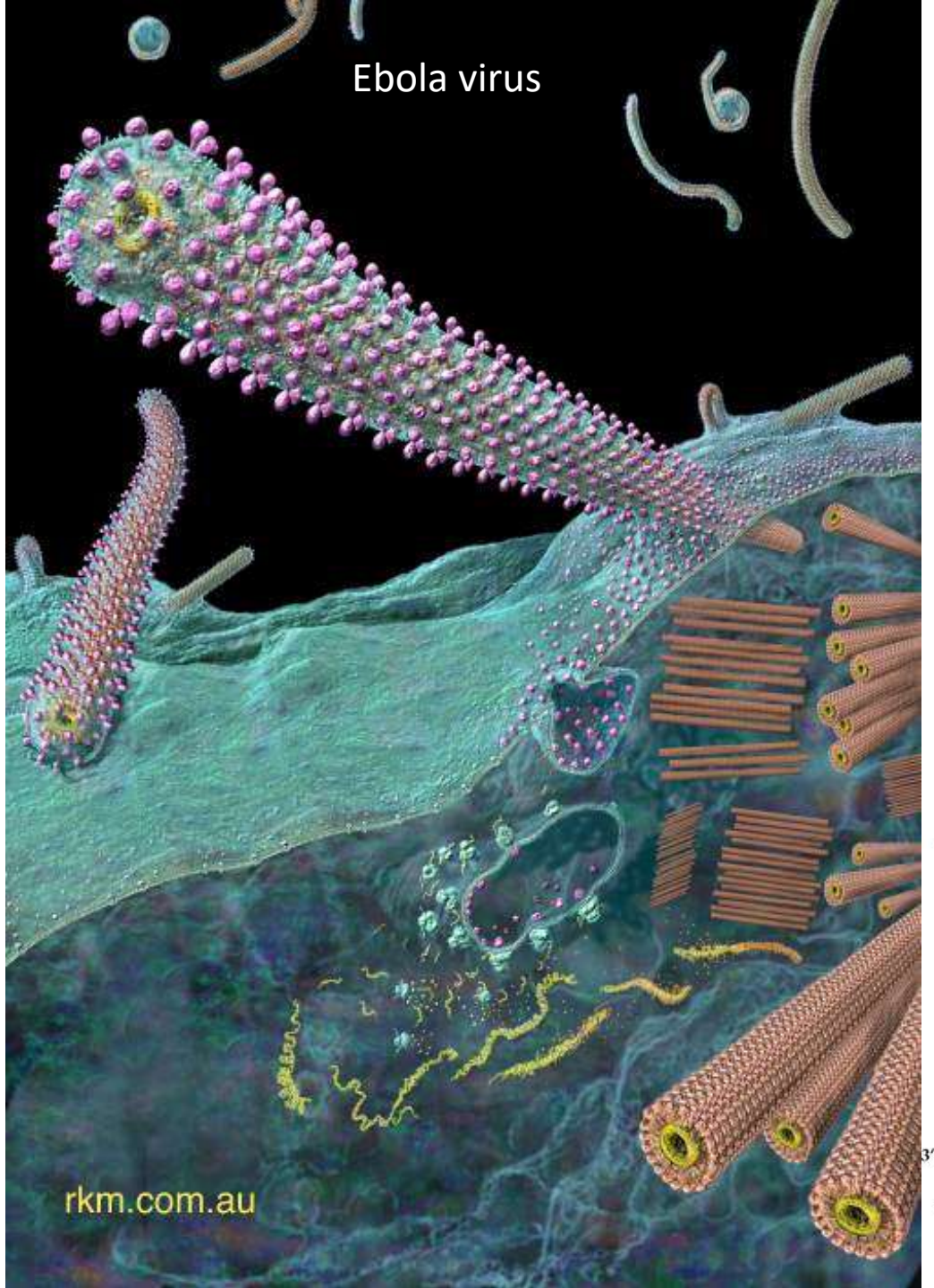


Fooks ym, Lancet 2014

BLV=bat lyssavirus

Figure 2: Phylogenetic tree of the lyssavirus phylogroups and their respective species

Nokireki et al 2018

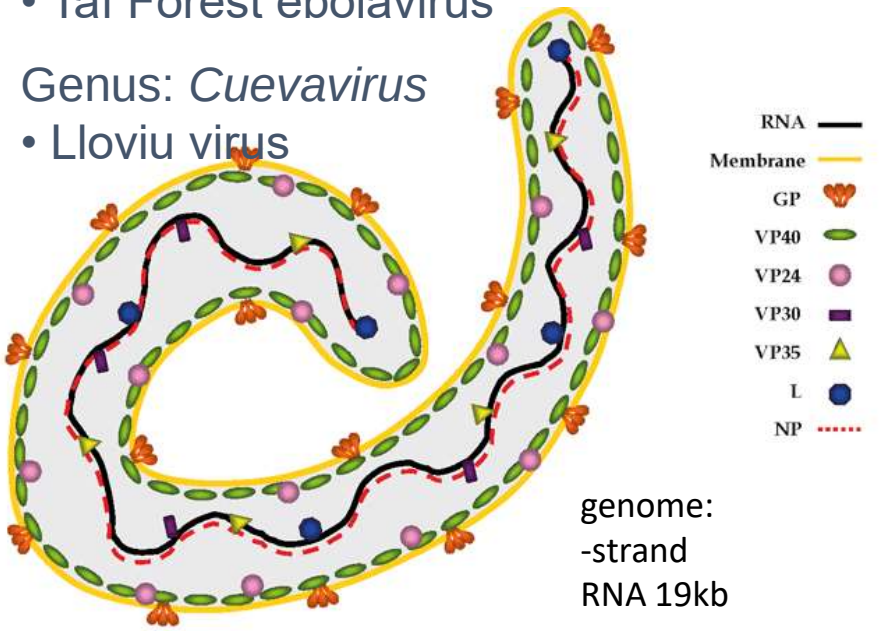


Family Filoviridae

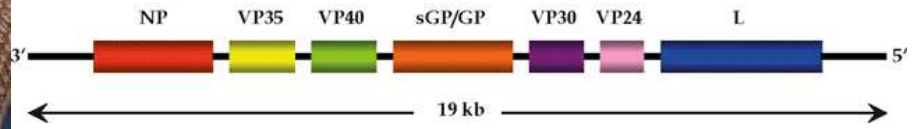
Genus: *Marburvirus*
- Marburgvirus

Genus: *Ebolavirus*
- **Zaire ebolavirus**
- **Sudan ebolavirus**
- Bombali ebolavirus
- Reston ebolavirus
- **Bundibugyo ebolavirus**
- Taï Forest ebolavirus

Genus: *Cuevavirus*
- Lloviu virus



genome:
-strand
RNA 19kb



Kuhl and Pöhlmann, Zoonoses Public Health, 2012

rodent/shrew/bat-borne disease agents.
(Zoonotic viral agents from wildlife)

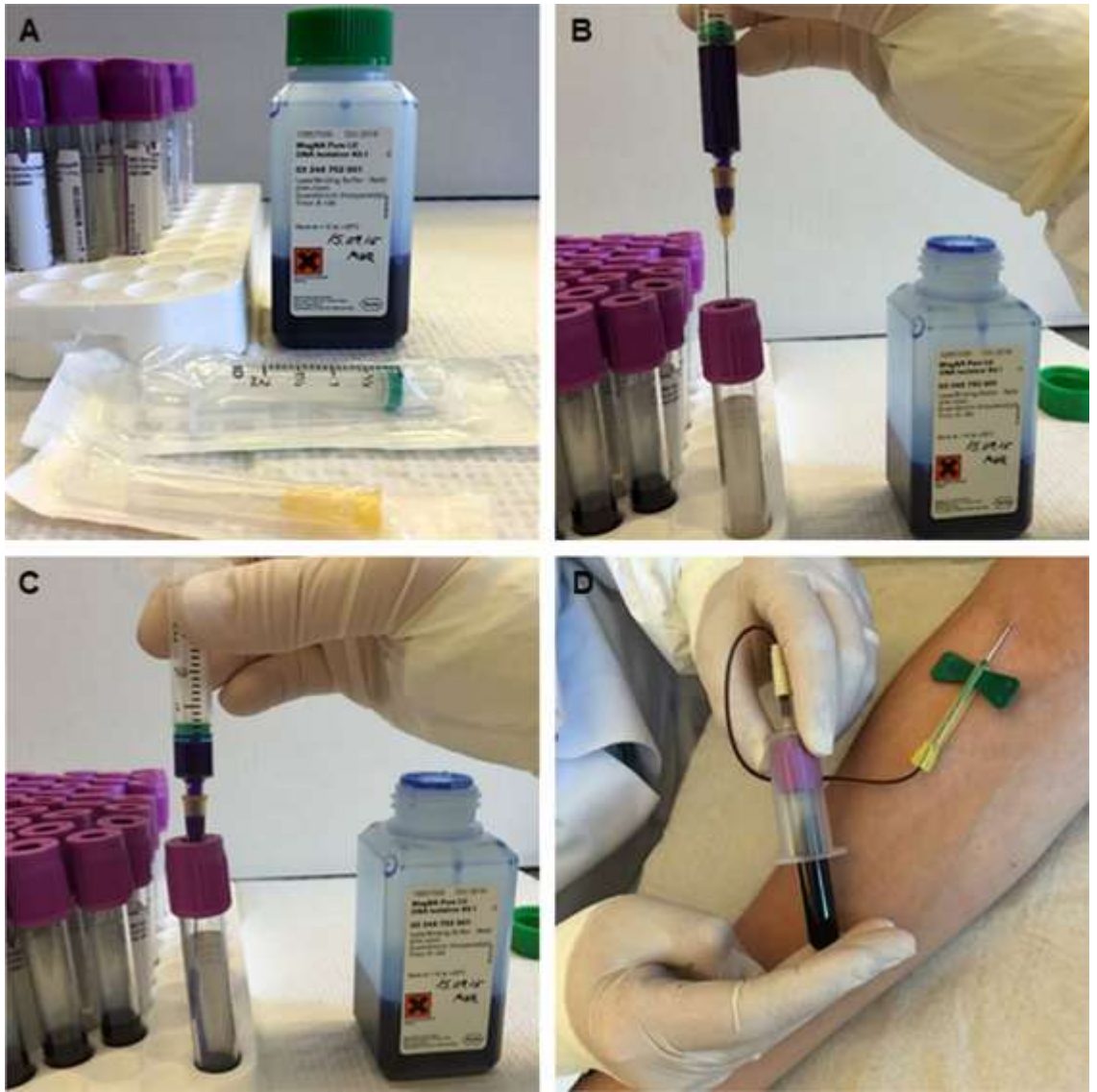
	hanta	arena (LCMV)	ortho-pox	borna	lyssa	TBEV
• Surveillance in Europe	notifiable reported to ECDC	none	none-alert and RRA on Monkeypox	none-alert and RRA on emergence	animal and human cases reported	notifiable reported to ECDC
• Protective measures	avoid inhaling rodent-contaminated. dust (use masks, gloves, rodent control) inactivation by 30 min 56°C or detergents		gloves smallpox vaccine	avoid exotic squirrels	pre-exposure vaccination PEP	pre-exposure vaccination - avoid tick bites and unpasteurized goat milk
• Potential treatments	- dialysis (5%)	(antivirals)	antivirals	-	PEP	-
• Cases in Europe	thousands mainly PUUV	rare	rare	rare	rare	thousands mainly Eur subtype

diagnostic samples

inactivation for transport+ preservation

developed for ebola bed-side inactivation Rosenstierne MW JCM 2016

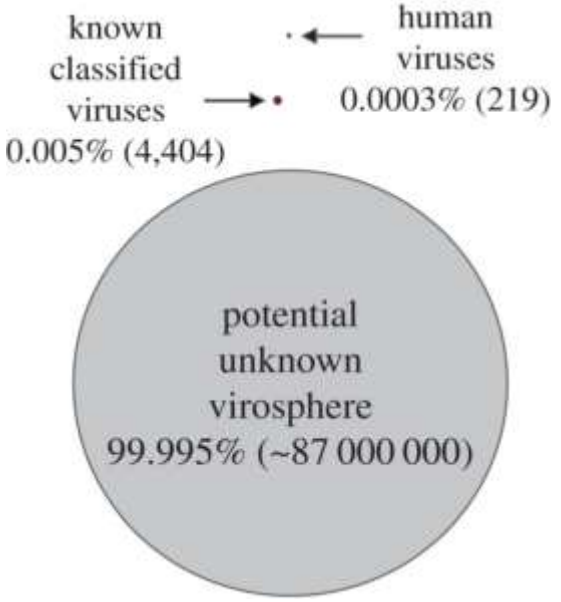
→ applicabel also for veterinary samples



How **to screen** for new/emerging (wildlife) viruses ?

