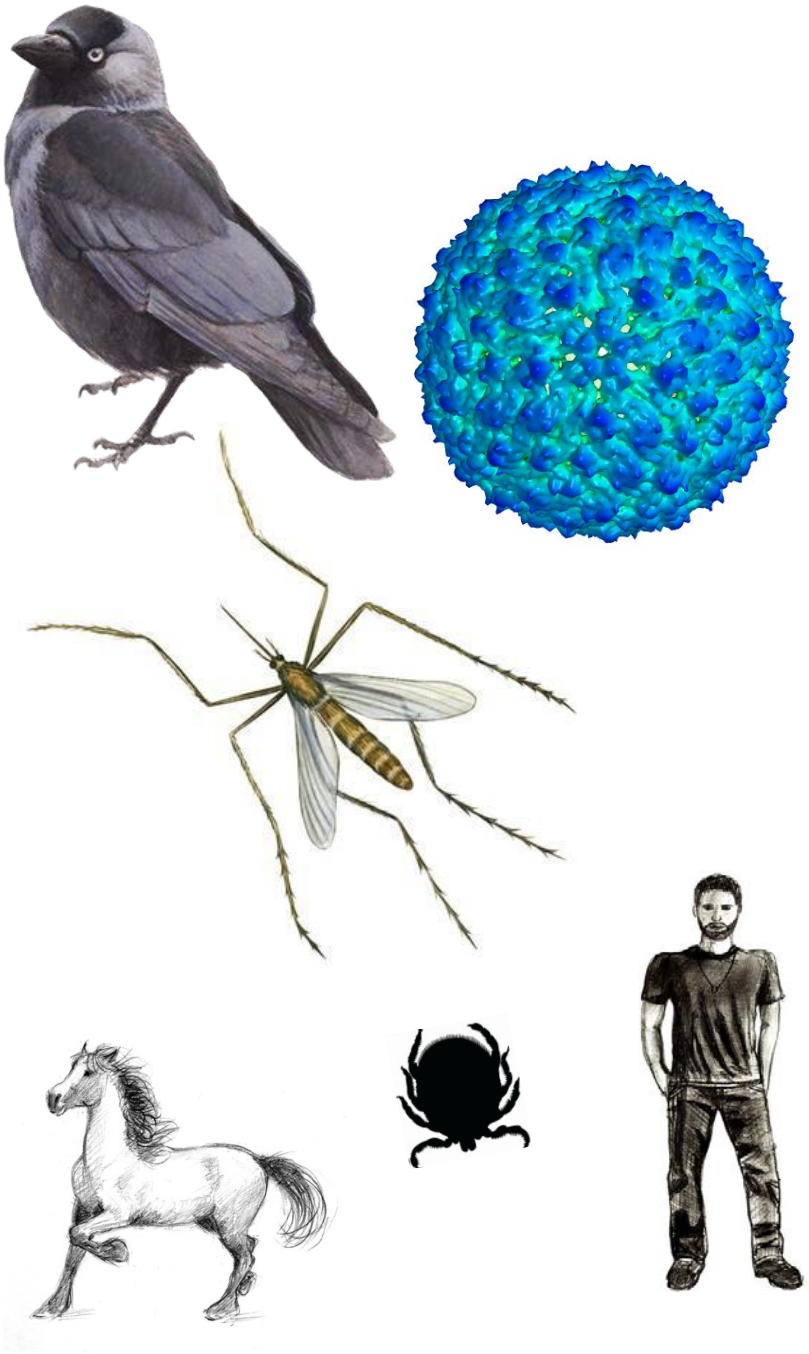


Rijksinstituut voor Volksgezondheid
en Milieu
Ministerie van Volksgezondheid,
Welzijn en Sport

Emerging arboviruses in Europe; the essentials

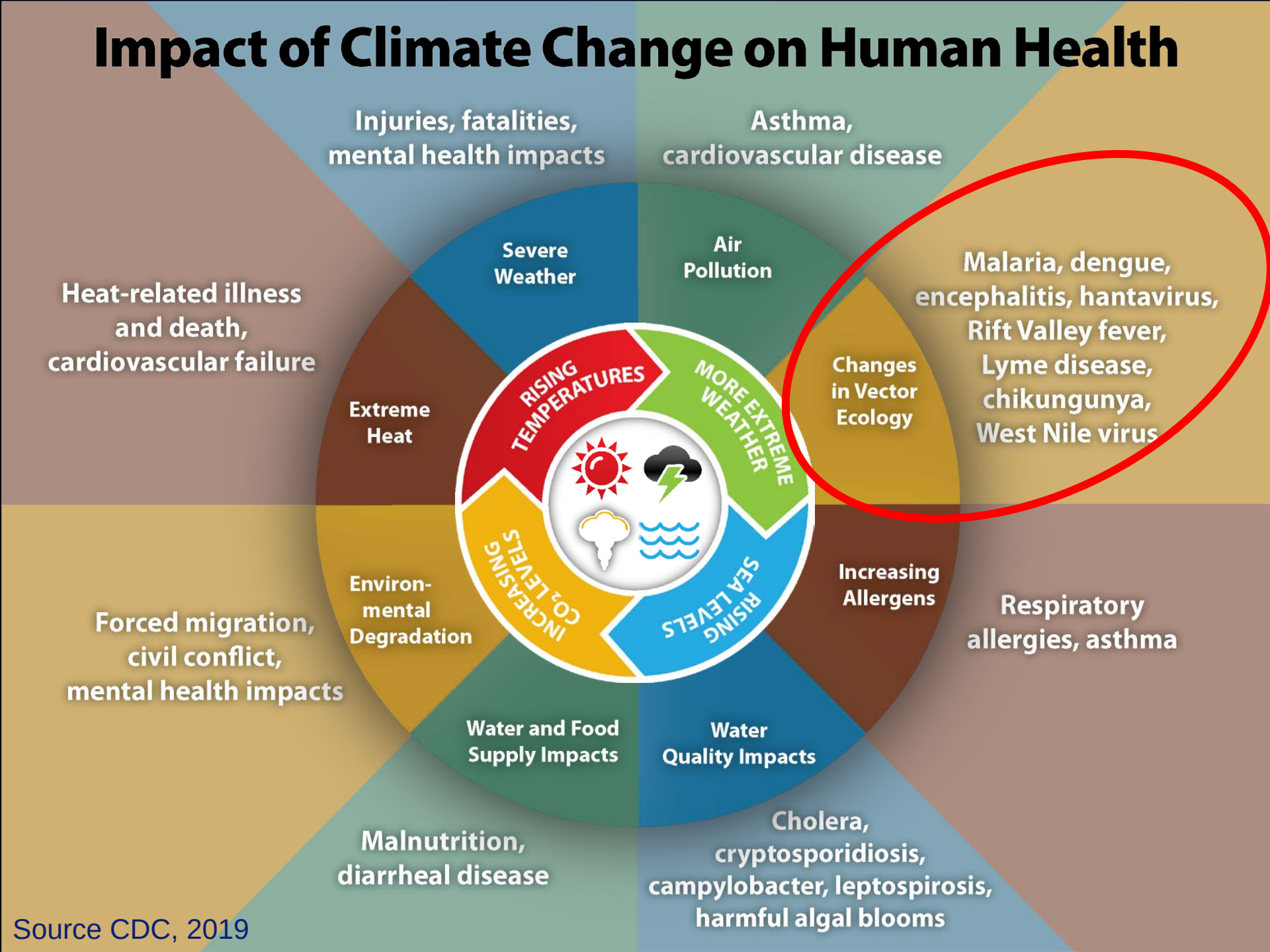
Chantal Reusken

Centre for Infectious Disease Control – RIVM

chantal.reusken@rivm.nl

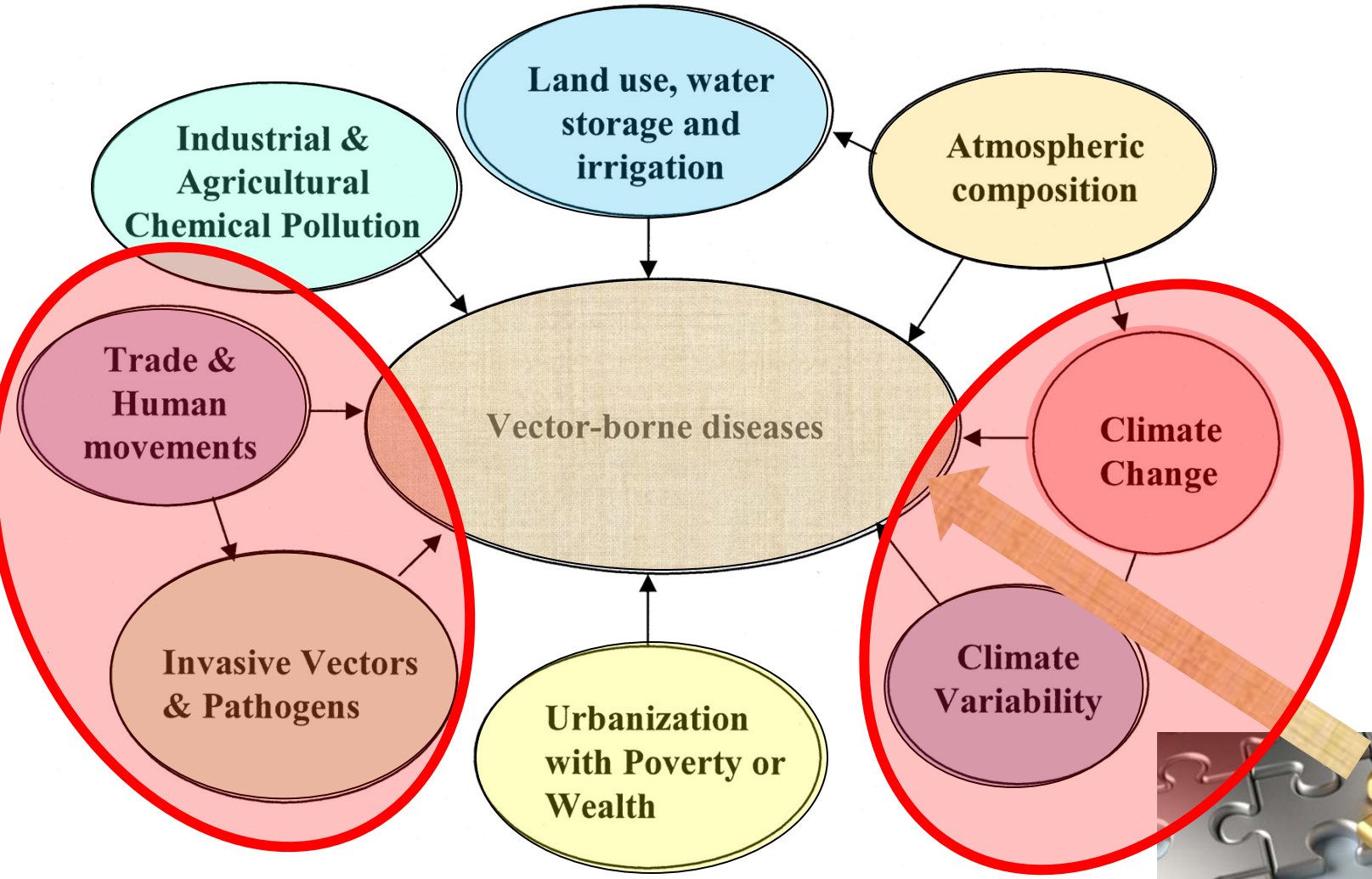
Sanquin | January 2019

Impact of Climate Change on Human Health



Source CDC, 2019

Human disease is result of complex interactions between human, pathogen, vector-related risk factors with spation-temporal variation: CONTEXT



Drivers of global change considered in relation to potential changes in the status of vector-borne diseases.

