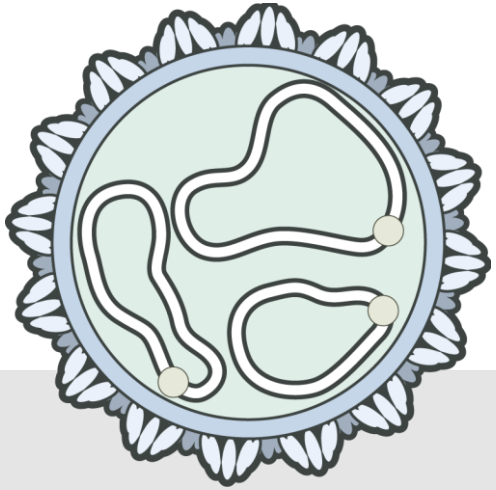
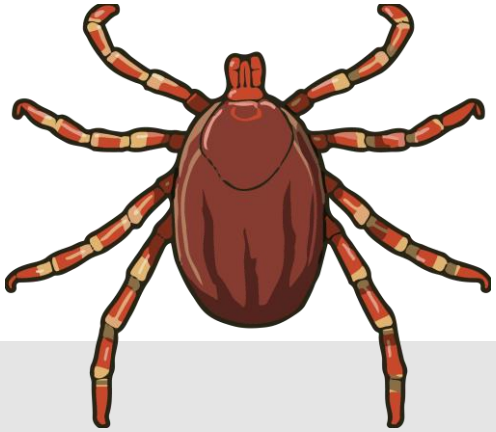


KUISCID
KOÇ UNIVERSITY - İŞBANK
CENTER FOR INFECTIOUS DISEASES



Crimean Congo Hemorrhagic Fever and Other Viral Hemorrhagic Fever

Önder Ergönül, MD, MPH
Koç University School of Medicine
Infectious Diseases & Clinical Microbiology
24 October 2025