PCR

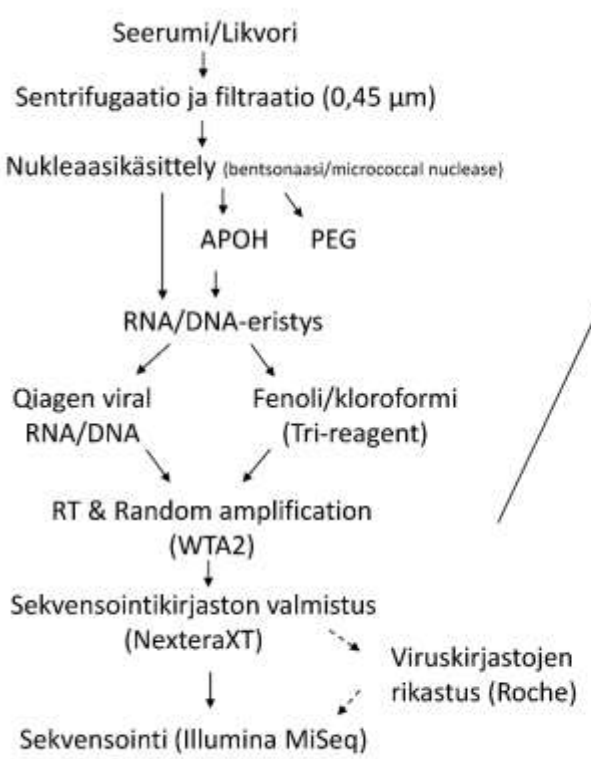
NGS

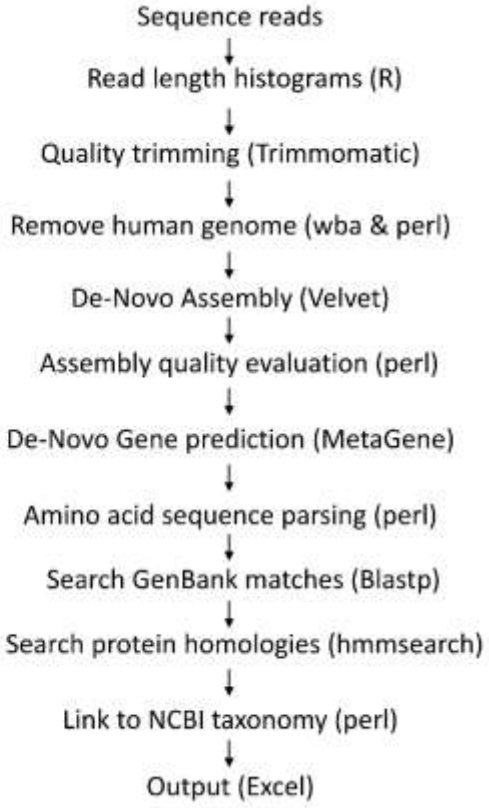


Antibodies

- Less biased / 'Hypotesis-free'
  - for wildlife particularly suitable
- Less sensitive to genetic variation
- Emerging infections
- Co-infections

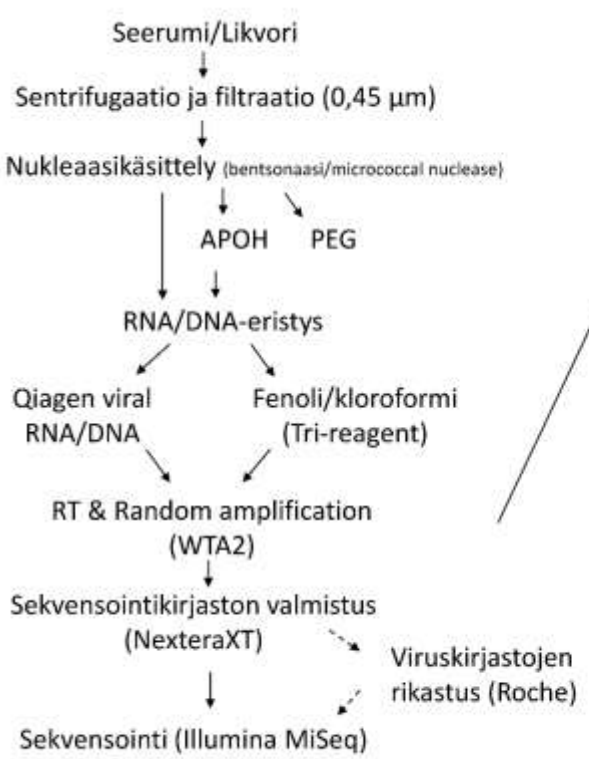
Wet lab: Bioinformatics:

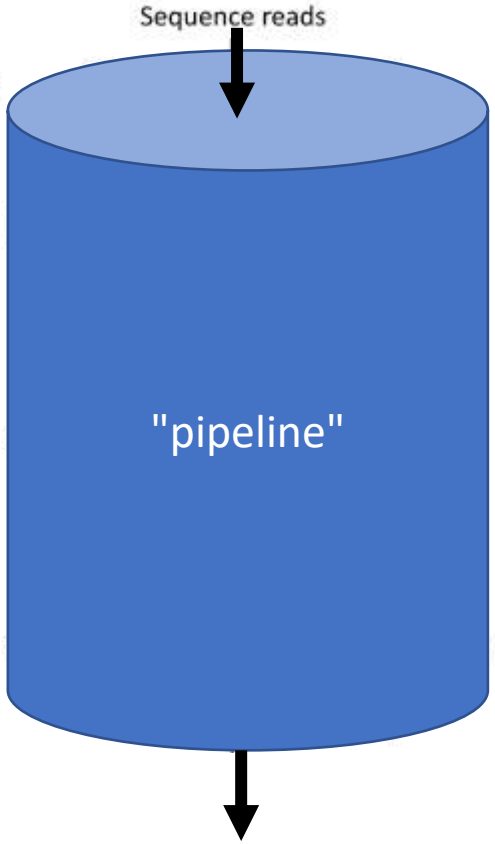




Smura T, Plyusnin I, et ak, "Lazypipe"

Wet lab: Bioinformatics:





"Lazypipe"

Detection of any virus up to 30 % identity with previously characterized viruses
e.g. new virus genera

Smura T, Plyusnin I, et al, "Lazypipe"

	origins
Hep A	rodents?
Hep B	bats?
Hep C	rodents?
Hep D	?? none
Hep E	rodents, deer..

Hetzel U, Szirovicza L, Smura T, Prähauser B, Vapalahti O, Kipar A, Hepojoki J (submitted, available at BioRxiv)

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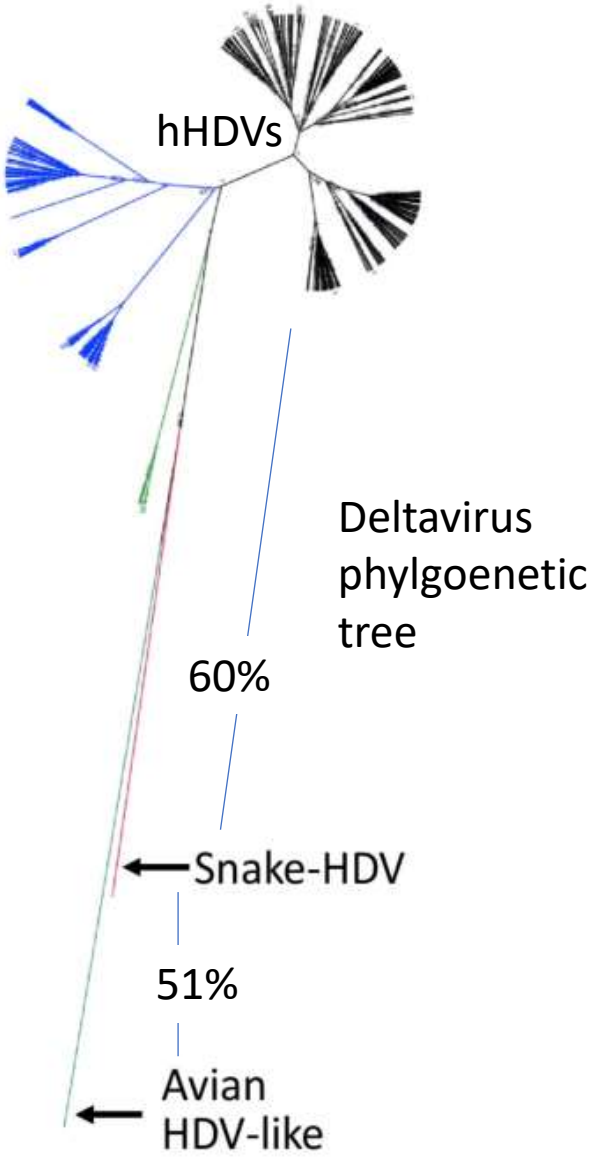
Discovery (with NGS) of new snake deltavirus

— replicates in tissues without hepadnavirus helper



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- Snake deltavirus D-ag expression