Sutherst et al., 2004

Arboviruses are zoonoses

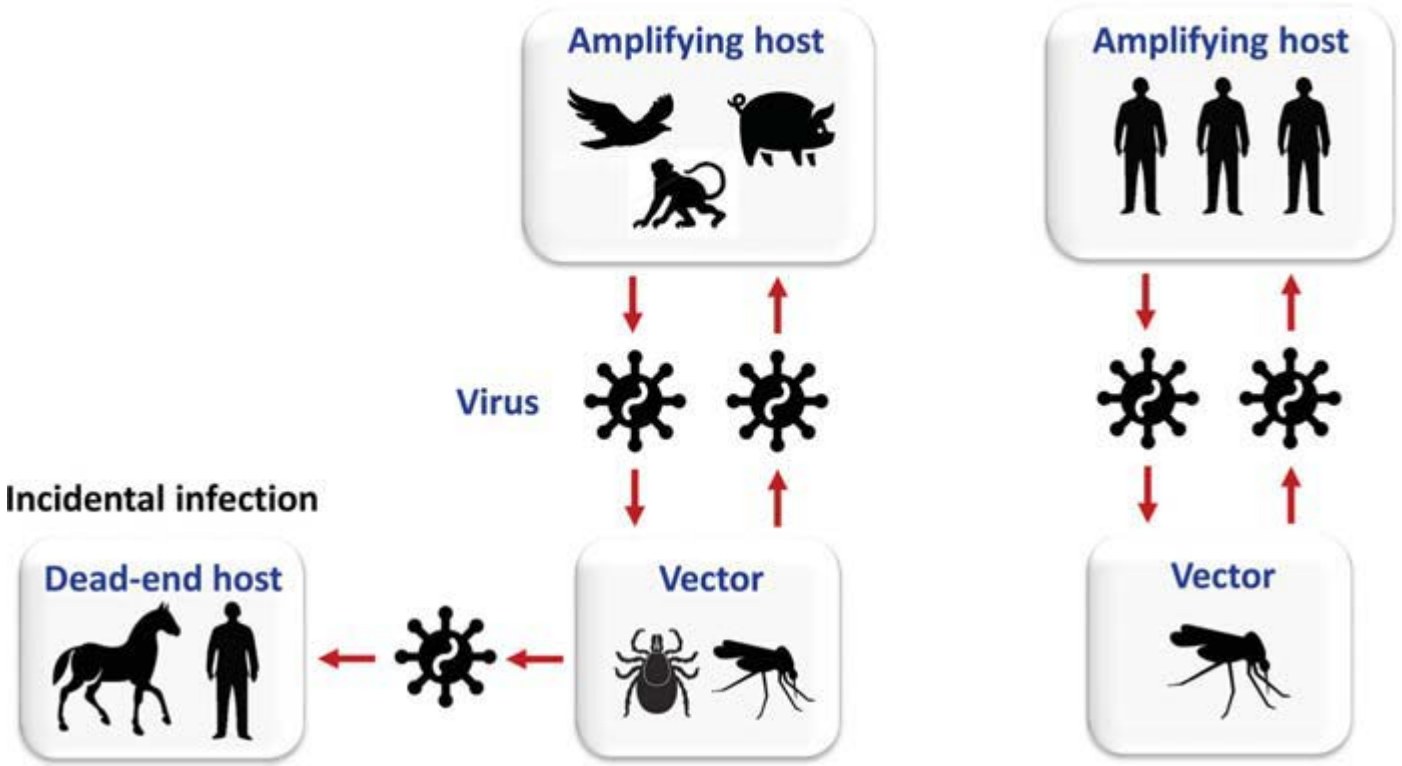
Europe

Enzootic/epizootic cycle

WNV, JEV, TBEV, CCHFV, TOSV, USUV

Urban epidemic cycle

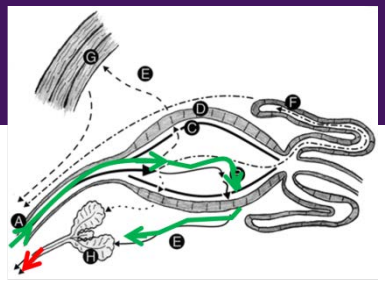
DENV, YFV, CHIKV, ZIKV



One health surveillance pyramids

Adapted from Barzon et al., 2019
Reusken et al., 2018; Braks et al., 2014

Not all mosquito species will transmit virus “X”



susceptibility + transmissibility = infected -> infective

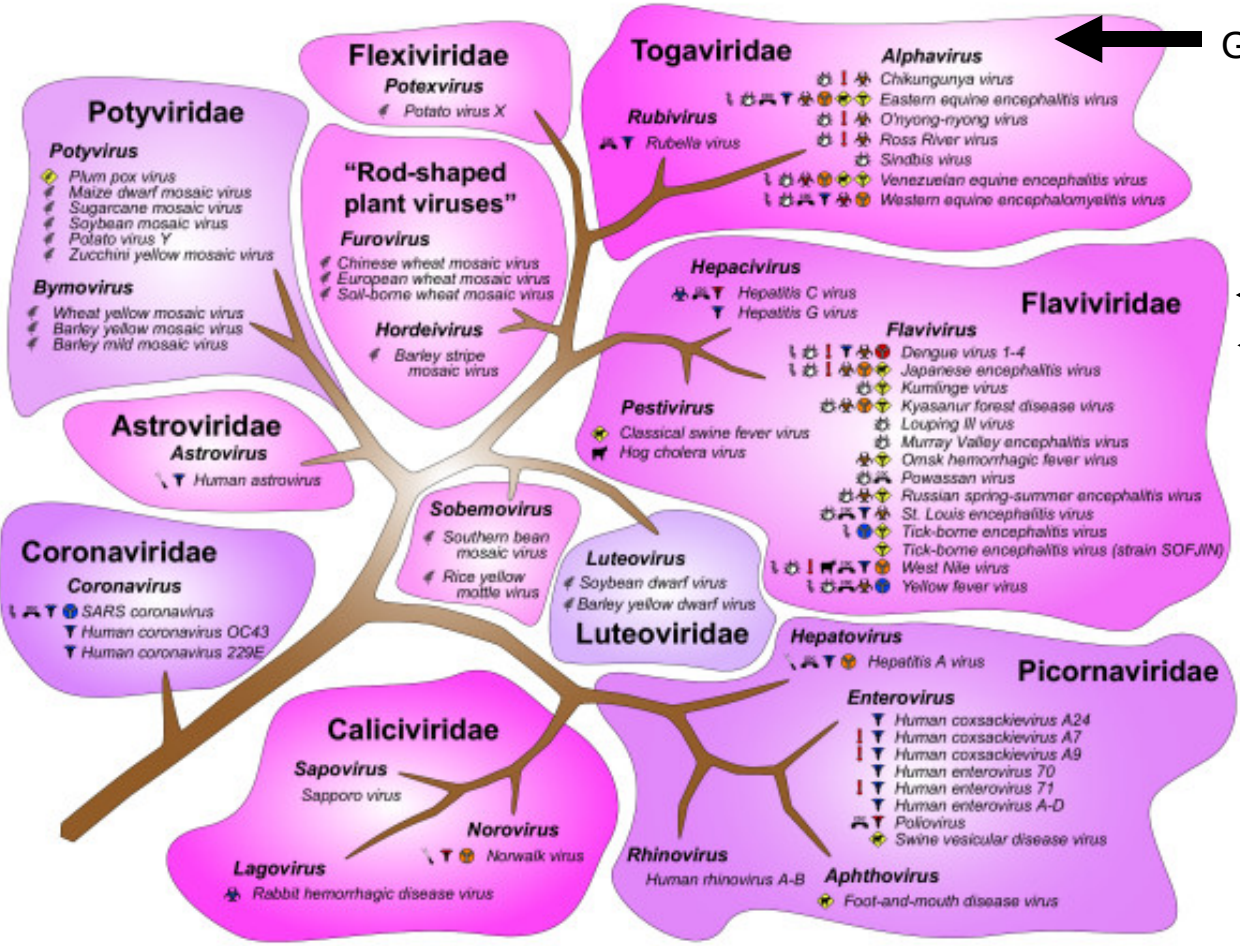
Table A: Important mosquito-borne pathogens that cause disease in humans

Pathogen	Disease	Case fatality rate (%)	Important vectors to human
***Togaviridae* arboviruses**			
Chikungunya	Febrile to severe illness	Very low	*Ae. aegypti, Ae. albopictus*
Eastern equine encephalitis	Encephalitis	50–75	*Coquillettidia perturbans, Ae. vexans*
Ross River	Febrile	0	*Culex annulirostris*
Sindbis	Febrile	0	*Ae. cinereus, Cx. pipiens*
Venezuelan equine encephalitis	Encephalitis	0.1–20	*Cx. pipiens*
Western equine encephalitis	Encephalitis	5–10	*Cx. tarsalis*
***Flaviviridae* arboviruses**			
Dengue 1-4	Febrile to haemorrhagic	3–12	*Ae. aegypti, Ae. albopictus*
West Nile	Febrile to encephalitis	3–15	*Culex spp.* (*Cx. pipiens, Cx. modestus*)
Japanese encephalitis	Encephalitis	30–40	*Cx. tritaeniorhynchus*
Murrey Valley encephalitis	Encephalitis	20–70	*Cx. annulirostris*
St. Louis encephalitis	Encephalitis	4–20	*Cx. pipiens, Cx. nigripalpus*
Yellow fever	Haemorrhagic	5–20	*Ae. aegypti, Ae. africanus, Haemagogus* spp.
***Bunyaviridae* arboviruses**			
La Crosse encephalitis	Encephalitis	<1	*Ae. triseriatus*
Rift Valley fever	Febrile	<1	*Aedes spp., Cx. pipiens*
***Plasmodium* protozoa**			
Malaria	Febrile to renal failure	1–7 (< 5 years)	*Anopheles* spp.

Source: Beaty & Marquardt 1996; Schaffner 2003

Taxonomy

positive stranded RNA viruses



Genus

Endemic birds:

Sindbis virus

Imported:

- chikungunya virus
- Ross river virus

Family

Genus

Endemic with human infections NL:

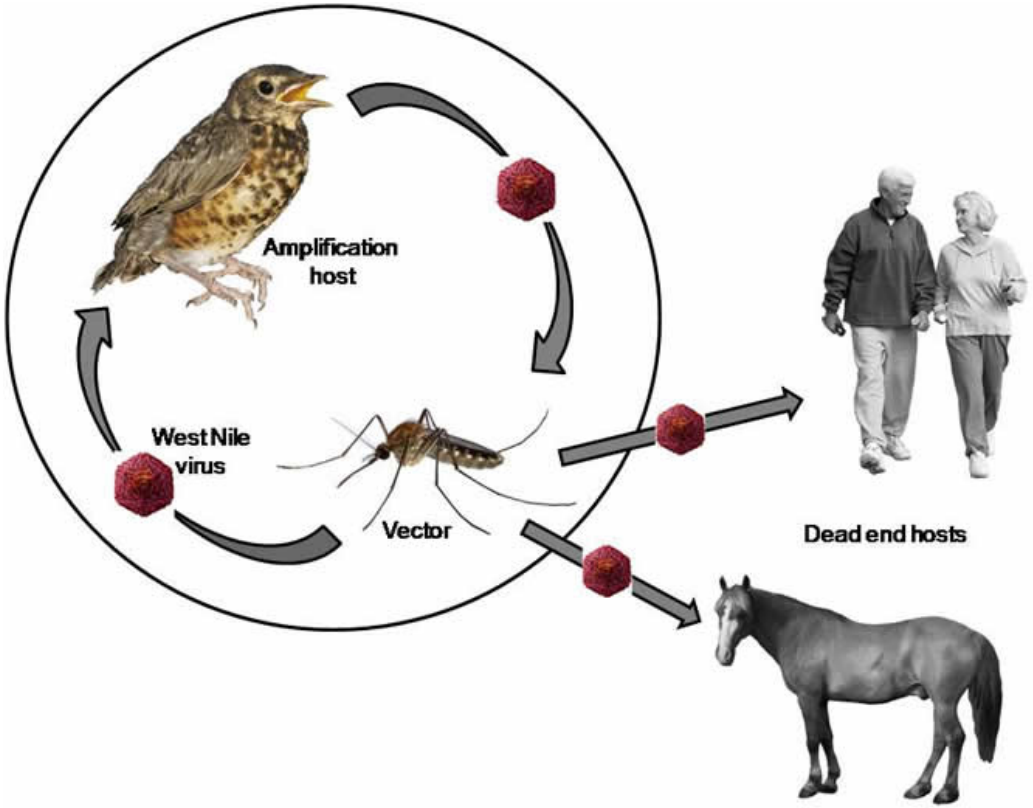
- **tick-borne encephalitis virus (TBEV)**
- Usutu virus (USUV)