Content

Epidemiology

Diagnosis

Pathogenesis

Transmission dynamics

Treatment

Ebola

Lassa

CCHF

Hanta

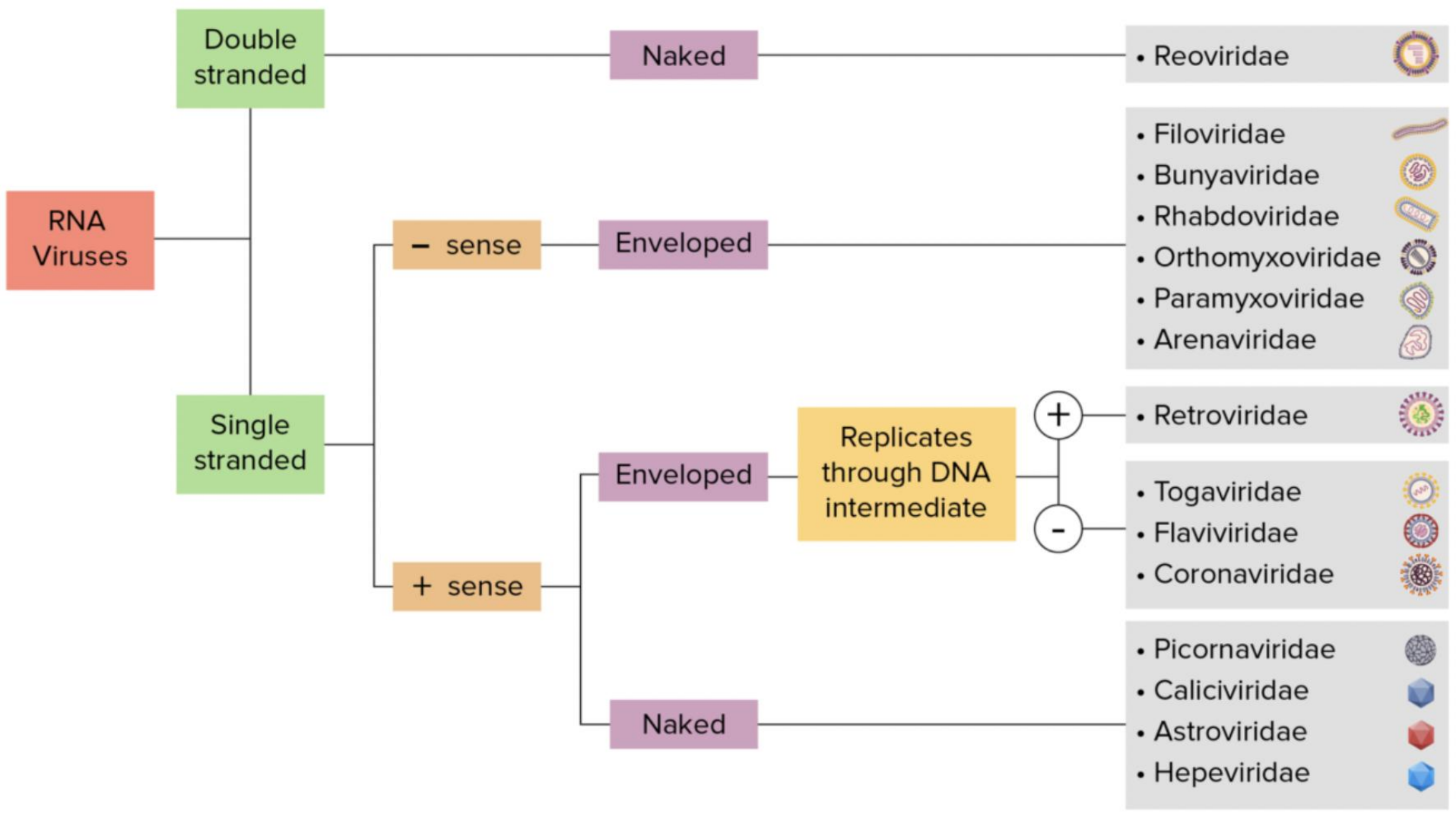
Rift Valley

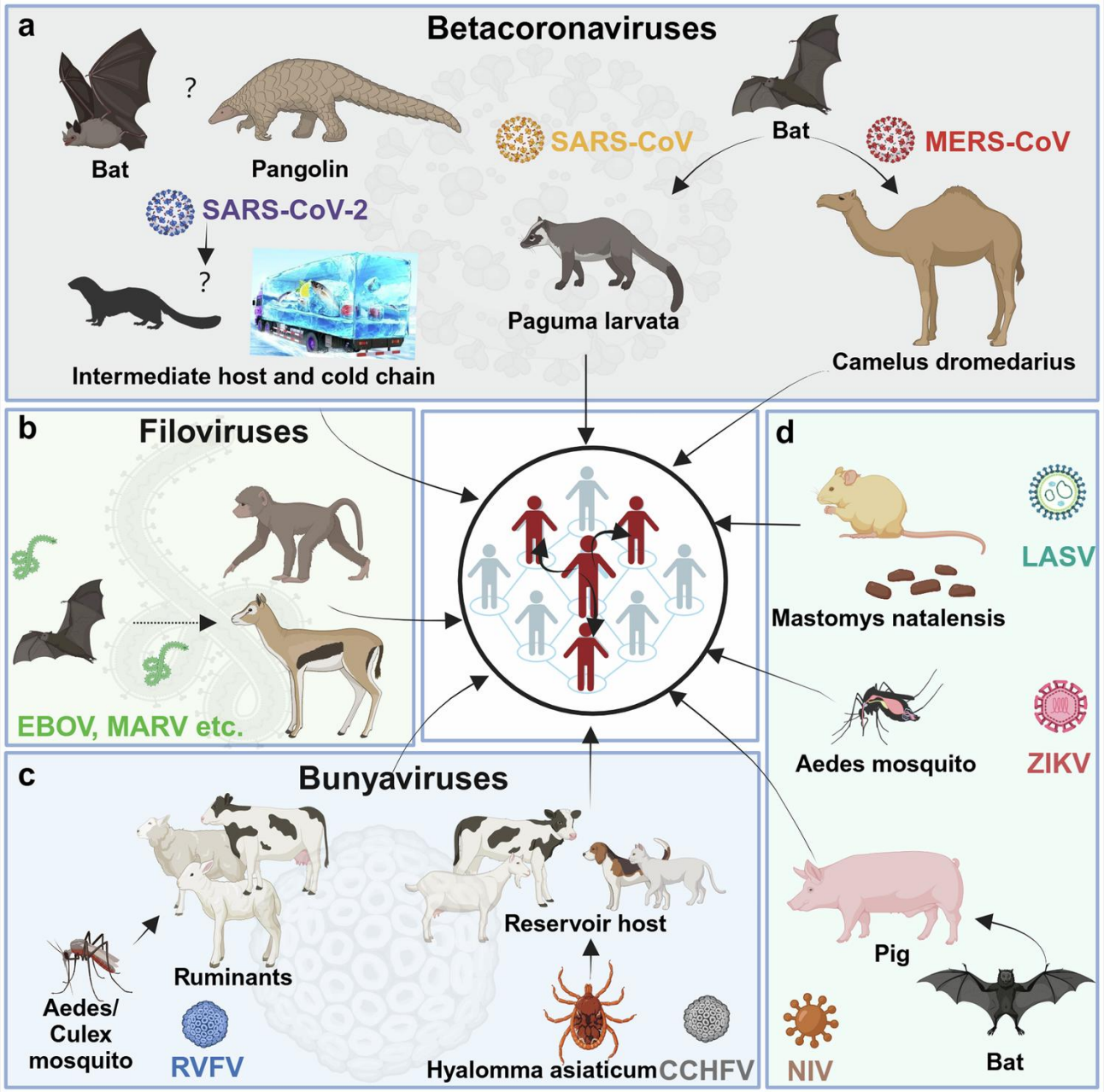
Dengue

Yellow Fever

Viruses and Liver

Hepatit viruses	Hepatitis A, B, C, D, E	
Immunosuppressed patients	Herpes, Adeno, CMV, EBV	
Respiratory and systemic infections	Measles, influenza, SARS-CoV, Parvo, entero, rubella	
“Exotic” agents (in specific geographic areas)	Arenaviridae	Lassa
	Bunyavirales	CCHF, Hanta, Rift Valley
	Filoviridae	Ebola, Marburg
	Filaviviridae	Dengue, Yellow Fever


RNA Viruses
Double stranded
Single stranded
Naked
− sense
Enveloped
+ sense
Enveloped
Replicates through DNA intermediate
+
-
Naked
• Reoviridae
• Filoviridae
• Bunyaviridae
• Rhabdoviridae
• Orthomyxoviridae
• Paramyxoviridae
• Arenaviridae
• Retroviridae
• Togaviridae
• Flaviviridae
• Coronaviridae
• Picornaviridae
• Caliciviridae
• Astroviridae
• Hepeviridae


a
Betacoronaviruses
Bat
?
Pangolin
SARS-CoV-2
?
Intermediate host and cold chain
SARS-CoV
Bat
MERS-CoV
Paguma larvata
Camelus dromedarius
b
Filoviruses
EBOV, MARV etc.
d
LASV
Mastomys natalensis
Aedes mosquito
ZIKV
Pig
Bat
NIV
c
Bunyaviruses
Reservoir host
Ruminants
Aedes/
Culex
mosquito
RVFV
Hyalomma asiaticum
CCHFV

Transmission of the VHFs

	Vectors and Transmission
Ebola	Bats, Direct contact or via bodily fluids (nosocomial, sexual)
Crimean Congo	Ticks, Hyalomma spp. via bodily fluids (nosocomial, sexual)
Dengue	*Aedes aegypti*, *Aedes albopictus*
Hanta	Virus containing aerols in rodent excreta
Lassa	Virus containing aerols in rodent excreta
Rift valley	Aedes and Culex
Yellow fever	*Aedes africanus, Sabethes* spp, *Aedes aegypti*