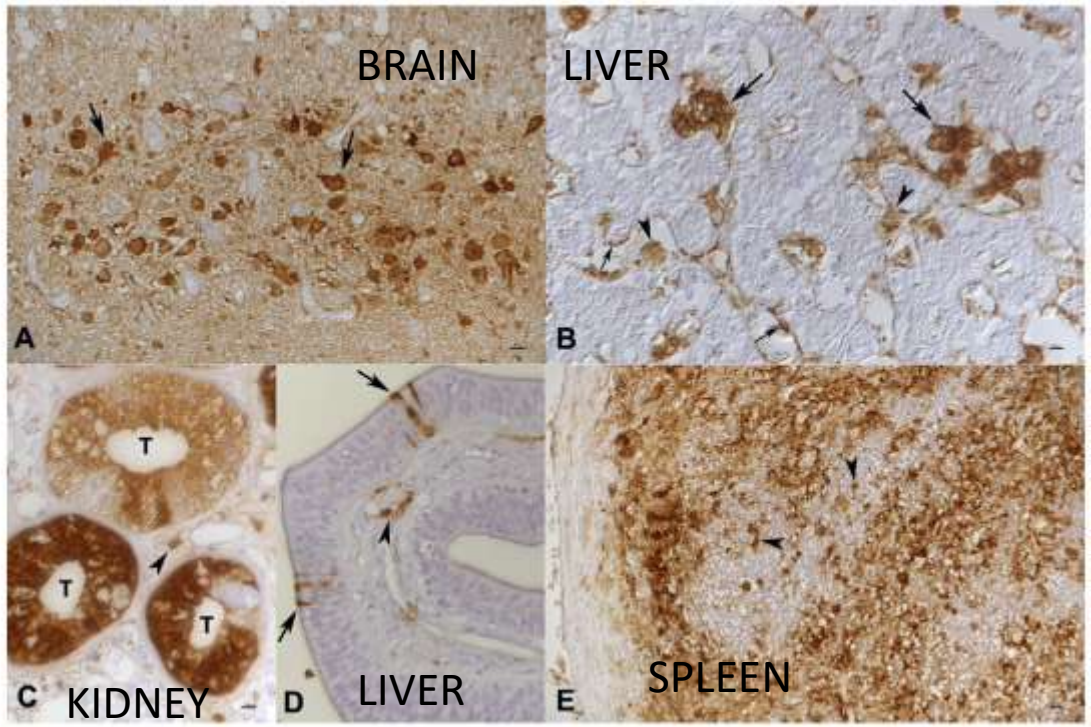
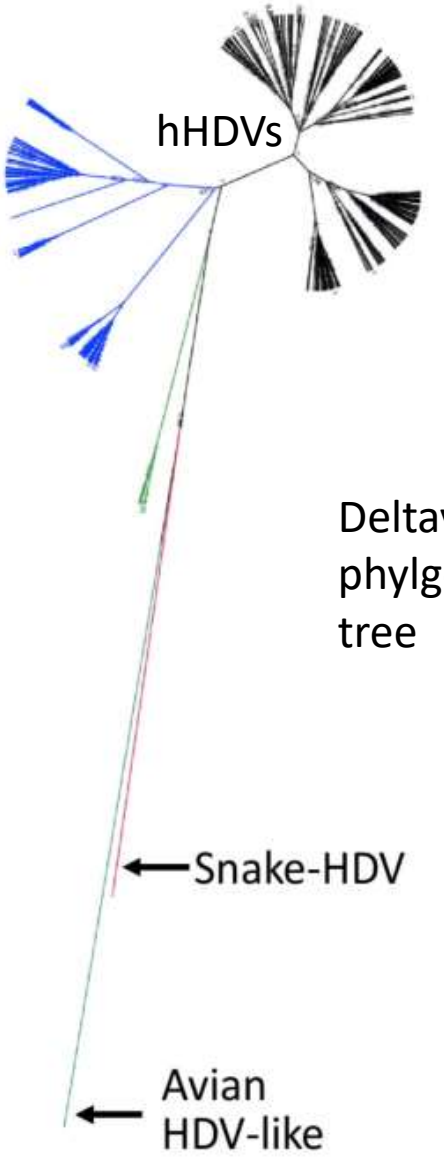
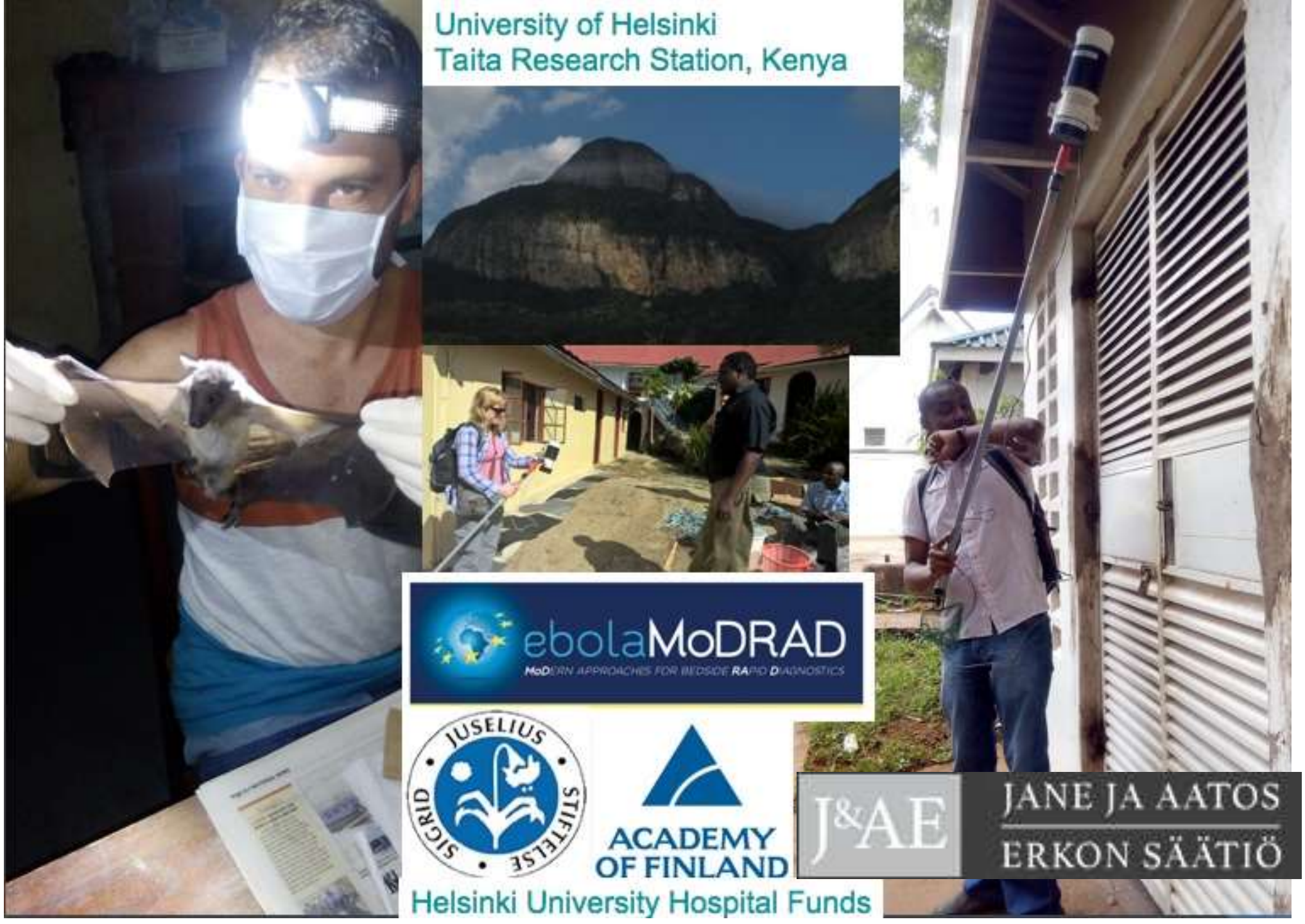


Figure 2.



Deltavirus phylgoenetic tree


University of Helsinki
Taita Research Station, Kenya
ebolaMoDRAD
MoDERN APPROACHES FOR BEDSIDE RAPID DIAGNOSTICS
JUSELIUS SIGRID STIFTELSE
ACADEMY OF FINLAND
J&AE
JANE JA AATOS ERKON SÄÄTIÖ
Helsinki University Hospital Funds

9th European Meeting on
Viral Zoonoses

September 29 – October 2, 2019
St. Raphaël, France

Organizing committee
Noël Tordo, Åke Lundkvist, Alain Kohl
Alexander Plyusnin, Olli Vapalahti

VENUE
St Raphaël Palais des Congrès
Côte d'Azur, France
(1h from Nice airport)

info

www.euroviralzoon.com

Lazypipe:

a new pipeline for NGS assembly and annotation

Ilja plyusnin: manuscript

- UNIX/perl script
- Input: Illumina paired-end libraries

1. Quality control: filter short reads, adapter sequences, low quality sequences with Trimmomatic
2. Filter host genome with BWA MEM
3. Assemble with Velvet or Megahit
4. De novo gene detection with MetaGene
5. Taxonomic annotation of contigs with SANSparallel and custom perl scripts
6. Realigning reads to assembly with BWA MEM
7. Generating taxonomic abundance tables, contig annotation tables and binning contigs by taxa
8. Realigning contigs within taxa with R
9. Quality control: generating plots for post assembly and post annotation quality control
10. Collect files for sharing and cleanup

Hetzel U, Szirovicza L, Smura T, Prähauser B, Vapalahti O, Kipar A, Hepojoki J (submitted, available at BioRXiv)

Discovery with NGS of new snake deltavirus

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- Snake deltavirus D-ag expression

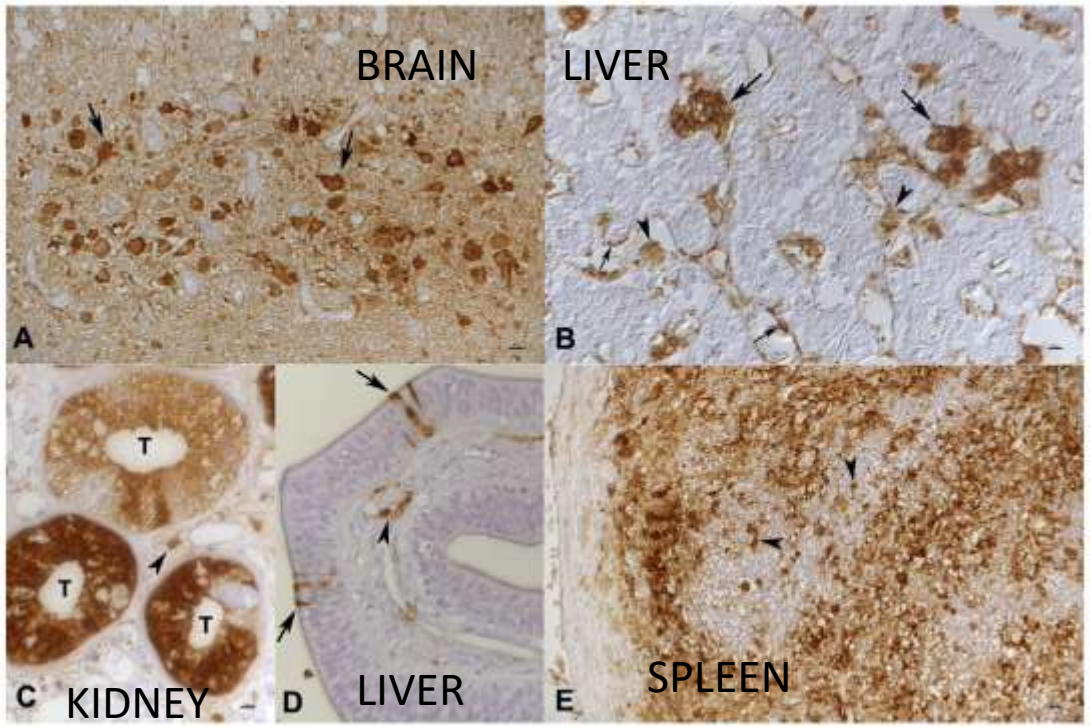
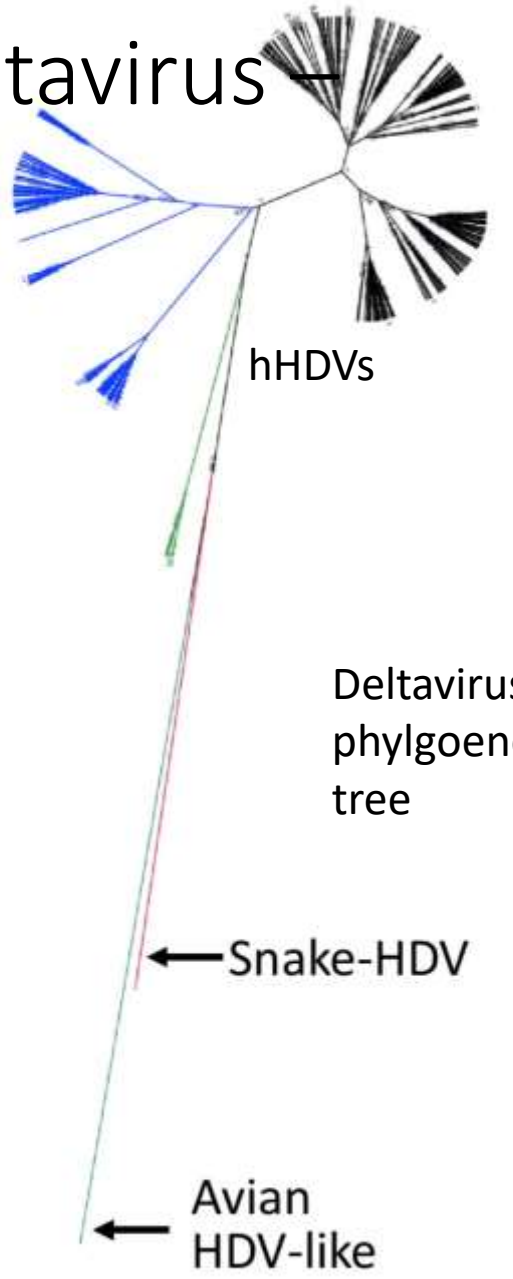
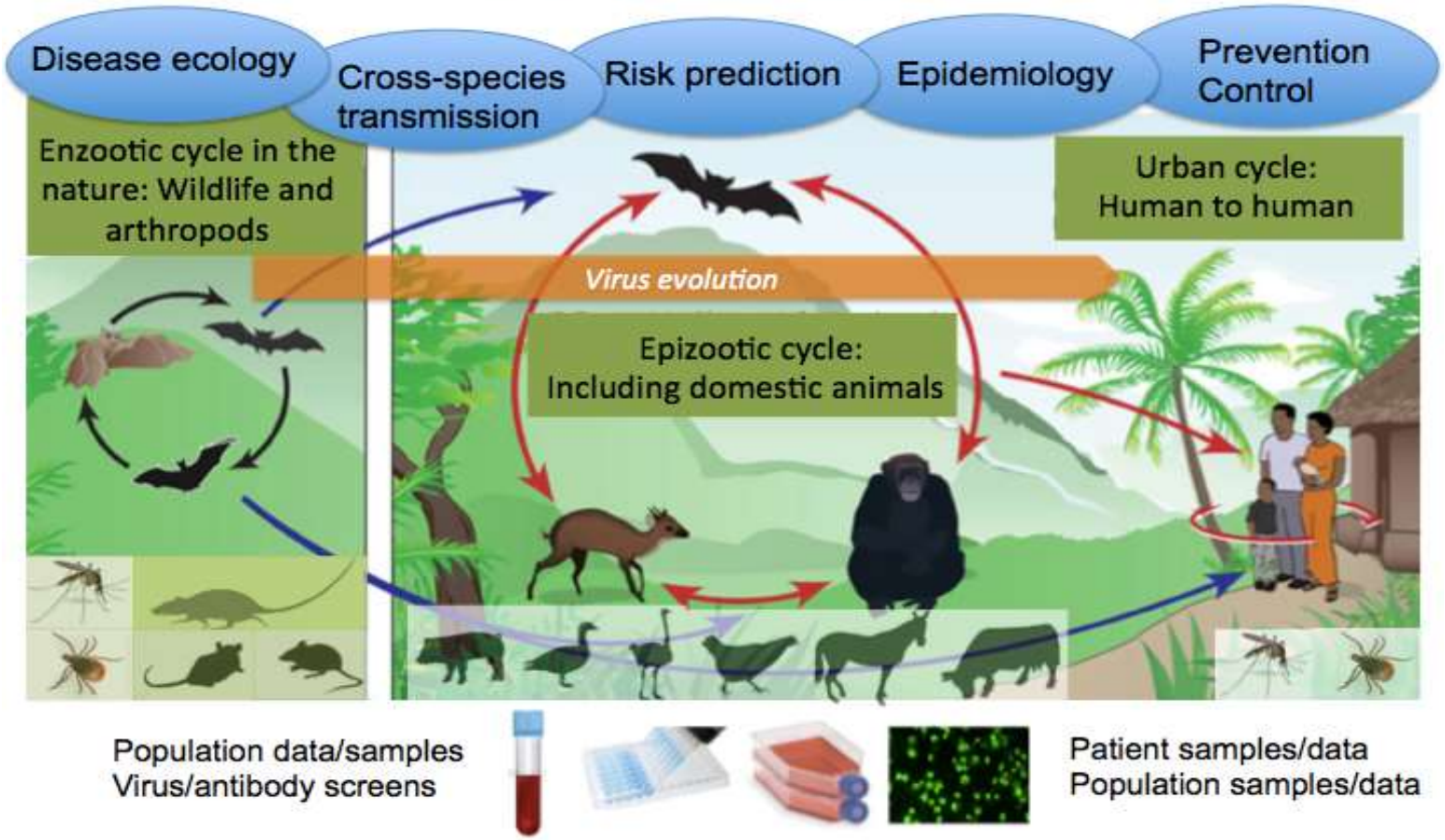