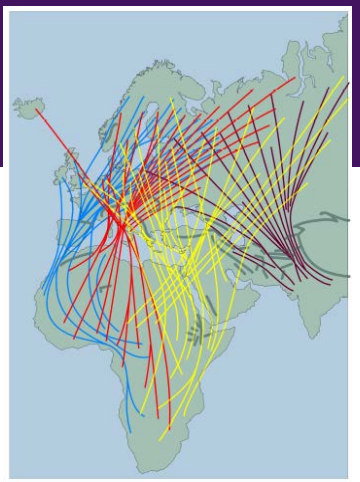
Imported through returning travellers:

- **dengue virus (DENV)**
- Zika virus (ZIKV)
- West Nile virus (WNV)
- **yellow fever virus (YFV)**
- **Japanese encephalitis virus (JEV)**

Ecker et al., 2005

West Nile virus life cycle

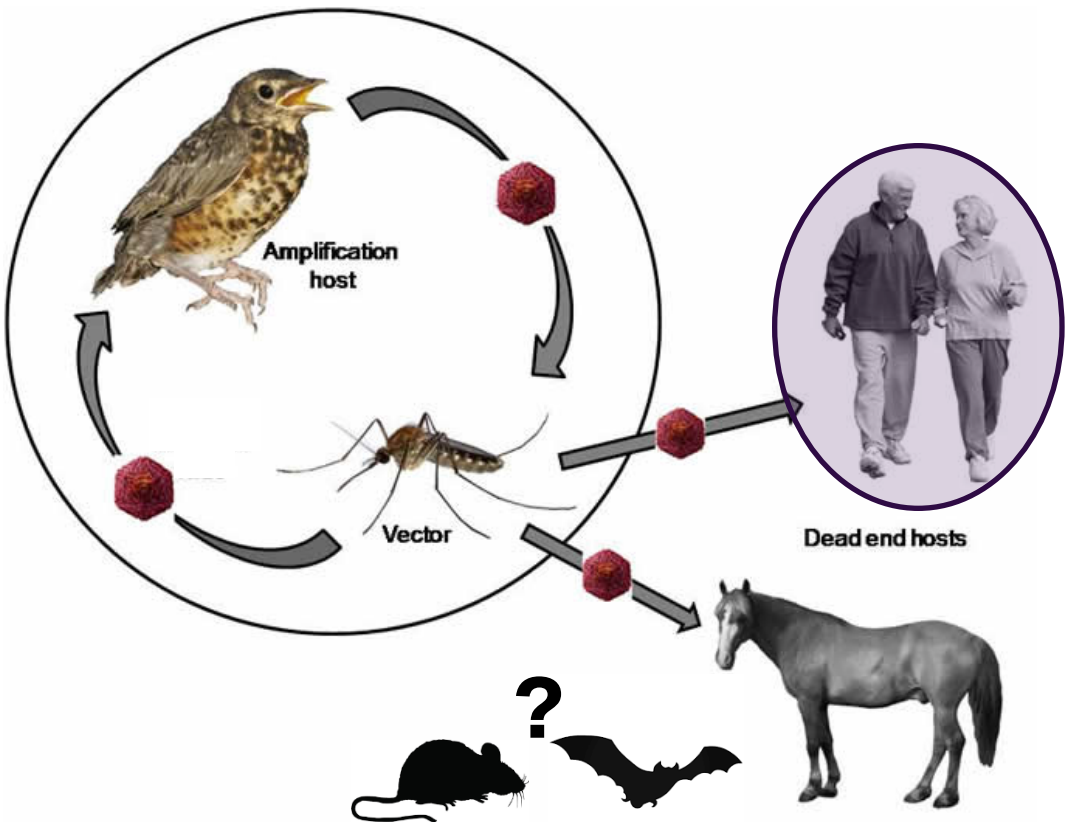


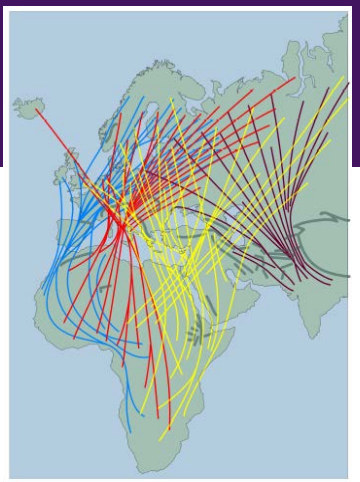


Alternative transmission routes:

- ❖ blood transfusion
- ❖ organ transplantation
- ❖ intra-uterine transmission
- ❖ breast feeding
- ❖ needle stick accidents (lab)
- ❖ dissection infected animals (lab)

Usutu virus life cycle



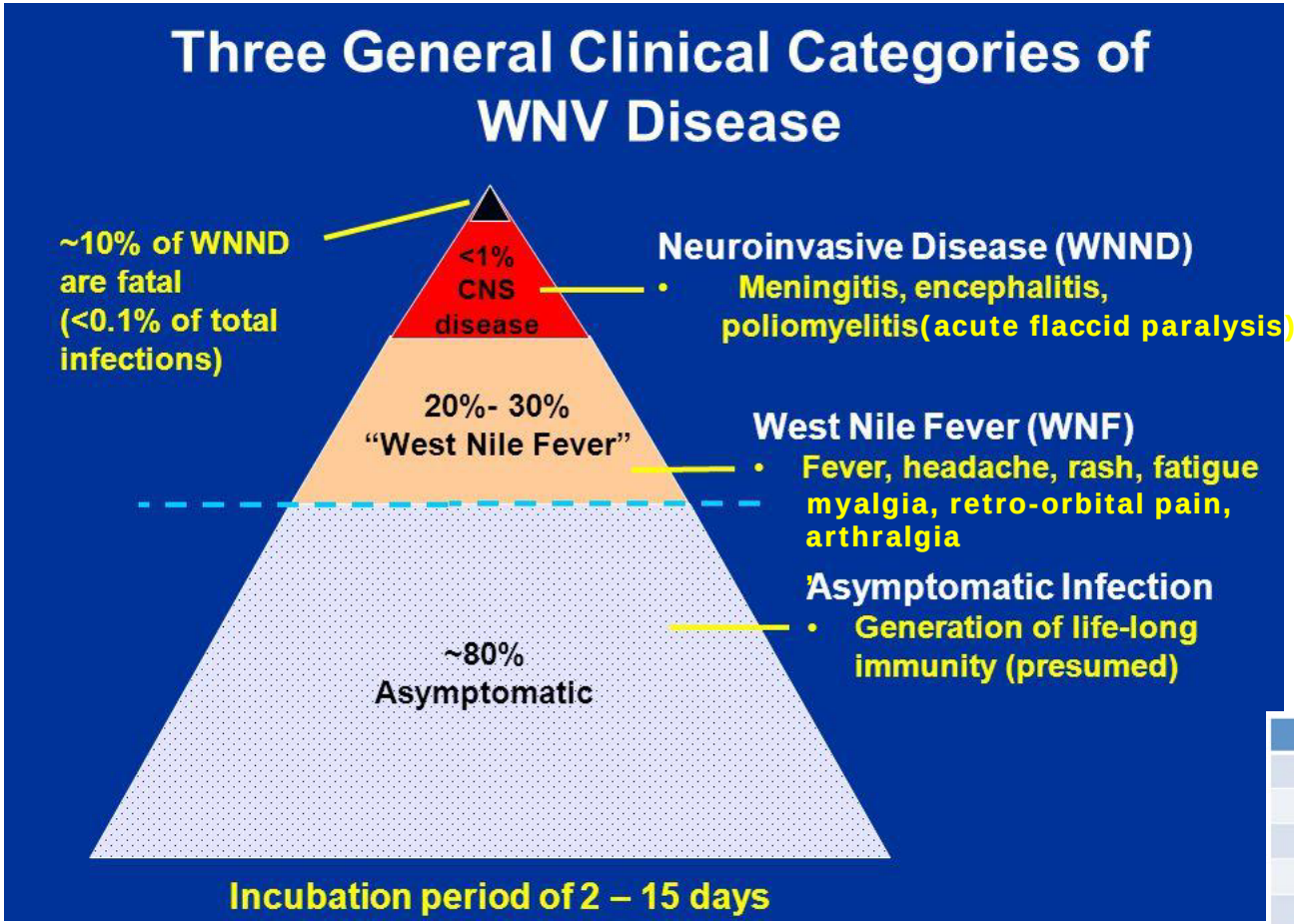


Alternative transmission routes:

- blood transfusion (suggested)
- more research needed:
  - Organ donation?
  - Breast-feeding?
  - Intra-uterine?
  - Dissection animals?

Cadar et al., EID, 2013 ;Engel et al., Mbio, 2016
Cadar et al., Eurosurveillance, 2016;Gaibani&Rossini, Microb. Inf. , 2017
Diagne et al., Viruses, 2019

West Nile virus clinical categories



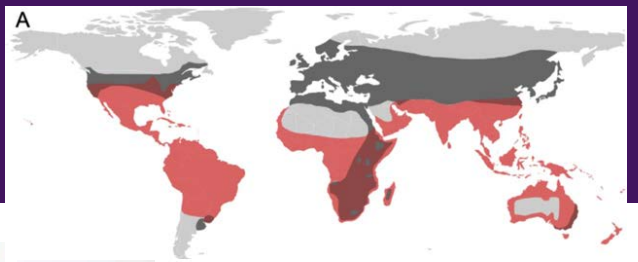
1 CNS disease case
=
~225 total infections all age categories
=
~60 total infections > 65 yrs of age

Age (years)	Males	Females
16-24	719	1231
25-44	356	330
45-64	248	387
≥65	50	61
All ages	220	244

Source: USA CDC

EID 2012

WNV epidemiology virus



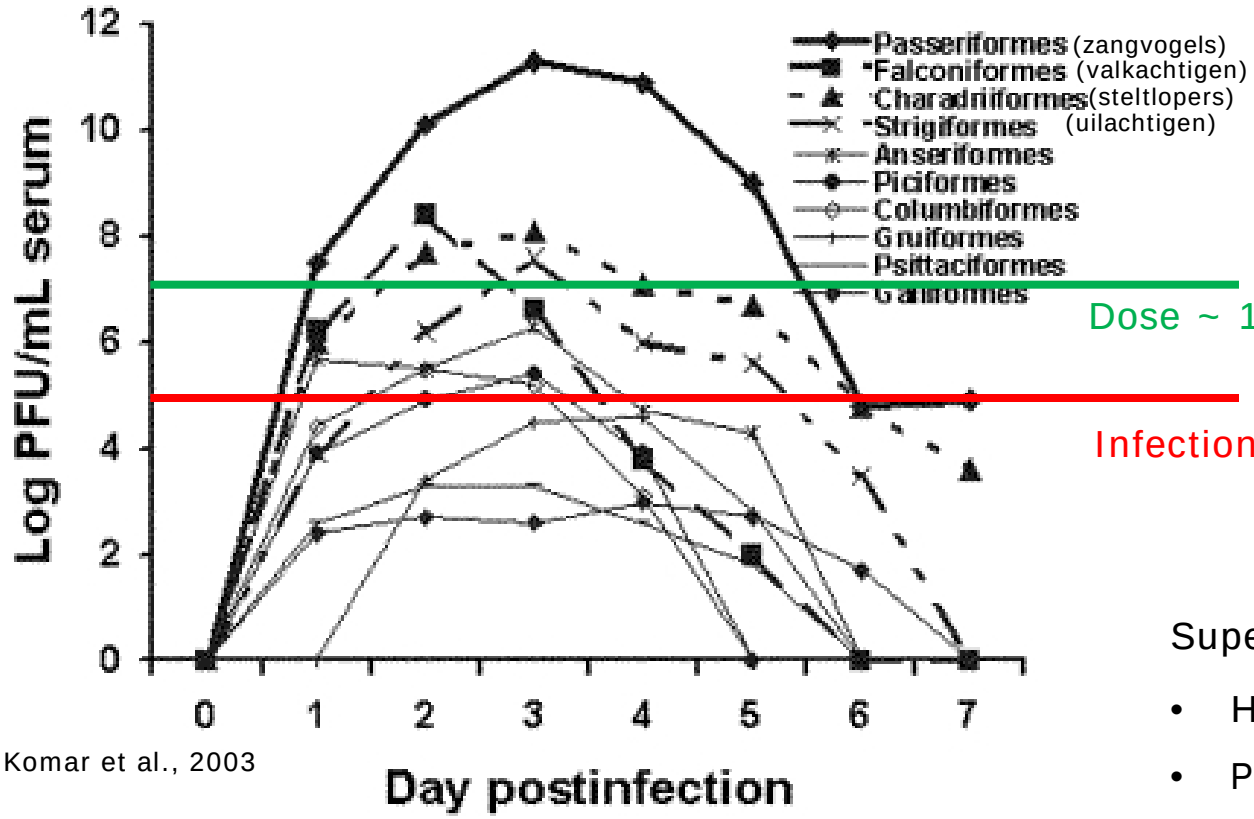
Cx. pipiens
Cx. quinquefasciatus
Cx. tarsalis

Lineage 1a
Lineage 1b (Kunjin)
Lineage 1c (India)
Lineage 2 2018
Lineage 3* (Rabensburg)
Lineage 4* (tick isolates)
Lineage 5* (India)
Spanish lineage*
Malaysian lineage*
Serological data only

*Putative lineage 5-25% nt difference between lineages

Ciota and Kramer, 2013; Papa et al., 2011; Shocket et al.,2019

WNV epidemiology reservoir



Komar et al., 2003

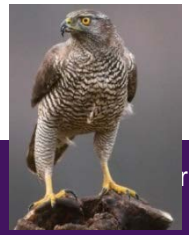
Dose ~ 100% *Culex* spp. get infected

Infection treshold for most *Culex* spp.