Bunyavirales

Crimean Congo Hemorrhagic Fever

Severe Thrombocytopenic Fever Syndrome:

- First in Chinia in 2011 (N Eng J Med 2011)
- 2010-2018: 7725 cases, CFR: 10% (Clin Infect Dis 2021)

Rift Valley Fever

Hantavirus infection

Sin Nombre virus

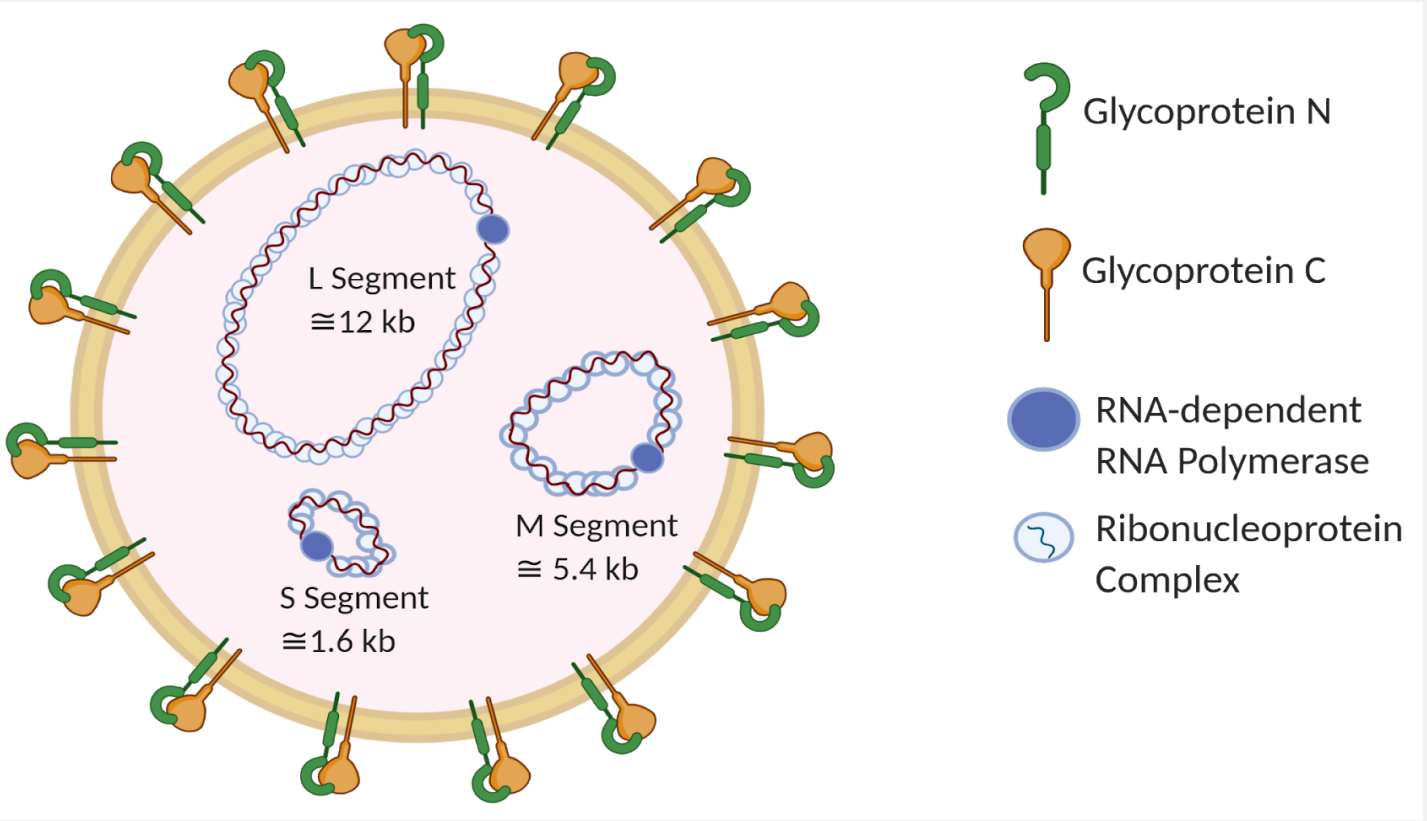
Sandly Fever

WHO 2018 Blueprint list of priority diseases (February 6-7, 2018) Updated in 2024