Figure 2.

A) Brain. D-ag expressed in neurons. **B)** Liver. Individual hepatocytes (large arrows), macrophages (arrowheads) and endothelial cells (small arrows) express D-ag **C)** Kidney. In tubules (T), intense viral antigen expression. **D)** Lung. individual epithelial cells (arrows); some leukocytes express viral antigen (arrowhead). **E)** Spleen with extensive viral antigen expression.



Emerging zoonoses



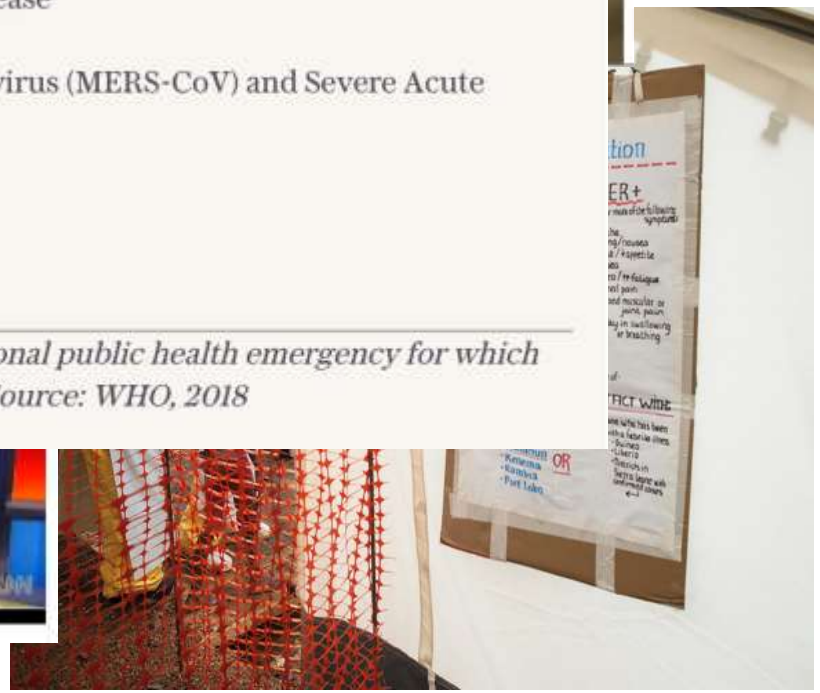
Modified from https://www.cdc.gov/vhf/ebola/resources/virus-ecology-fr.html.

Emerging infections

Watchlist | Diseases threatening a public health emergency

- Crimean-Congo haemorrhagic fever (CCHF)
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever (RVF)
- Zika
- Disease X

Diseases posing significant risk of an international public health emergency for which there is no, or insufficient, countermeasures. Source: WHO, 2018



Emerging infections

INDEPENDENT News Voices Culture Lifestyle

Watchlist | Diseases threatening a public health emergency

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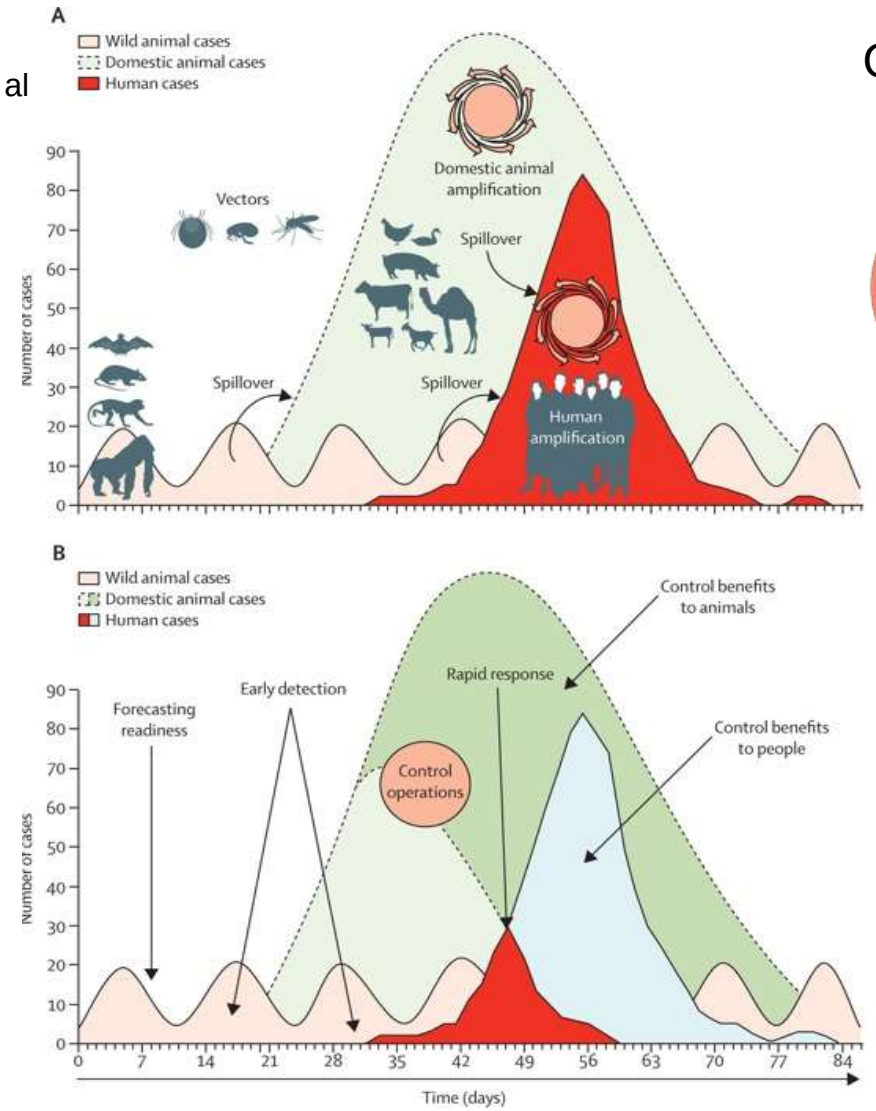
- Zika
- Disease X

'Disease X' | The mystery killer keeping scientists awake at night

A WHO committee of leading virologists, bacteriologists and infectious disease experts has identified a new global threat. 'Disease X' joins the ranks of Ebola, Zika, and SARS with its potential for epidemics or pandemics.

But what is it? And how could it manifest?

Karesh et al
Lancet
2012



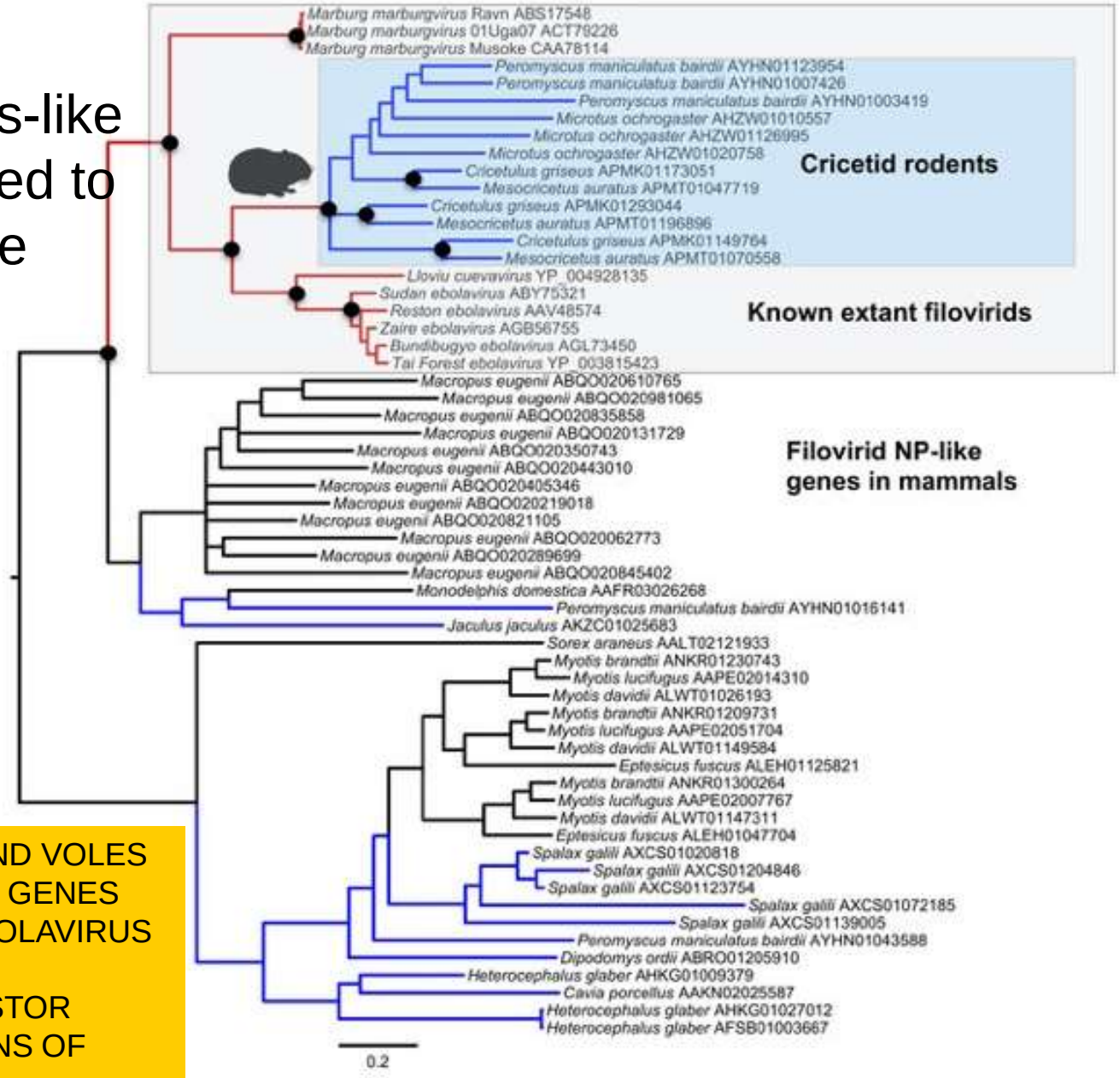
One Health approach

Pylogenetic tree of filoviruses + filovirus-like sequences integrated to mammalian genome

Taylor et al

Evidence that ebolaviruses and cuevaviruses have been diverging from marburgviruses since the Miocene. Peer J 2014

PeerJ. 2014 Sep 2;2:e556. 2014



➔N THE GENOME OF MICE AND VOLES CAN BE FOUND INTEGRATED GENES OR PARTS OF GENES OF EBOLAVIRUS /CUEVAVIRUS ANCESTORS

➔FILOVIRUS COMMON ANCESTOR INFECTED MAMMALS MILLIONS OF YEARS AGO

Figure 1: Phylogenetic relationships of filovirid NP-like paleoviruses in mammalian genomes and amino acid sequences from extant filovirids.