Superspreaders dependent on:

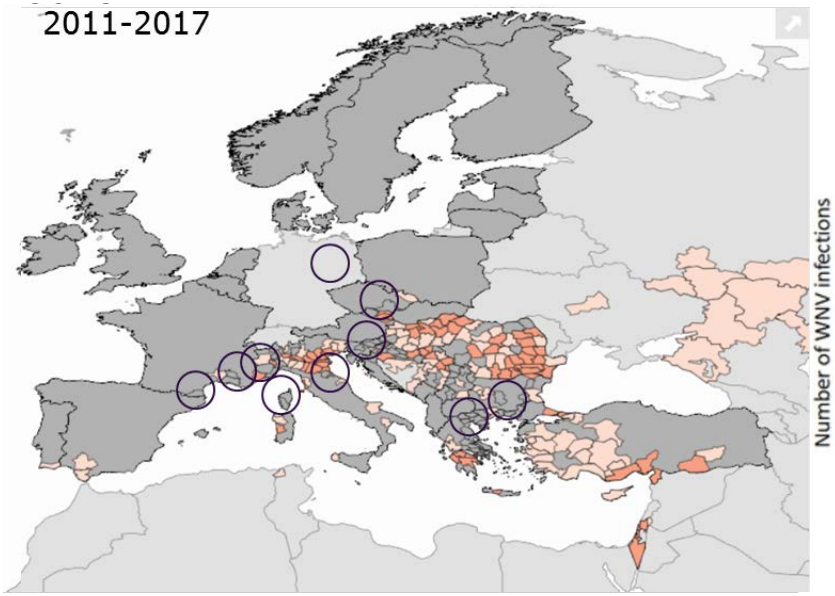
- High viremias
- Preferential fed upon mosquitoes
- (Minimal) clinical impact infection

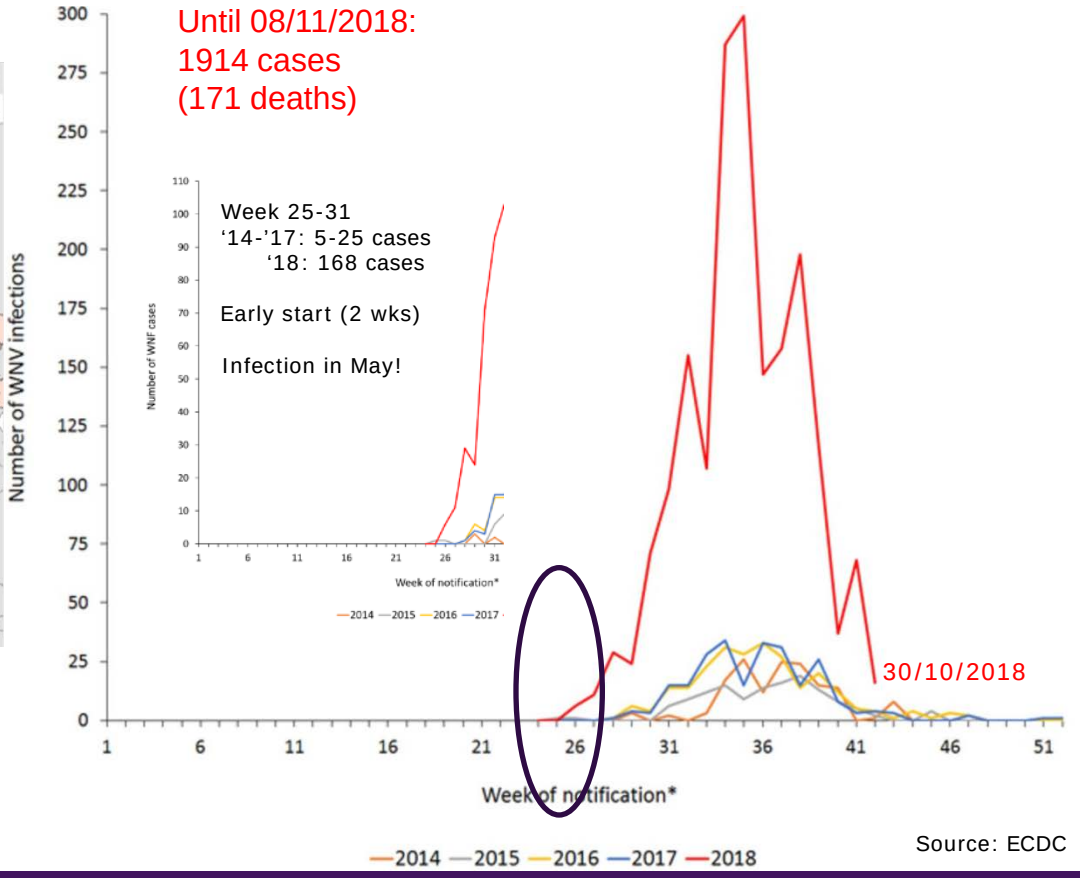




West Nile virus in 2018

West Nile virus notification human cases
EU/EEA and pre-accession countries 2014-2018





Source: ECDC

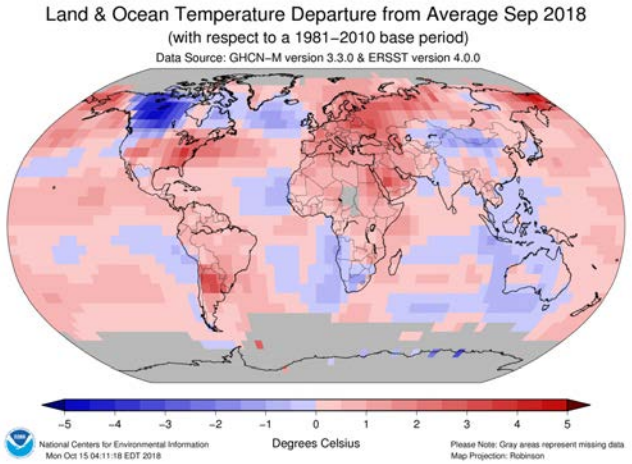
West Nile virus drivers

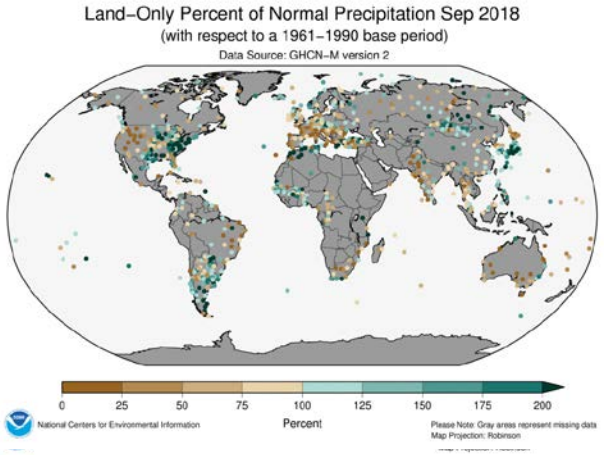
2018:
mild winter
wet, warm spring
dry, hot summer

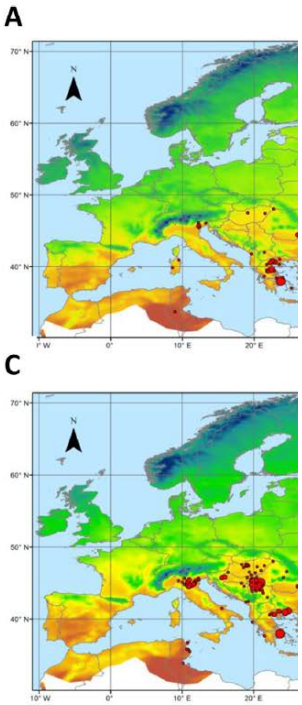
Key determinants for WNV incidence:

a.o. Climate anomalies:
-high precipitation in late winter/spring
-high summer temperatures
-summer drought

⇒ ↑ mosquito biting rates
⇒ ↑ mosquito development rates
⇒ ↑ virus replication rates (↓ EIP)
⇒ ↑ human exposure