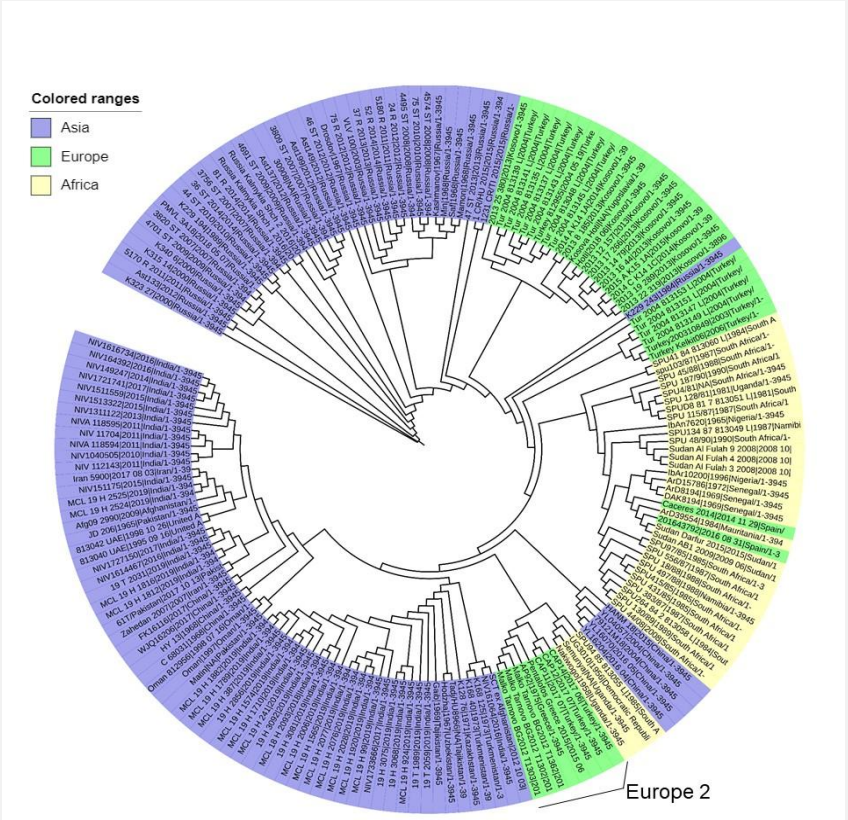
Given their potential to cause a public health emergency and the absence of efficacious medical countermeasures, there is an urgent need for accelerated research and development for:

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

CCHF Virus



L, M and S segments



Phylogenetic tree based on L segment:
11 different types

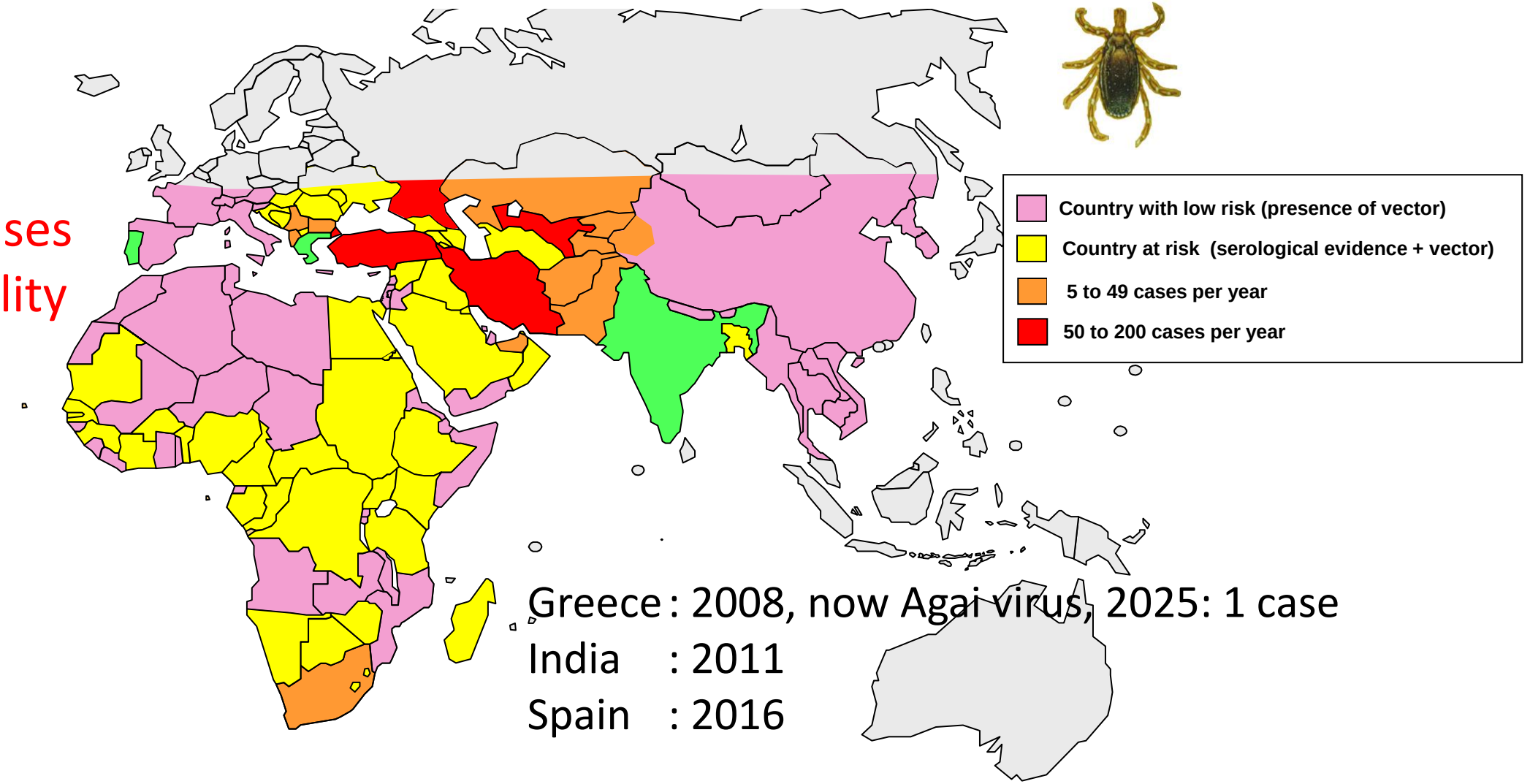
Büyükdağ C, et al. (unpublished)