Fighting Ebola

diagnostics — real-time-RT-PCRs, POC antigen and RNA tests
Jääskeläinen et al JCV 2015; bed-side inactivation Rosenstierne MW JCM 2016

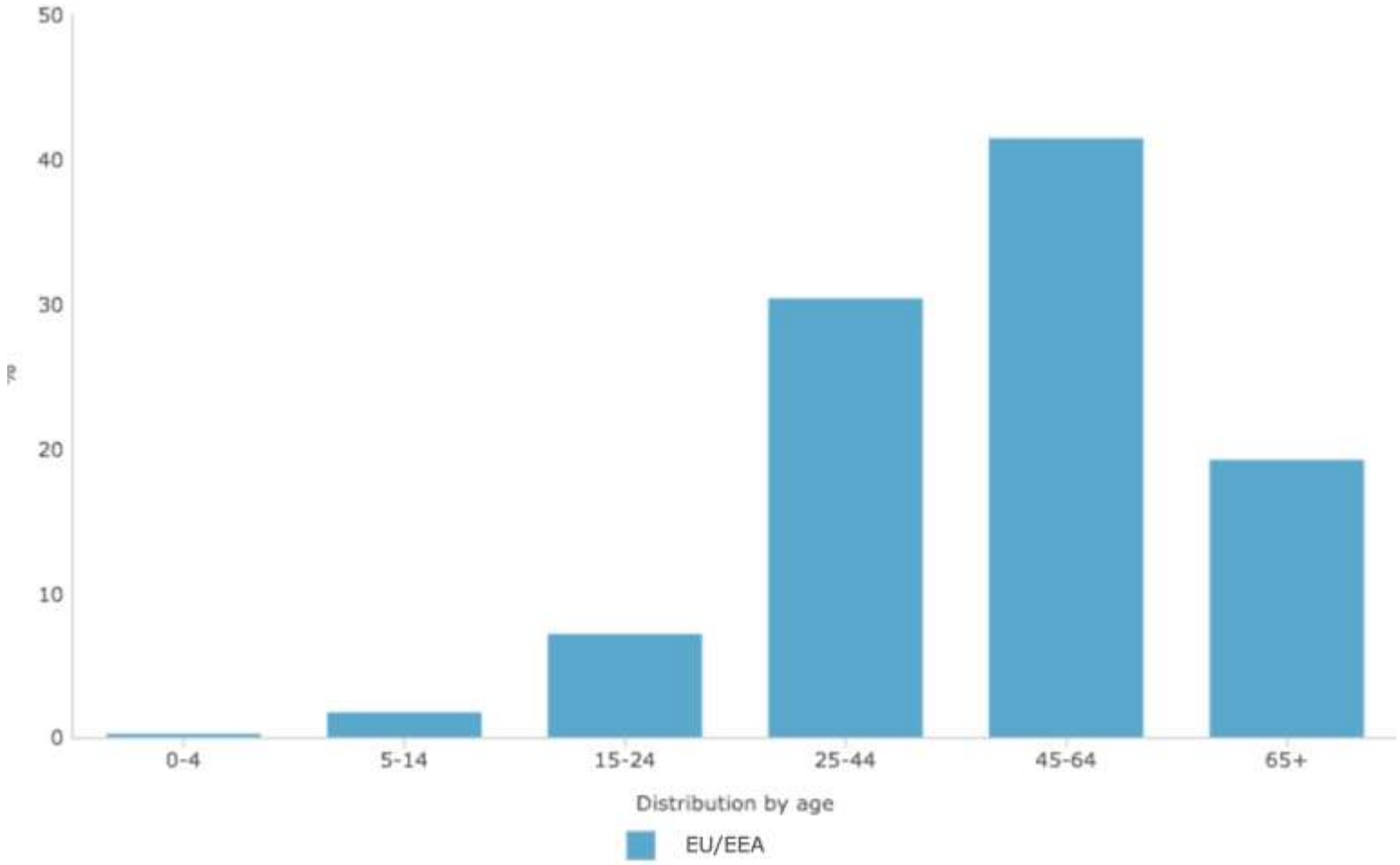
→ containment — control measures, quarantine

→ vaccines
.. → antivirals

Wolz A.
N Engl J Med 2014

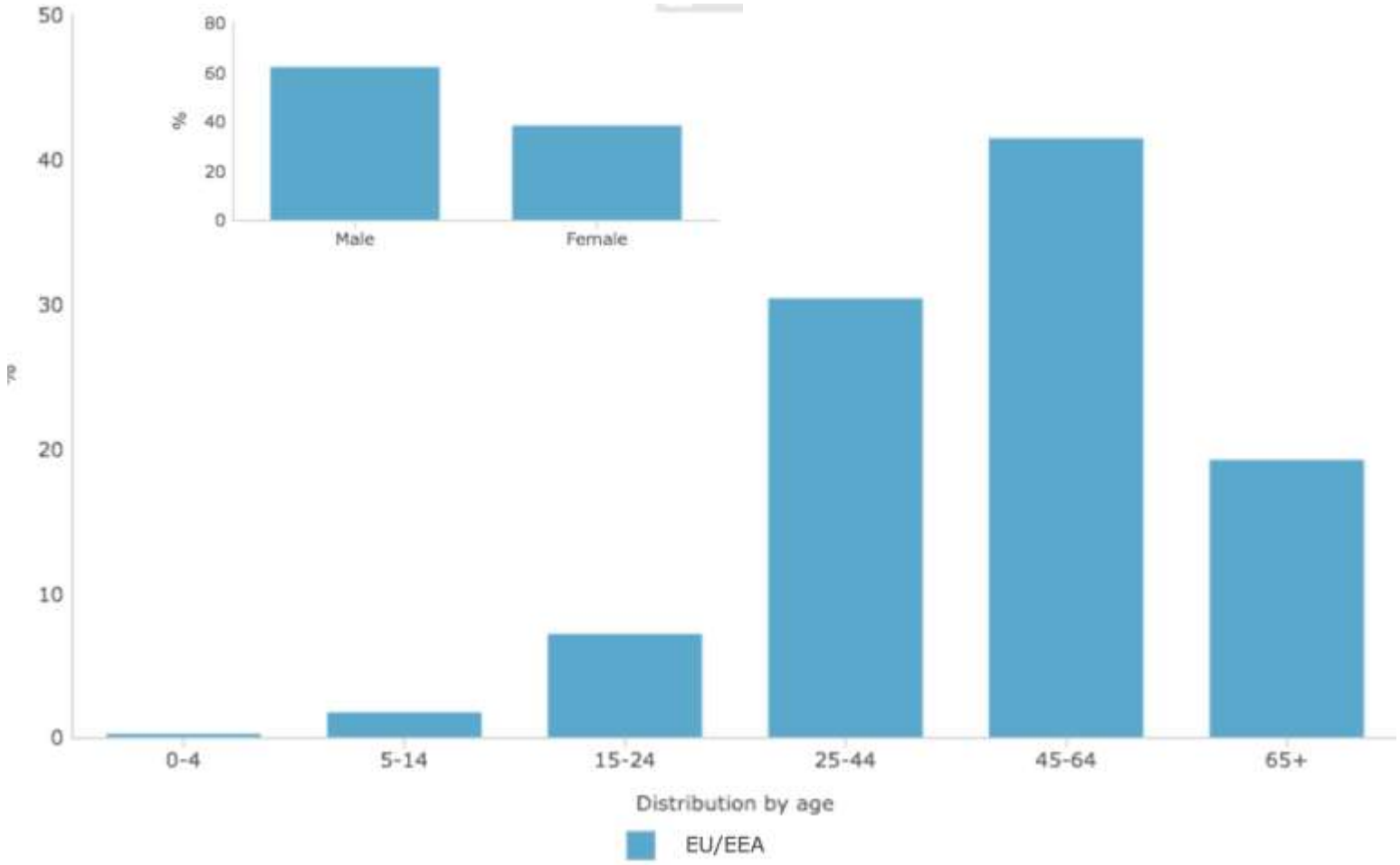
Control through containment: patient isolation, diagnostics, contact tracing, and safe burial practices