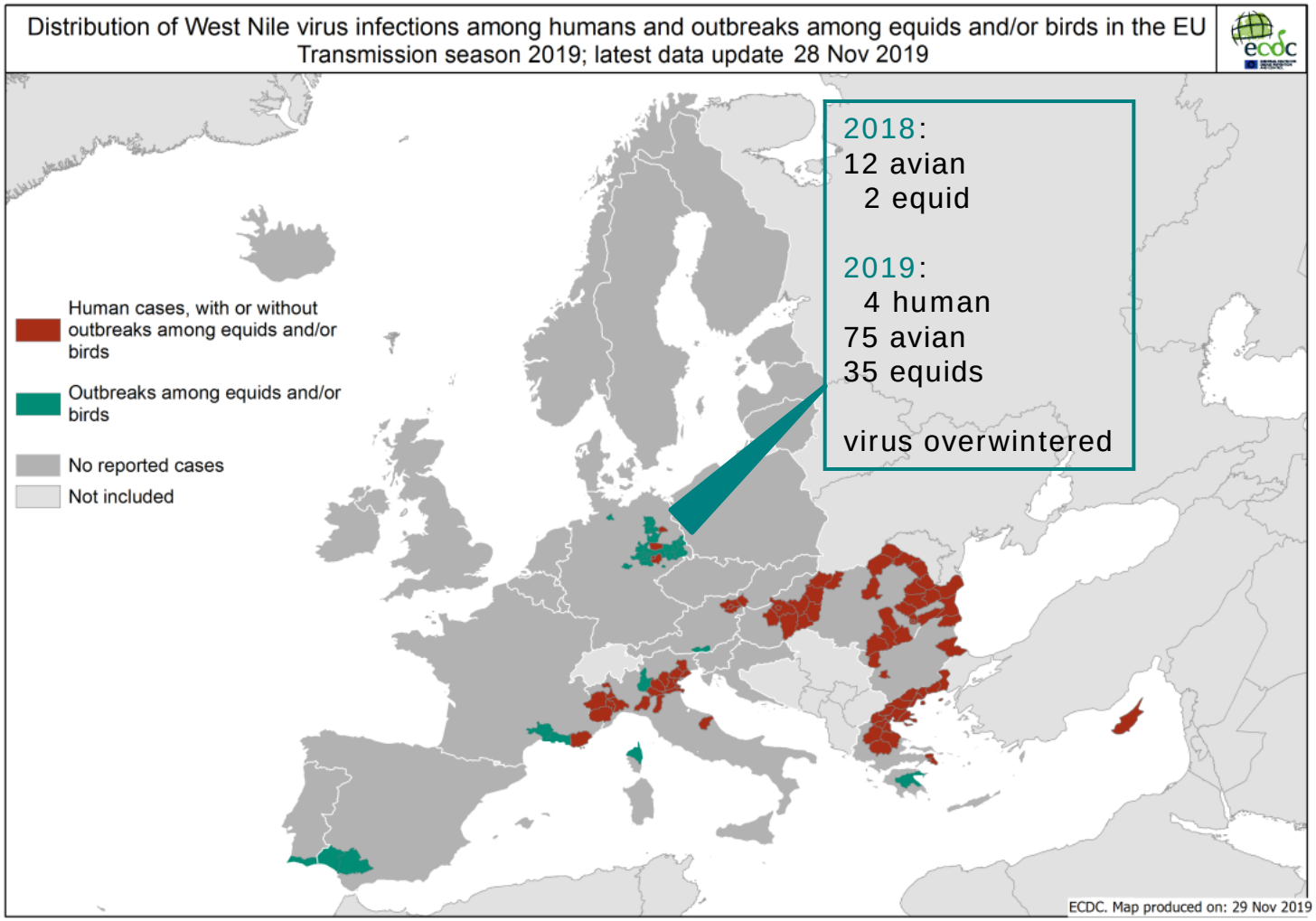




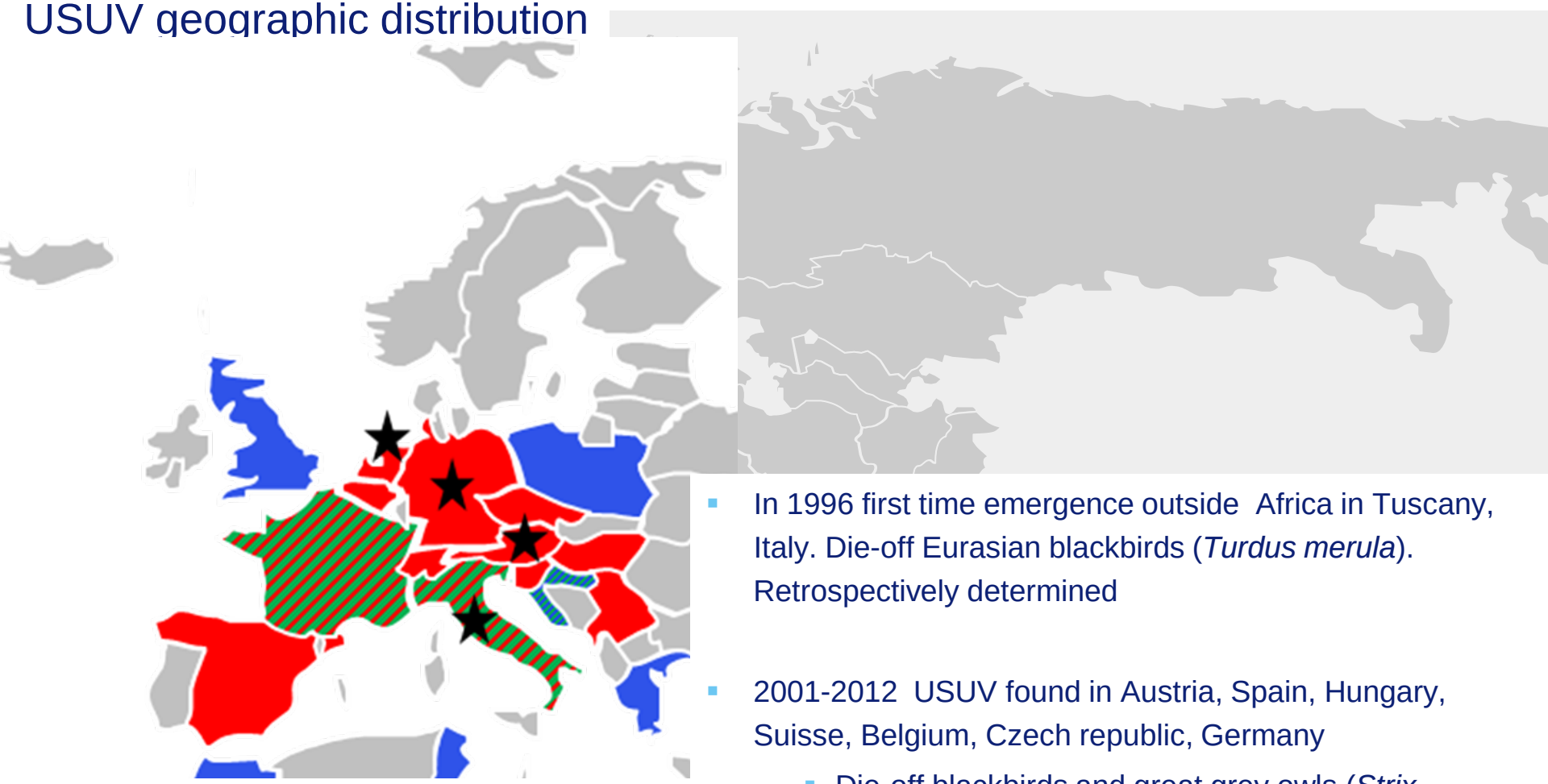
Mean diurnal sur

Marcantonio et al., 2015
Paz et al., 2013
Tran et al., 2014
Fros et al., 2015
Vogels et al., 2016

WNV Europe 2019



USUV geographic distribution



- In 1996 first time emergence outside Africa in Tuscany, Italy. Die-off Eurasian blackbirds (*Turdus merula*). Retrospectively determined
- 2001-2012 USUV found in Austria, Spain, Hungary, Suisse, Belgium, Czech republic, Germany
  - Die-off blackbirds and great grey owls (*Strix nebulosa*)

2005-2014 USUV antibodies in living birds Poland, Greece, UK

2016: large multi-country outbreak

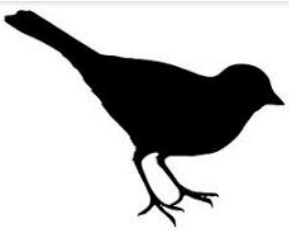
Virus in mosquitoes and/or birds

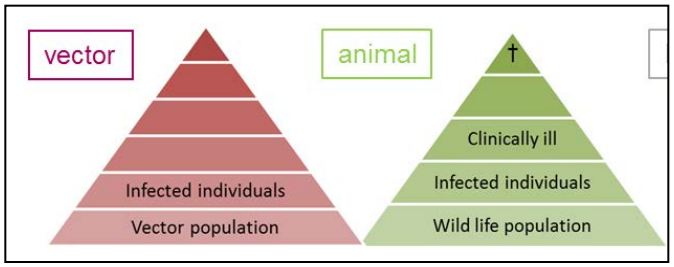
antibodies in birds and/or horses

Clinical human cases

★ *RNA + antibodies in blood donors*

Bird orders and mosquito species infected in the field





Aedes minutus
Ae. albopictus
Ae. caspius
Ae. detritus
Ae. japonicus
Anopheles maculipennis
Coquilettidia azuritis
Culiseta annulata
Culex quinquefasciatus
Cx. perfuscus
Cx. univitattus
Cx. neavi
Cx. pipiens
Mansonia africana

Accipitriformes
Anseriformes
Caprimulgiformes
Charadriiformes
Ciconiiformes
Columbiformes
Coracciformes
Falconiformes
Galliformes
Passeriformes
Phoenicopteriformes
Piciformes
Psittaciformes
Sphenisciformes
Strigiformes

multiple literature

Homo sapiens

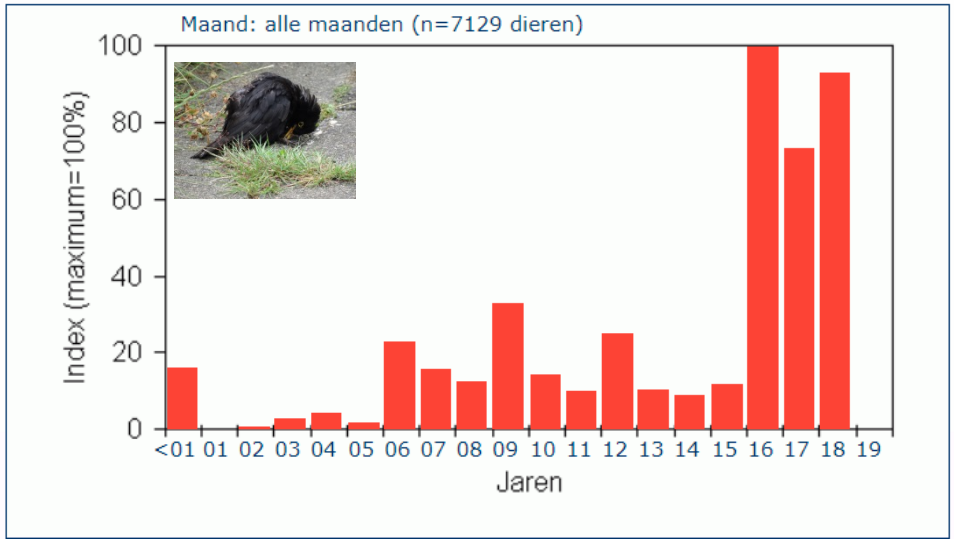
Braamsluiper
Chileense flamingo
grasmus
houtduif
huismus
ijsvogel
kea
knobbelzwaan
kramsvogel
Laplanduil
merel
pimpelmees
roodhalsgans
ruigpootuil
smient
sneeuwuil
Vlaamse gaai
zanglijster
zwarte zee-eend
zwartkop

USUV pos species in NL

Culiseta annulata
Culex pipiens

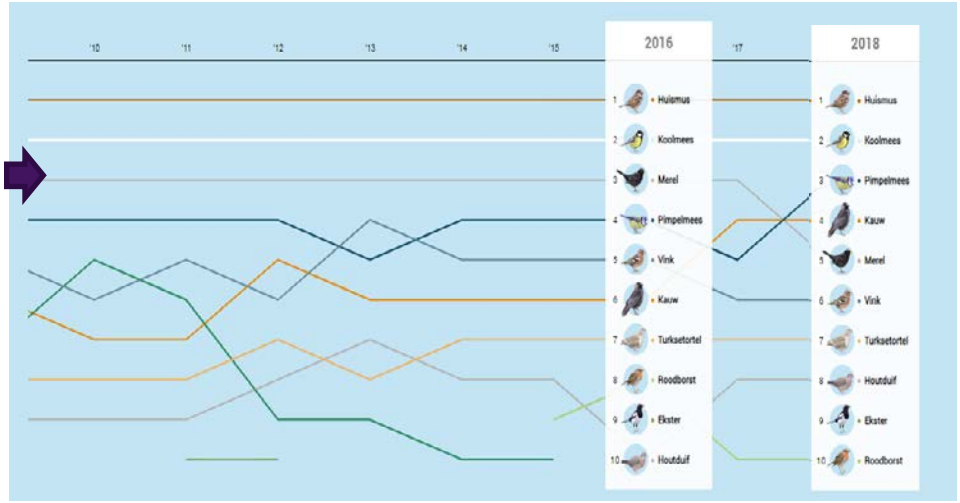
Vogeltrekstation
dwhc dutch wildlife health centre
Erasmus MC

Reusken et al., *in prep*



Sovon

Passive surveillance:
reported dead blackbirds per year ,
the Netherlands 2015-2018

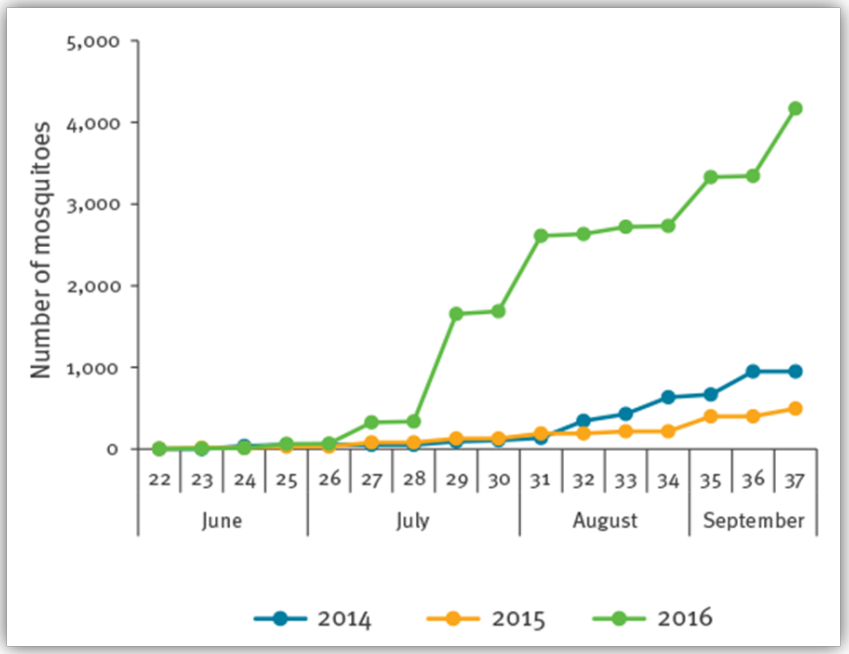


SOVON: -15%

(On average 650k-1100k breeding pairs in NL)

https://www.tuinvogeltelling.nl/opmerkelijk

2016 multi-country, multiple lineage outbreak



Cumulative number of mosquitoes found per year, at the sites of four used tyre companies, the Netherlands, week 22 to week 37 (end of May to mid-September)