Hantavirus infections – age distribution

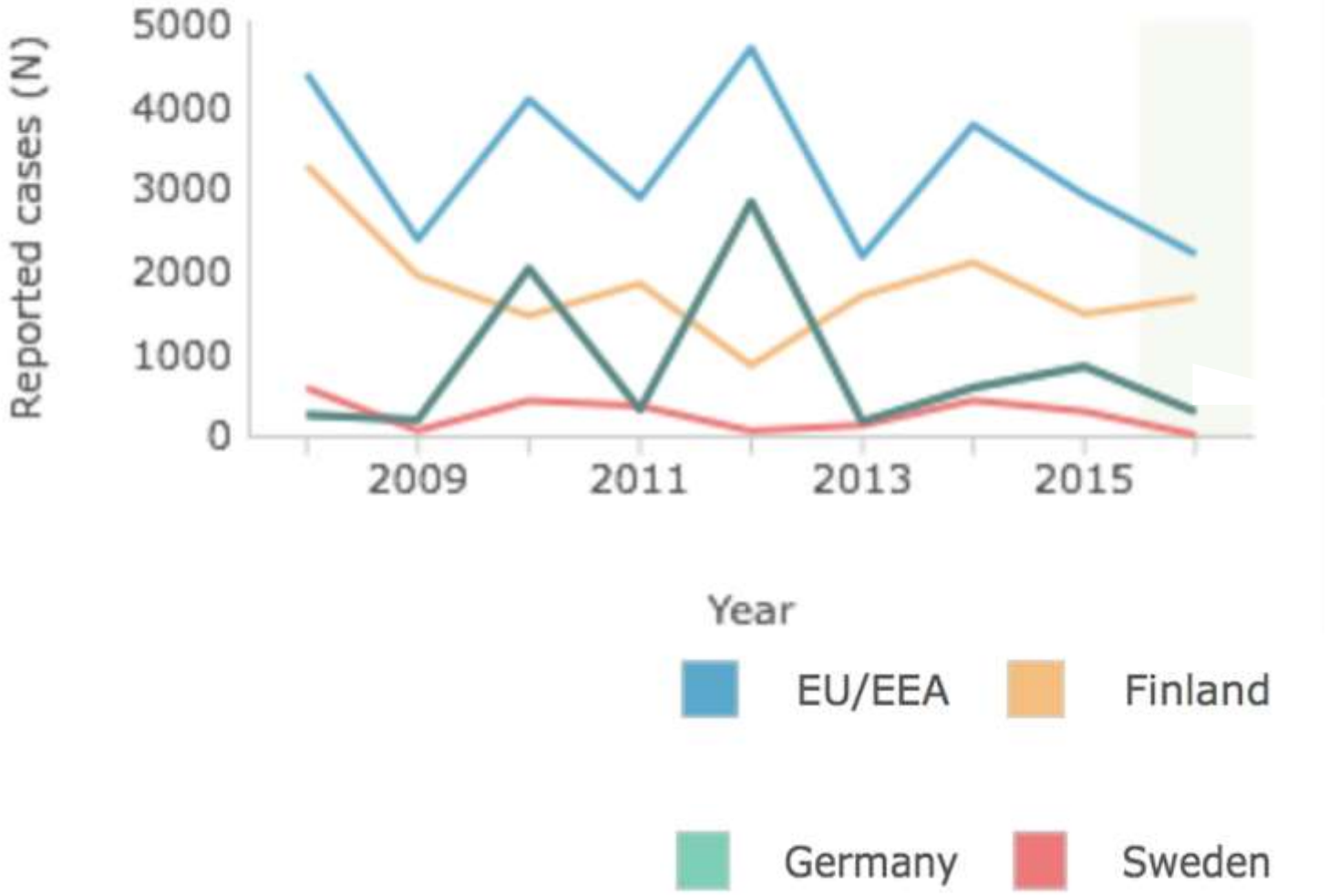


Hantavirus infections – age distribution

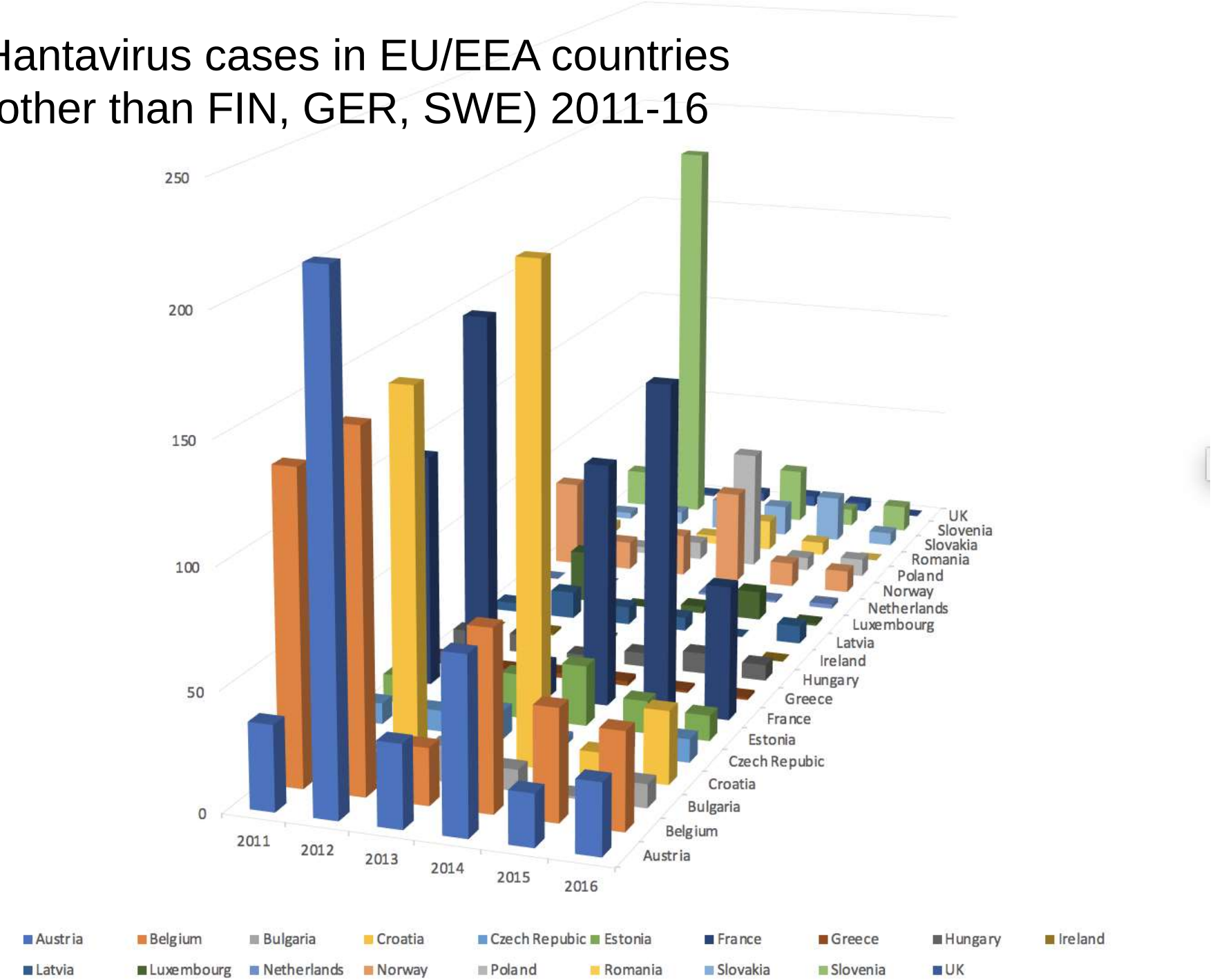
Gender distribution



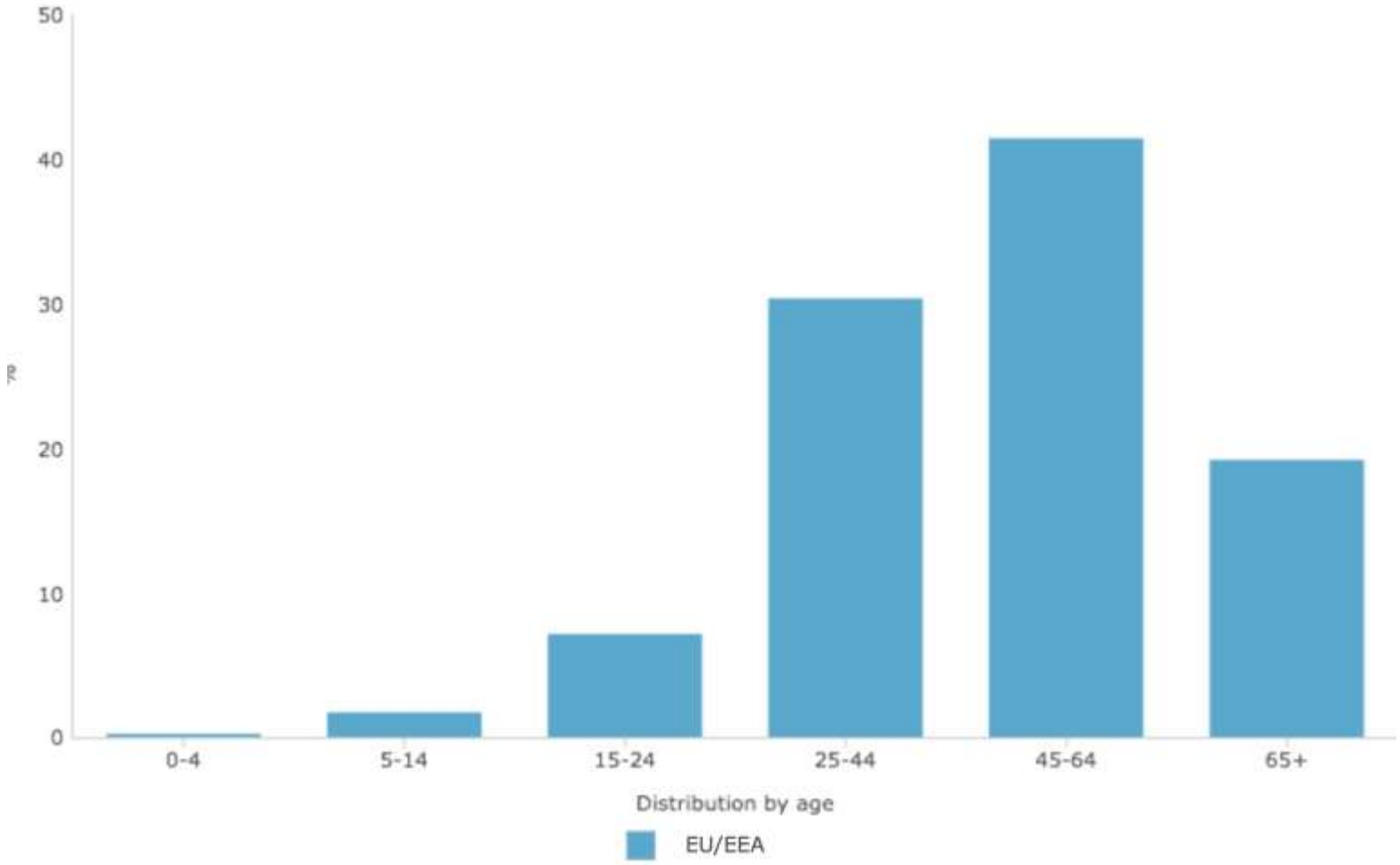
Hantavirus infections in Europe (EU/EEA) 2008-16 and Germany, Finland and Sweden



Hantavirus cases in EU/EEA countries (other than FIN, GER, SWE) 2011-16



Hantavirus infections – age distribution



Hantavirus infections – age distribution

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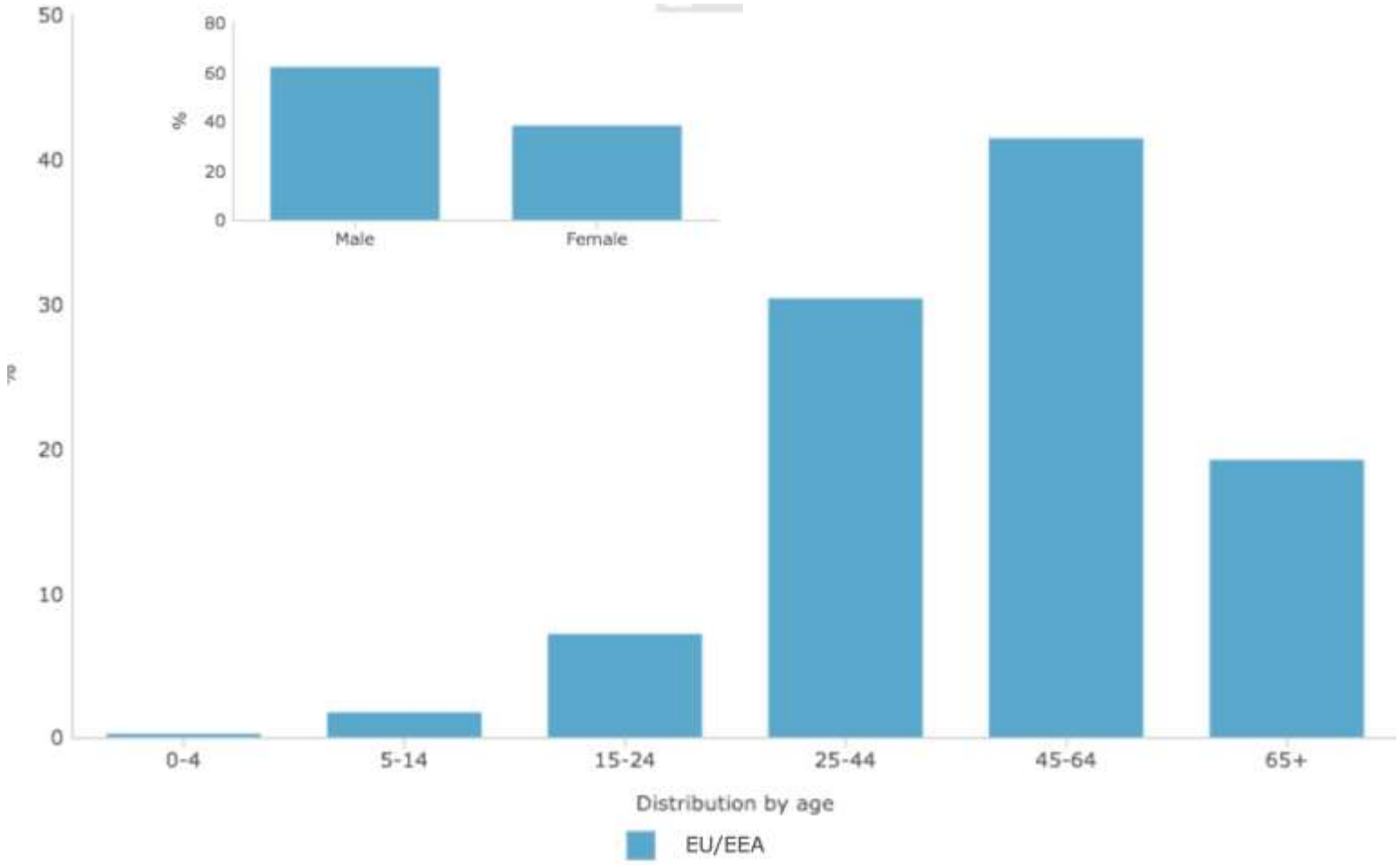
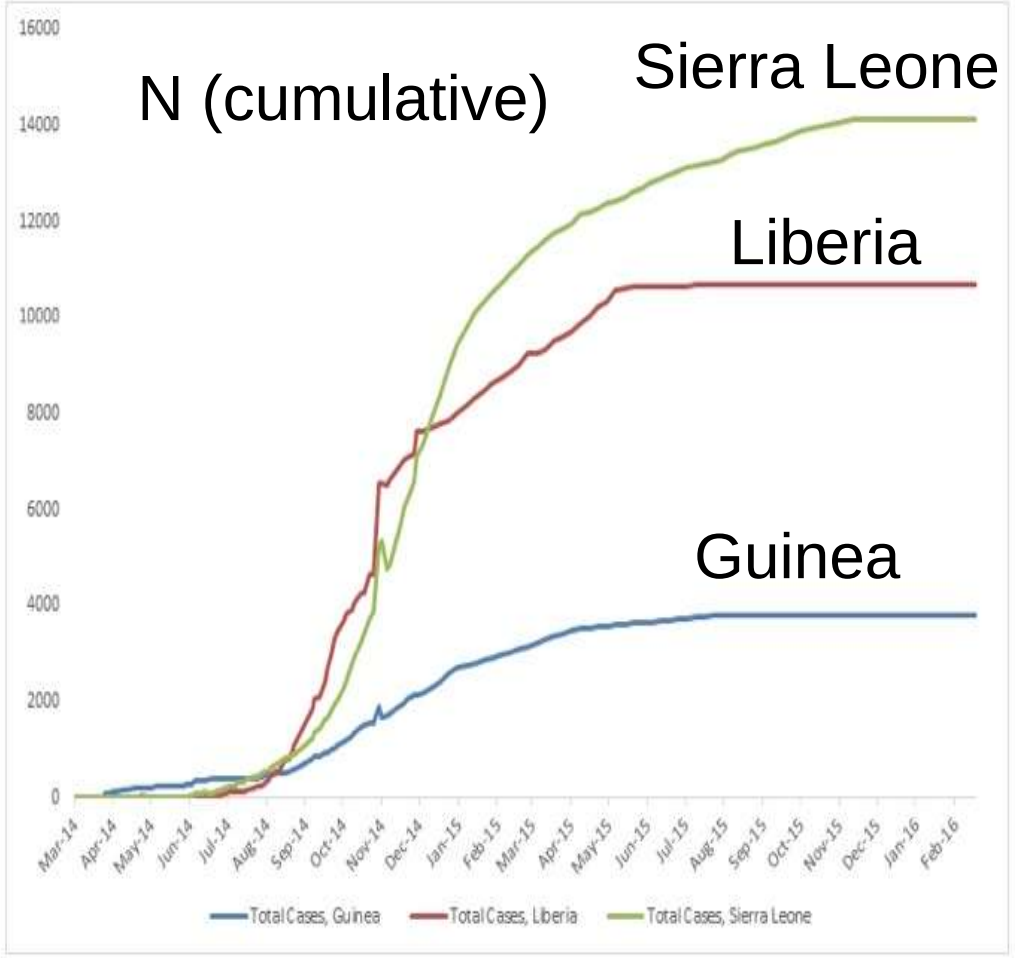


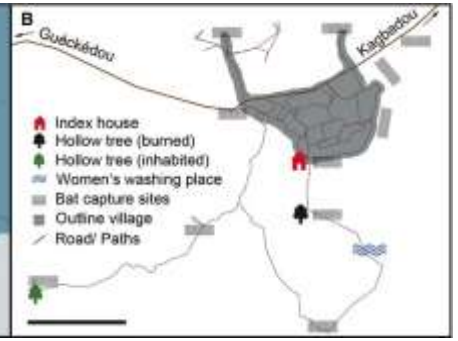
EBOLA - WEST AFRICAN outbreak

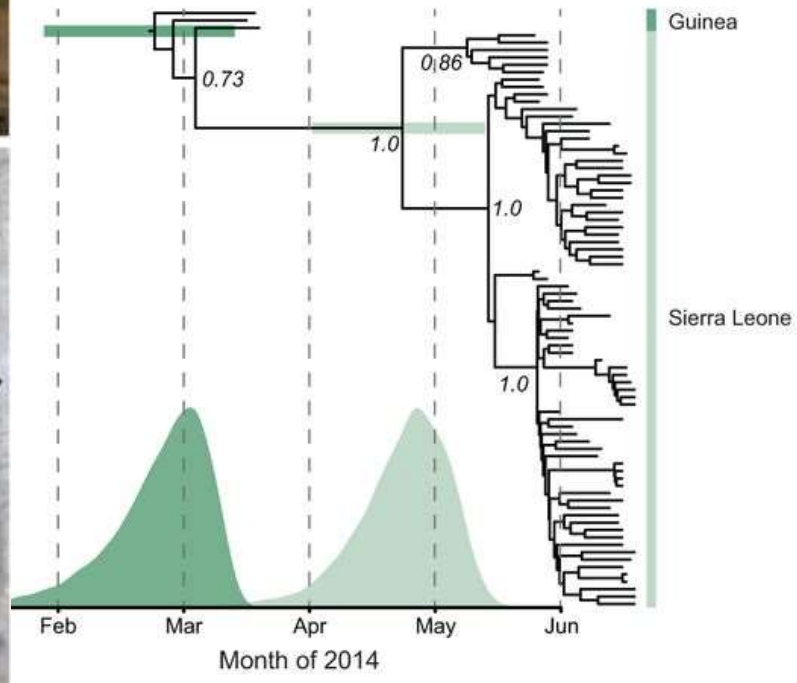
Country	Total Cases (Suspected, Probable, and Confirmed)	Confirmed Cases	Total Deaths
Guinea [2]	3811	3355	2543
Sierra Leone [3]	14124	8706	3956
Liberia [4]	10675	3160	4809
Total	**28610**	**15221**	**11308**

Graph 1: Total suspected, probable, and confirmed cases of Ebola virus disease in Guinea, Liberia, and Sierra Leone, March 25, 2014 – February 14, 2016, by date of WHO Situation Report, n=28603



Graph 1 shows the total reported suspected, probable, and confirmed cases in Guinea, Liberia, and Sierra Leone provided in WHO situation reports beginning on March 25, 2014 through the most recent situation report on February 17, 2016.





-IN FEBRUARY 2014 Ebola virus spread FROM GUINEA TO SIERRA LEONE
- THE WHOLE W AFRICA EPIDEMIC MOST PROBABLY ORIGINATES FROM A SINGLE ZOONOTIC TRANSMISSION EVENT - involving a 2-year-old boy in Meliandou, Guinea, who might have been infected by hunting or playing with insectivorous free-tailed bats living in a nearby hollow tree

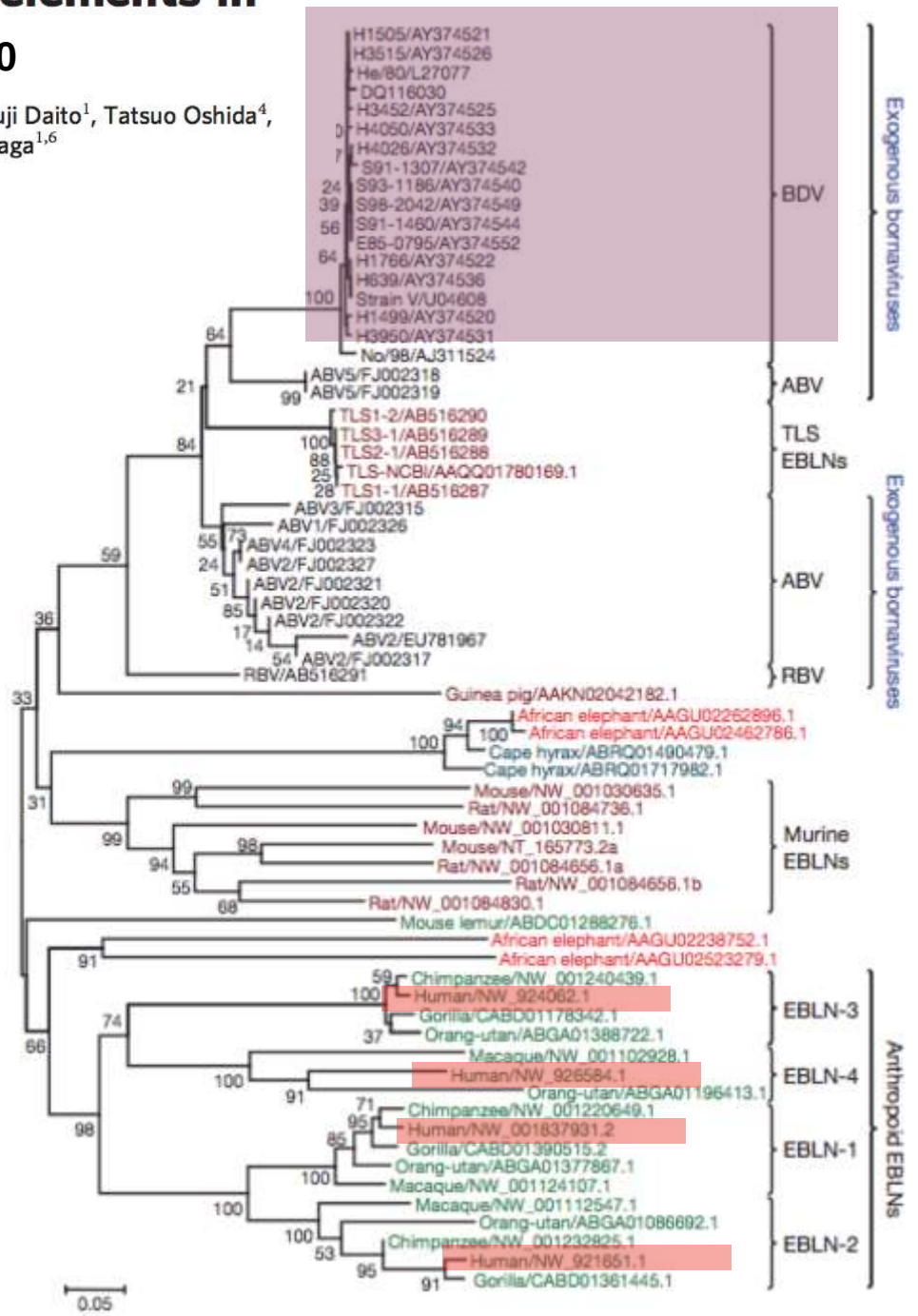
Marí Saéz A et al.
EMBO Mol Med. 2015;7:17-23

EMBO Molecular Medicine
Science
AAAS

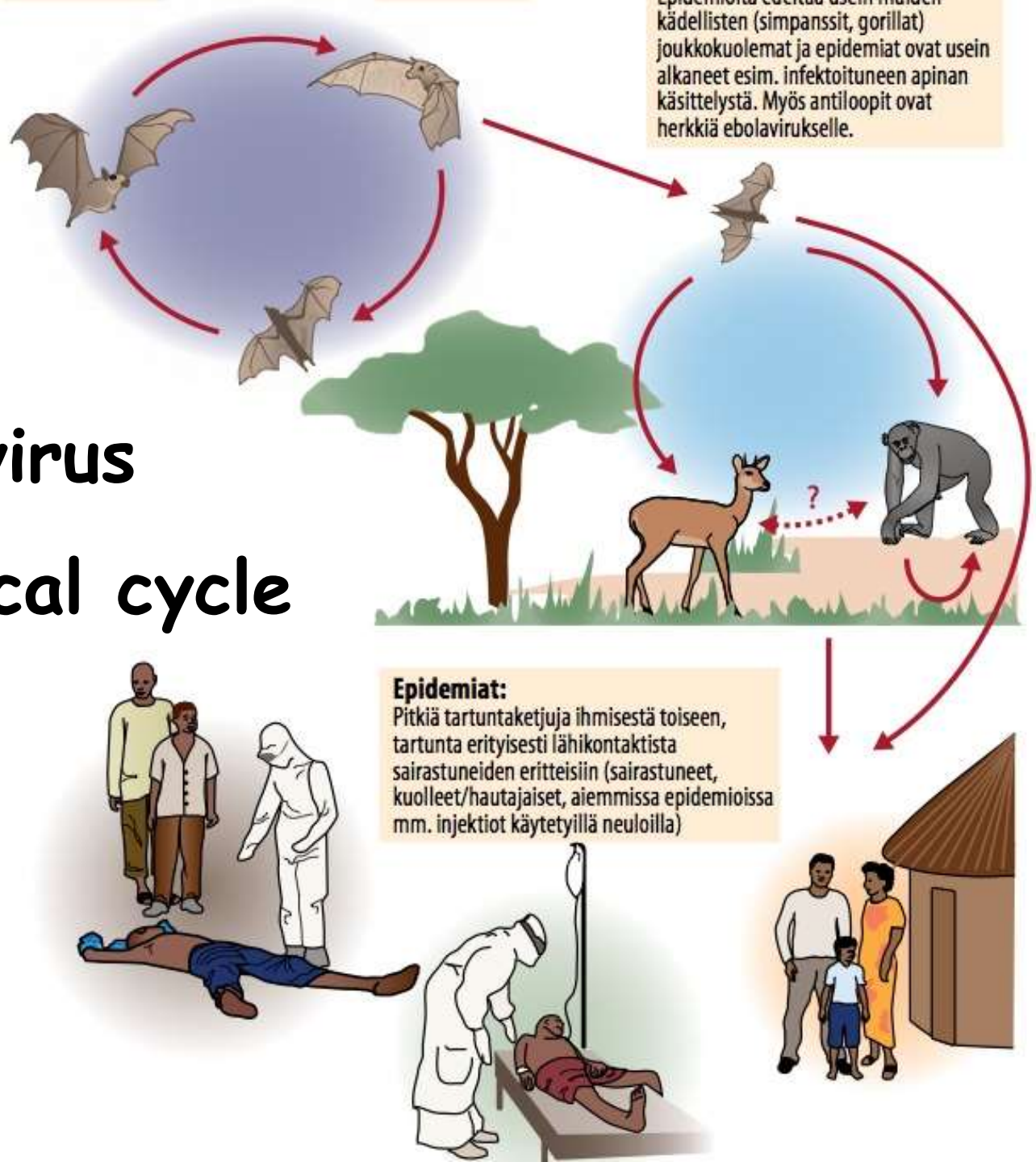
Endogenous non-retroviral RNA virus elements in mammalian genomes