FIGURE 1. *Number (panel A) and cumulative percentage (panel B) of outbreak-related USUV-positive live and dead birds, western Europe[a], 2016*

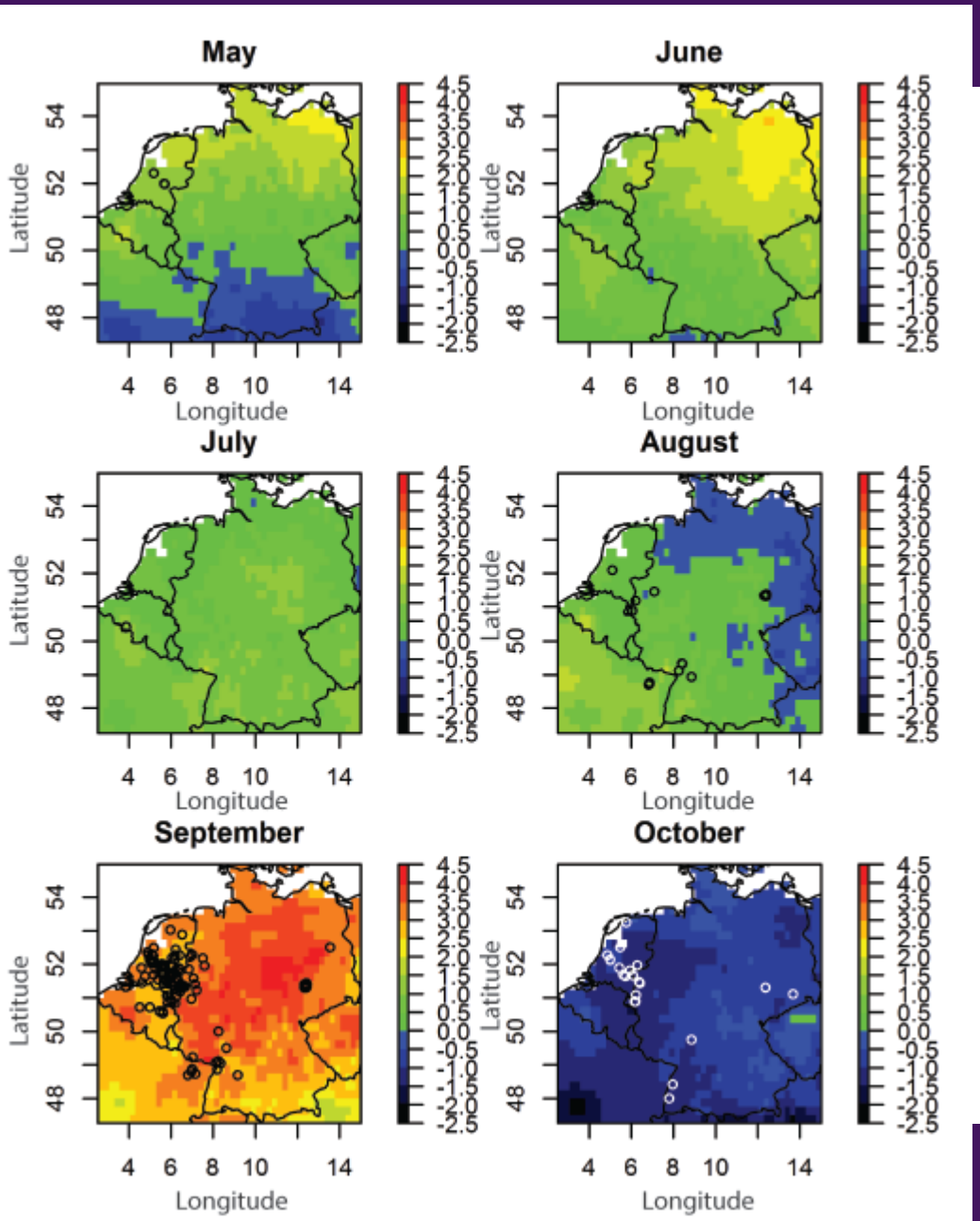


FIGURE 3. *Monthly temperature anomalies and distribution of outbreak-related USUV-positive birds, western Europe[a], 2016*

Cadar et al., Eurosurveillance 2017
Rijks et al., Eurosurveillance 2017

Molecular, WGS 115 blackbirds

-Two lineages:

2016: 73% Africa 3
2017: 71% Africa 3
2018: 93% Africa 3

-No clear geographical clustering of the different USUV lingeages

-"Shot-gun blast" introduction

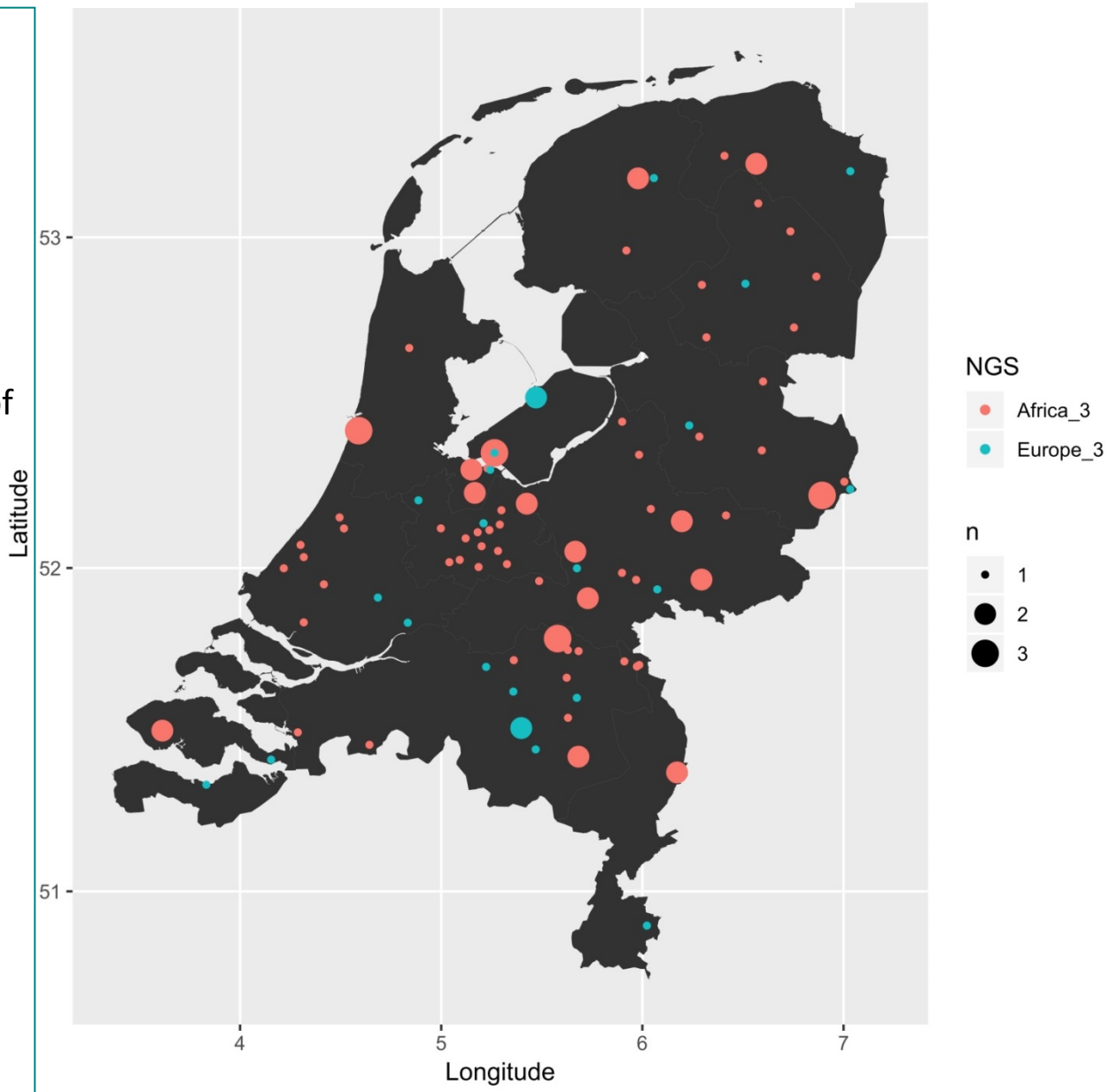
-MRCA : 2008-2011 Africa 3
2003-2007 Europe 3

-Continuous exchange with virus strains circulating elsewhere (Europe, Africa)

Serology, 534 blackbirds

- 12-15% seroprevalence
- Antibodies > 1 year

Cumulative 2016-2018; WGS 115 black birds



Bas OudeMunnink et al. *In press*.

Usutu virus, a zoonosis !

⇒ Up to date 30 confirmed CLINICAL human case in public domain

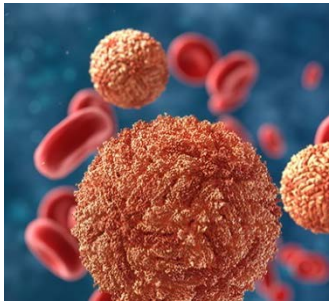
⇒ 18 cases of neuroinvasive disease (Italy, Croatia, France)
⇒ meningoencephalitis, encephalitis, polyneuritis, or facial paralysis

⇒ Fever, rash, althralgia, myalgia

⇒ RT-PCR screening
⇒ Positive blood donations (Italy, Germany, Austria, Netherlands)
⇒ Mixed cohort healthy/sick: 1.1% (0% WNV)

⇒ Sero-studies
⇒ In areas with co-circulation USUV,WNV: seroprevalence USUV > WNV
⇒ Healthy blood donors: 0.02% GER; 0.23- 1.11% ITA, 2% NL

⇒ Forestry workers, ITA: 18.1%
⇒ Persons + rash/mosquito bites, AUS: 25%
⇒ Healthy high risk mosquito bites, SER: 7.5%
⇒ Mixed cohort healthy/sick: 6.5%; 0.78% ITA



=> Consensus: conceivable underestimation burden of USUV-related disease

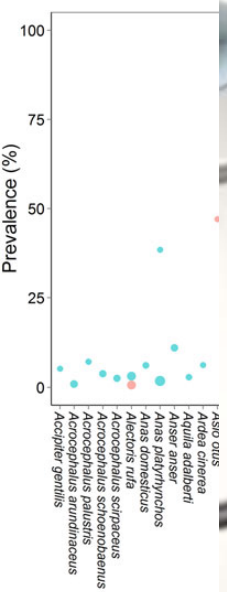
=> In vitro studies confirm deleterious effect USUV on human neural cells

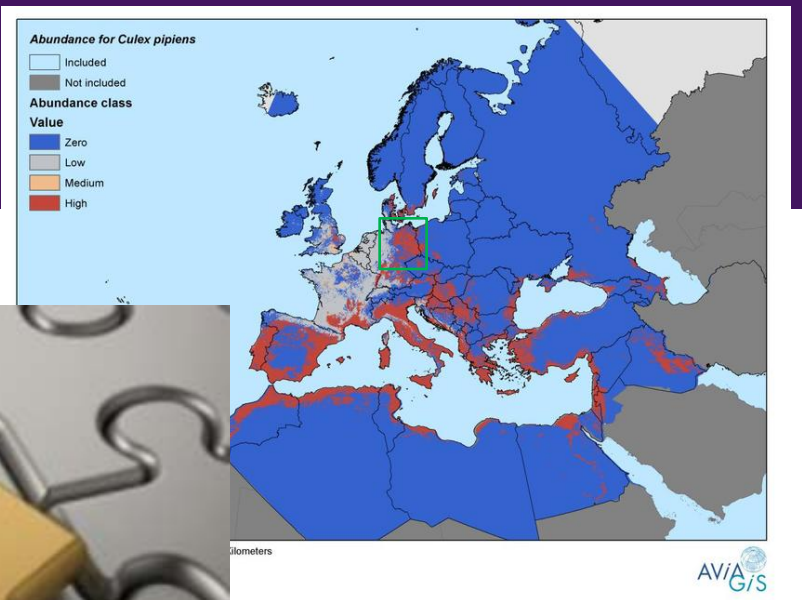
Gaibani and Rossini, 2017;Grottola et al., CMI 2016;Percivalle et al., 2017;Pierro et al., 2013 Fagionni, 2018;Barzon, 2018;Aberle, 2018;Cadar , 2017;Allerlng, 2017, Barzon, ECV 2019, Zaaijer et al., 2019, Salinas et al., 2017

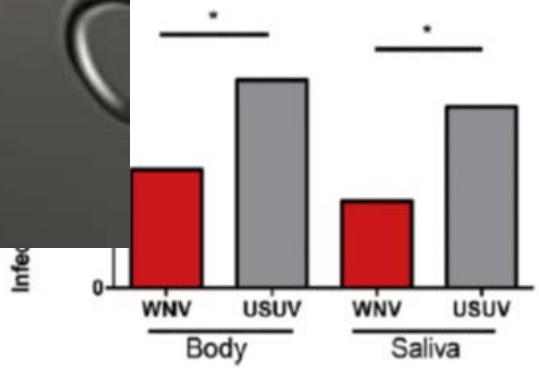
West Nile virus in NL?