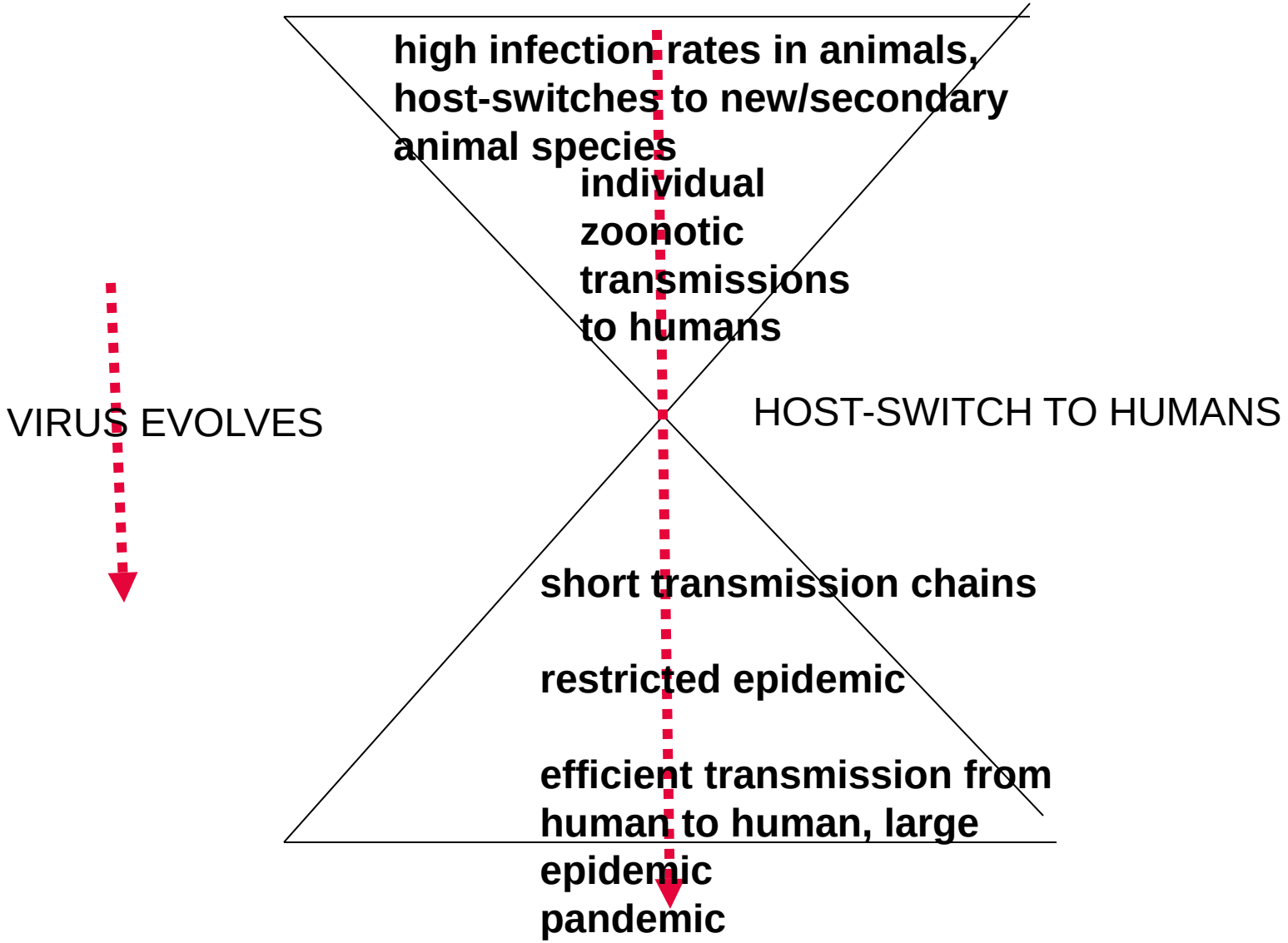
Nature, 2010

Masayuki Horie[1]*, Tomoyuki Honda[1,2]*, Yoshiyuki Suzuki[3], Yuki Kobayashi[3], Takuji Daito[1], Tatsuo Oshida[4], Kazuyoshi Ikuta[1], Patric Jern[5], Takashi Gojobori[3], John M. Coffin[5] & Keizo Tomonaga[1,6]

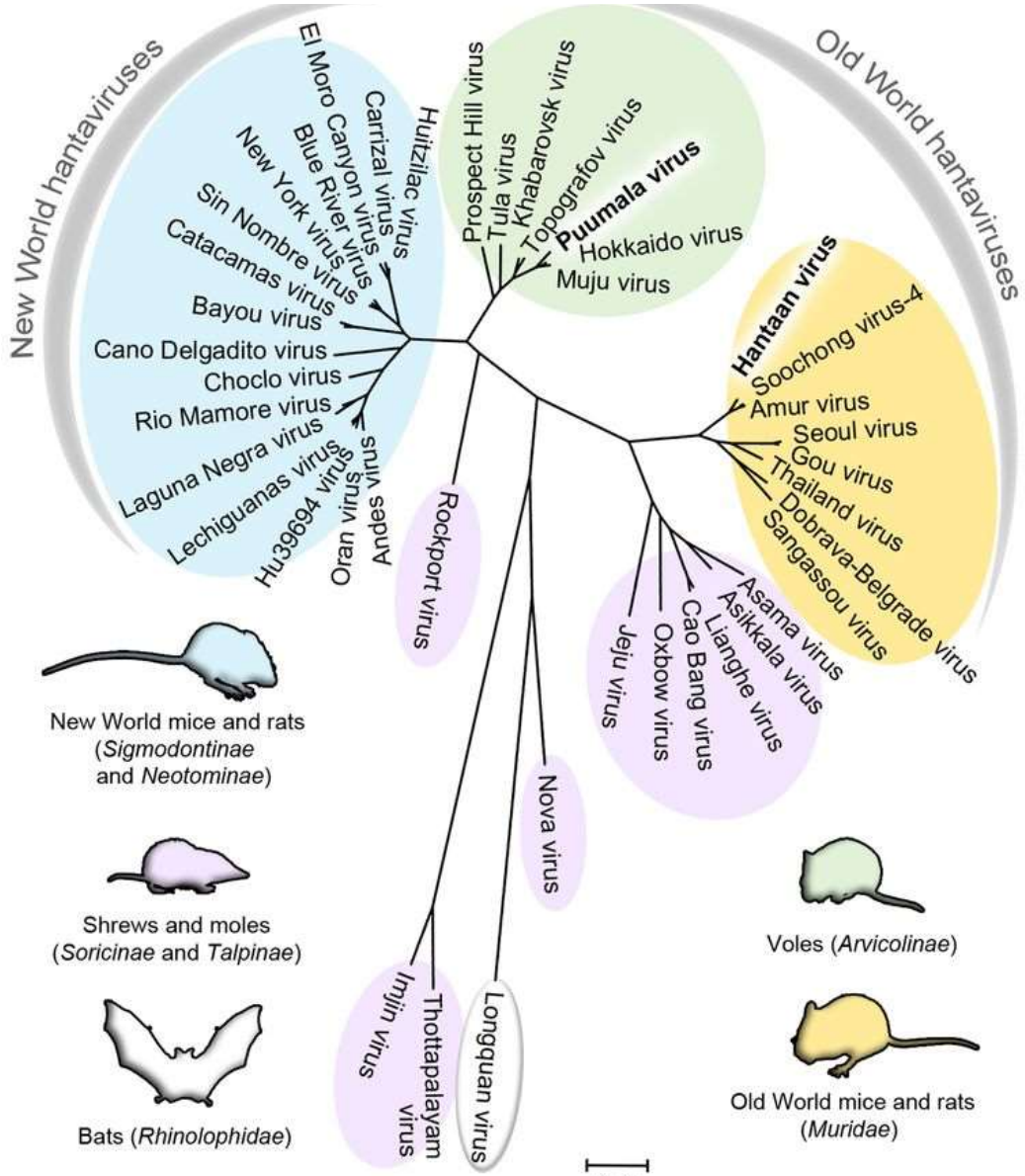


Ebola virus ecological cycle




high infection rates in animals, host-switches to new/secondary animal species
individual zoonotic transmissions to humans
VIRUS EVOLVES
HOST-SWITCH TO HUMANS
short transmission chains
restricted epidemic
efficient transmission from human to human, large epidemic
pandemic

Hantaviruses Gn phylogeny



Ilona Rissanen et al. J. Virol. 2017;91:e00378-17

Disease:

- Hemorrhagic fever with renal syndrome (HFRS)
  - Puumala -mainly mild, (NE)
  - Seoul –moderate
  - HTN, DOBV- more often severe.

0.1-0.4 %

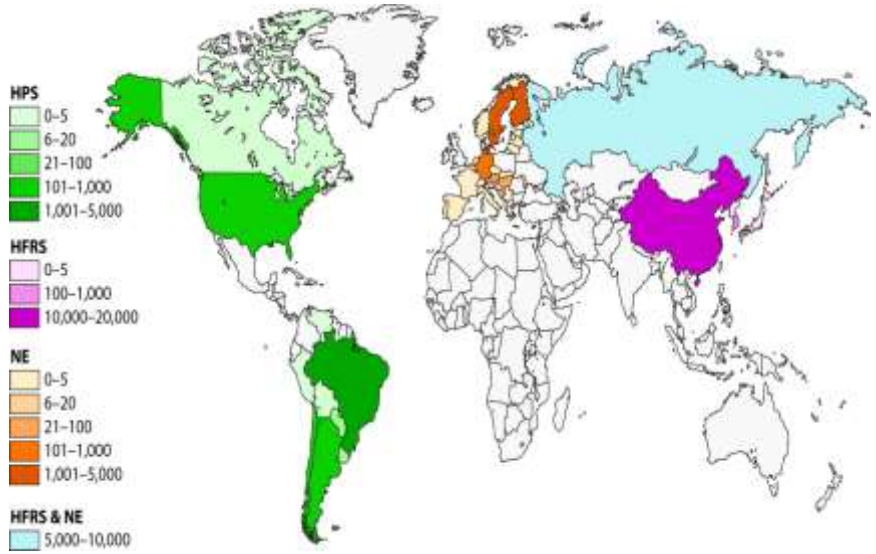
DOBV
- Saaremaa
- Kurkino
- Sochi
- Dobrava

- Hantavirus (cardio)pulmonarysyndrome
  - Sin Nombre
  - Andes
  - Araraquara (and others)

40 % †

Hantavirus disease burden

globally (cases per year)



Jonsson, de Figueiredo, Vapalahti, Clin. Microbiol. Rev. 2010x