WNV vs USUV:

- Identic
- Overla
- Overla
- Presen



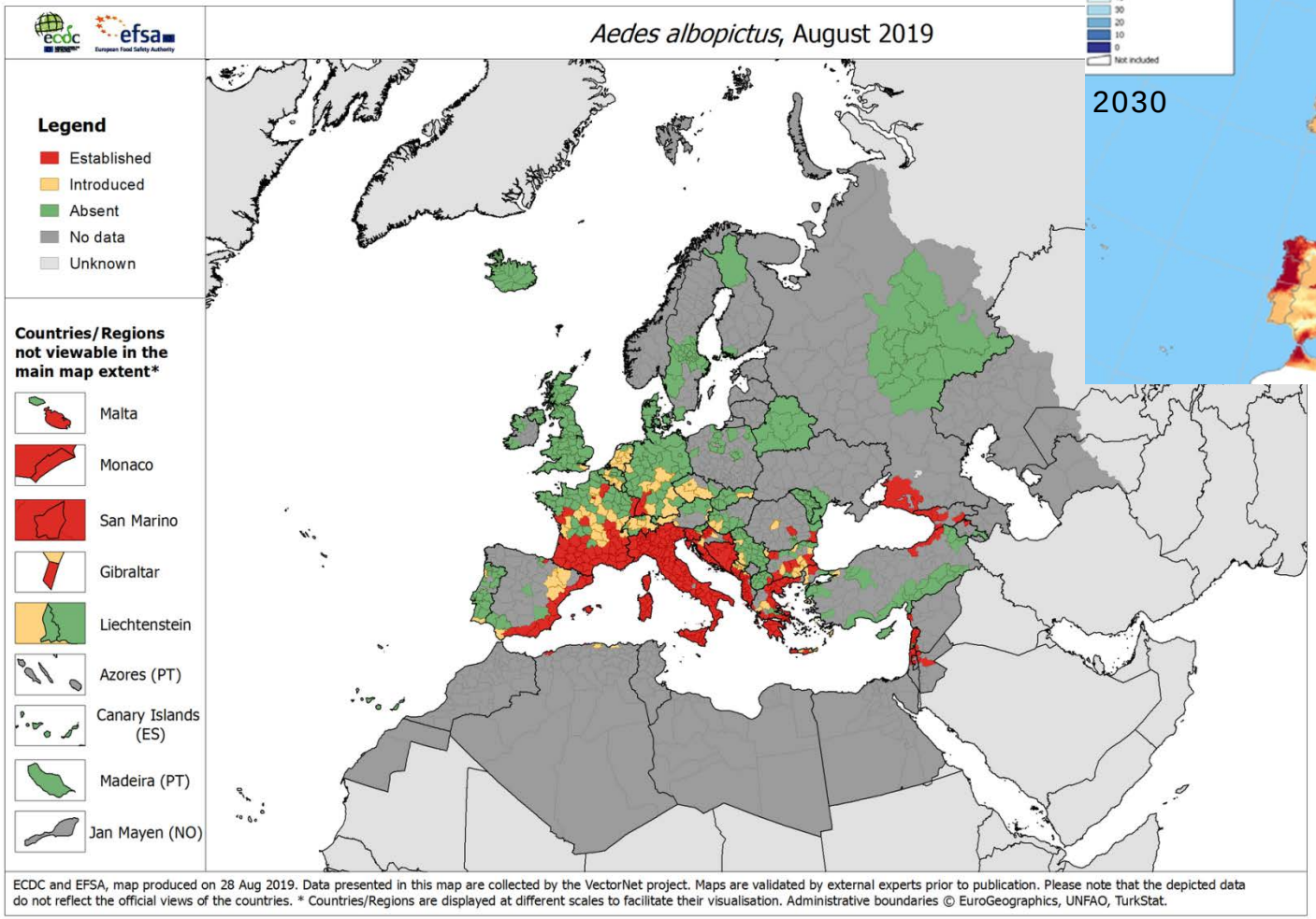


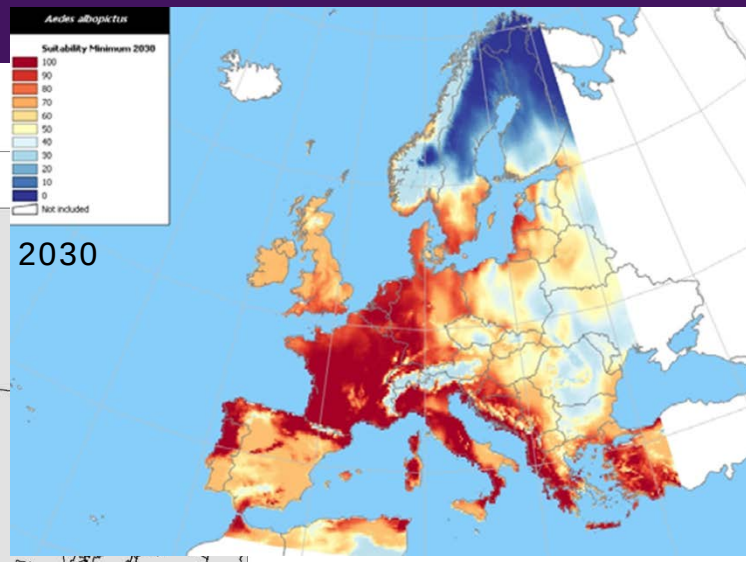


Ducheyne et al., 2013; Nickolay, 2015; Fros et al.,2015

Transient *Aedes albopictus* - driven arbovirus circulation: DENV, ZIKV, CHIKV

Current known distribution *Ae. albopictus*



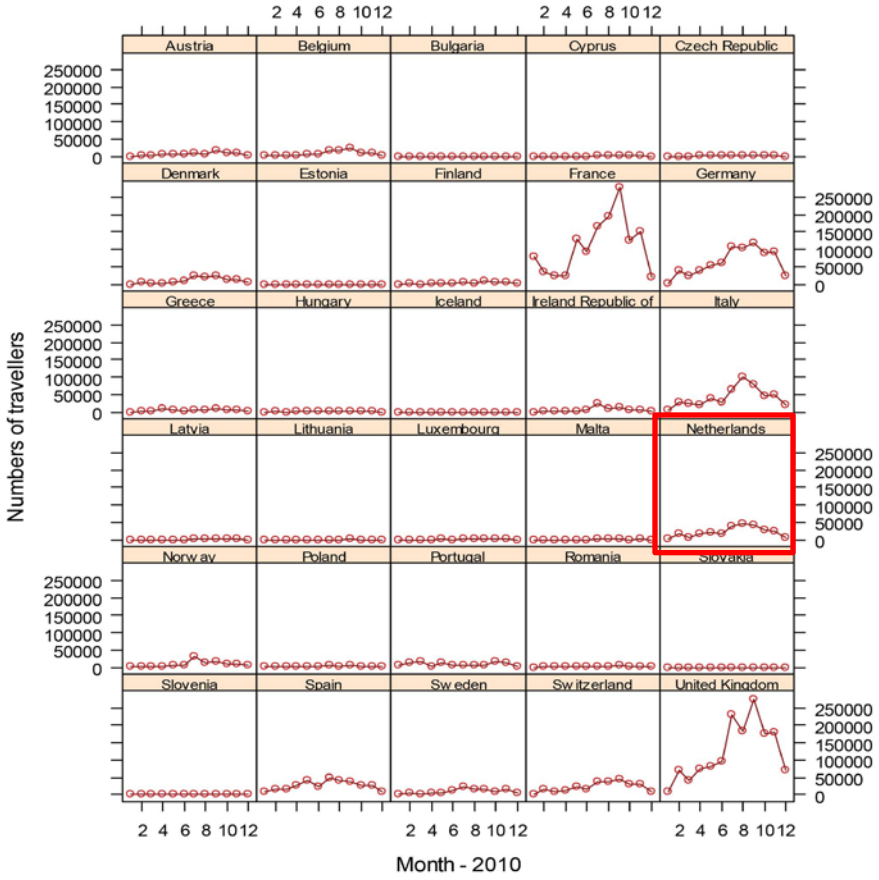


VectorNet: marieta.braks@rivm.nl
ECDC technical report, 2009

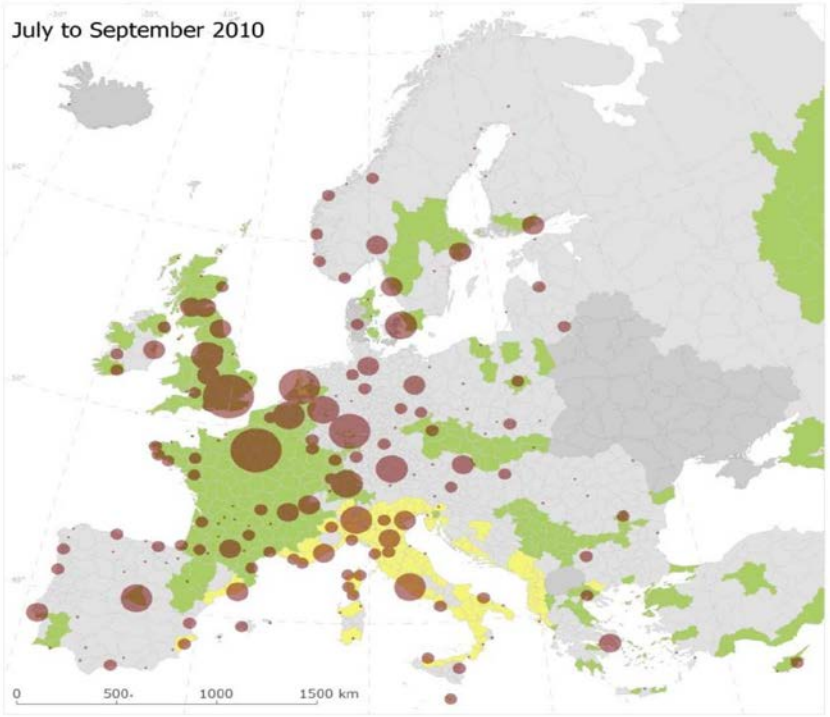
Transient *Aedes albopictus* - driven arbovirus circulation: DENV, ZIKV, CHIKV

Number of international air travellers from dengue affected areas to the EU:

by country and month, 2010

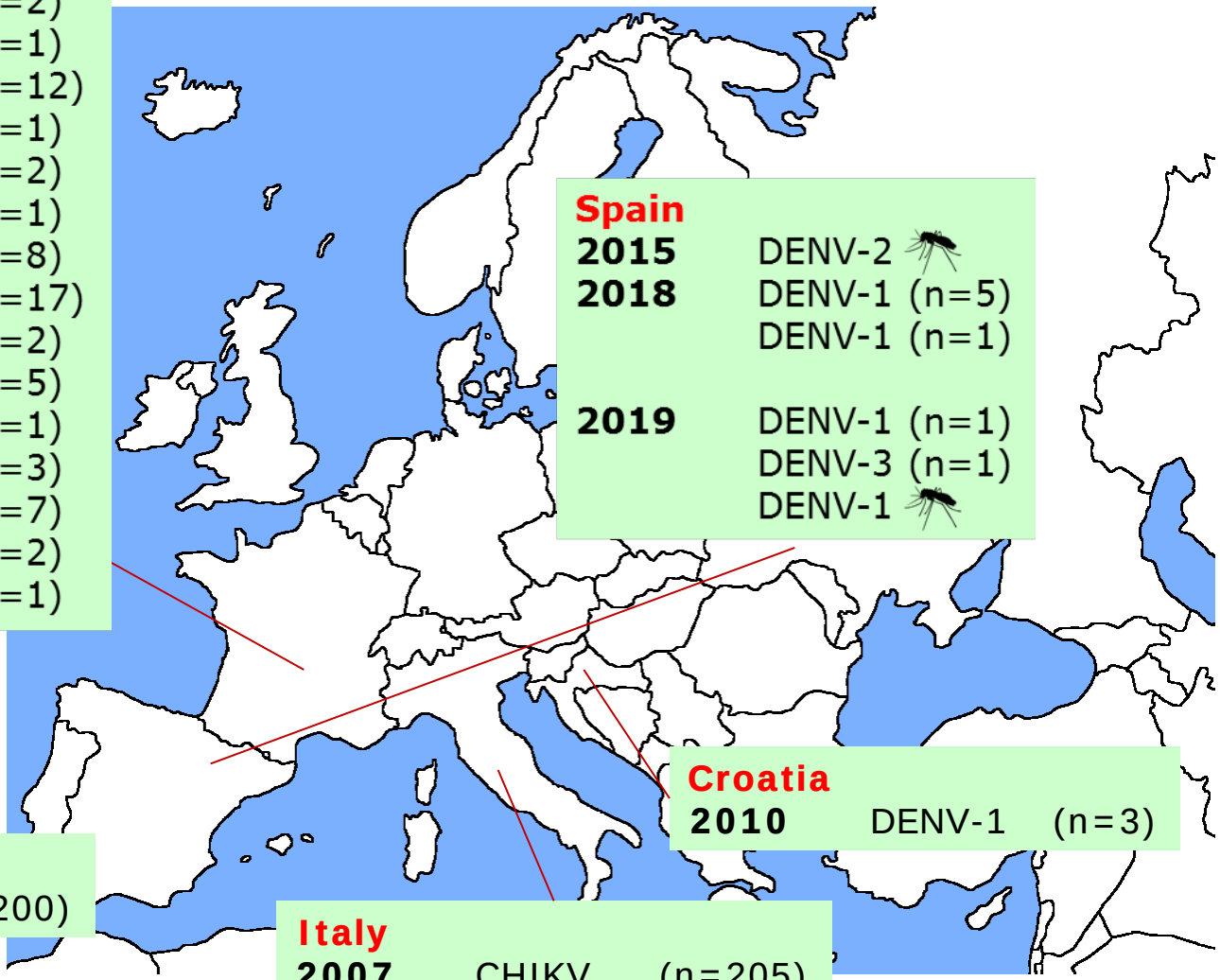


against presence *Ae. albopictus*, mosquito high-season



Semenza et al., 2014

European overview authochthonous transmission
Aedes spp. -borne exotic arboviruses



France

2010	CHIKV	(n=2)
	DENV-1	(n=2)
2013	DENV-2	(n=1)
2014	CHIKV	(n=12)
	DENV-1	(n=1)
	DENV-2	(n=2)
	DENV-2	(n=1)
2015	DENV-1	(n=8)
2017	CHIKV	(n=17)
2018	DENV-1	(n=2)
	DENV-2	(n=5)
	DENV-1	(n=1)
2019	ZIKV	(n=3)
	DENV-1	(n=7)
	DENV-?	(n=2)
	DENV-?	(n=1)

Spain

2015	DENV-2	
2018	DENV-1	(n=5)
	DENV-1	(n=1)
2019	DENV-1	(n=1)
	DENV-3	(n=1)
	DENV-1	

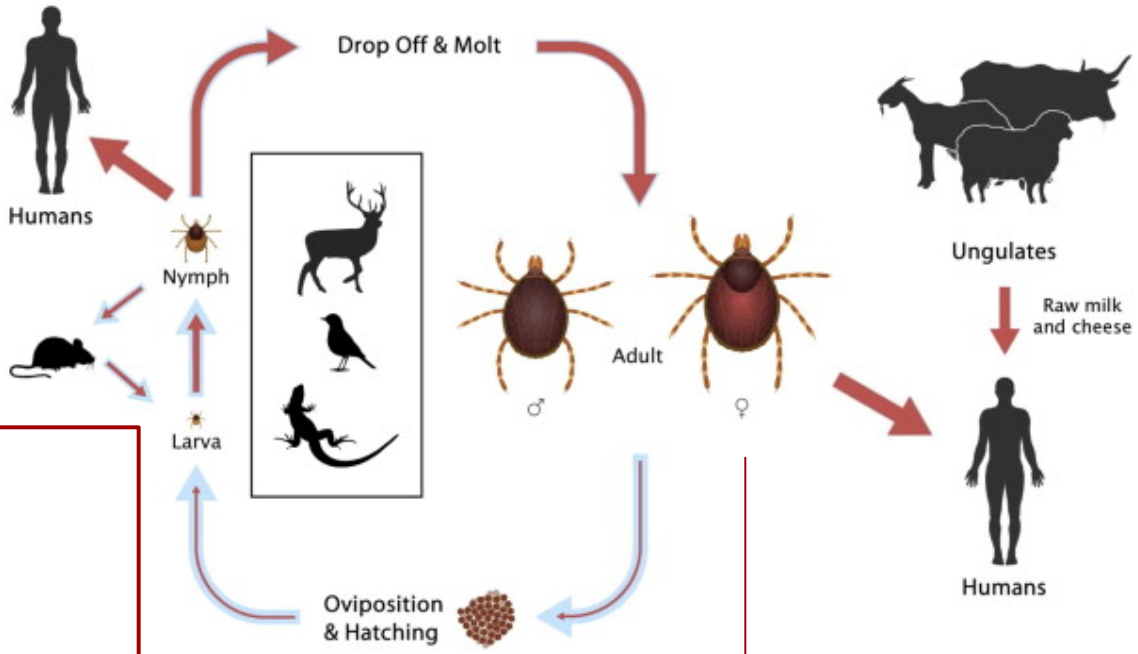
Croatia
2010 DENV-1 (n=3)

Portugal (Madeira)
2012-13 DENV-1 (n> 2200)

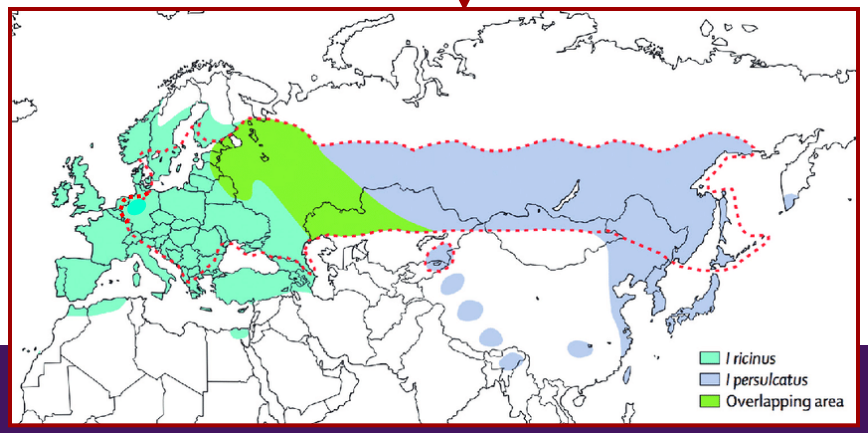
Italy

2007	CHIKV	(n=205)
2017	CHIKV	(n=282)

Tick-borne encephalitis virus



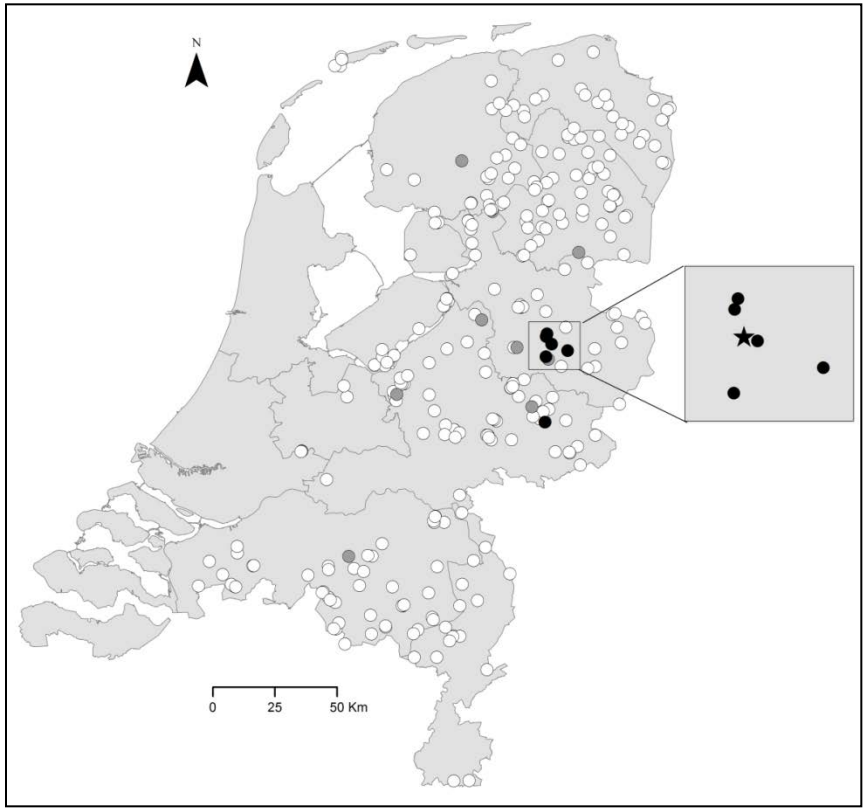
- 70-98% asymptomatic infections
- 2-30% symptomatic infections: neurological
  - ~ 75 % biphasic course
  - ~ 20% monophasic course
  - ~ 2 % abortive TBE (febrile illness with headache)
- chronic progressive TBE (Siberian TBEV, 1.7%)
- Mortality 0.5 – 2% (TBEV-EU)
- ~ 30-60 % develop post-encephalitic syndrome



Estrada-Peña & de la Fuente 2014; adapted from Jääskeläinen et al., 2011

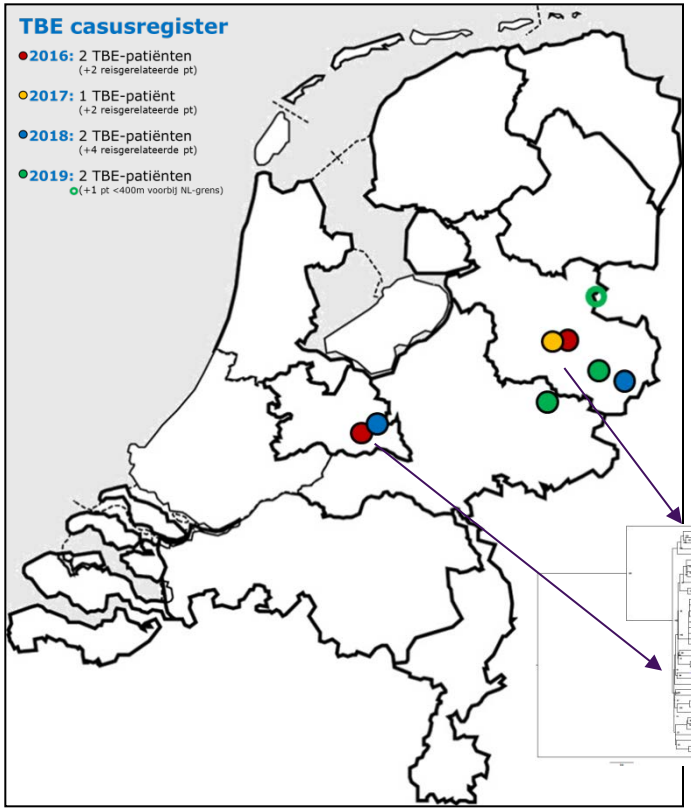
TBEV in the Netherlands

N=297 roe deer



● 6 TBEV positive deer sera (Vienna Units/ml > 125)
● 7 TBEV borderline positive deer sera (Vienna Units/ml 64-124)
○ 284 TBEV negative deer sera (Vienna Units/ml < 64)
★ Ticks tested TBEV-positive by RT-PCR

Human clinical infections, n=7



Seroprevalence 0.5% IgG in 3/563 high-risk group (95%-CI 0,1%–1,4%).

Jahfari et al.,2017
Hofhuis, October 2019

Thank you!

CHANTAL.REUSKEN@RIVM.NL