Crimean-Congo Haemorrhagic Fever Geographic Distribution

50° North limit for *Hyalomma* ticks

>30 000 cases

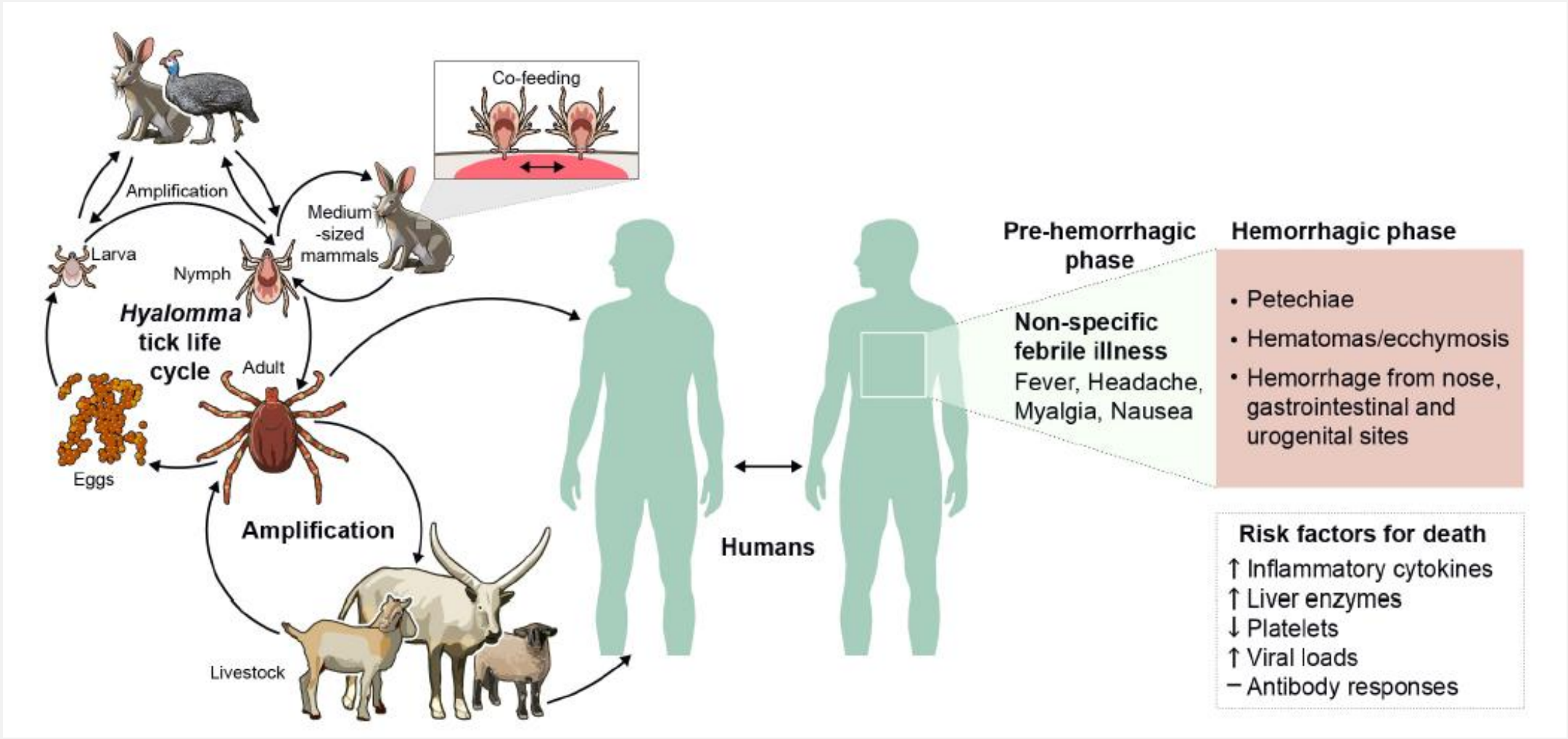
5-40% fatality



Greece : 2008, now Agai virus, 2025: 1 case

India : 2011

Spain : 2016



Feldman, 2018

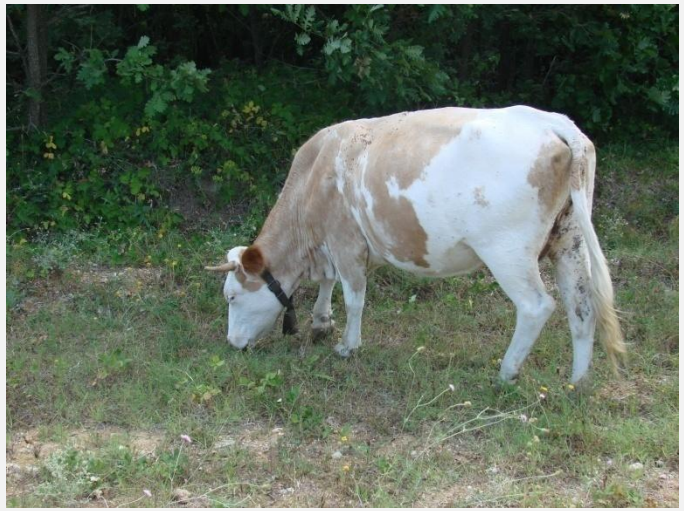
The Course of Infection in animals

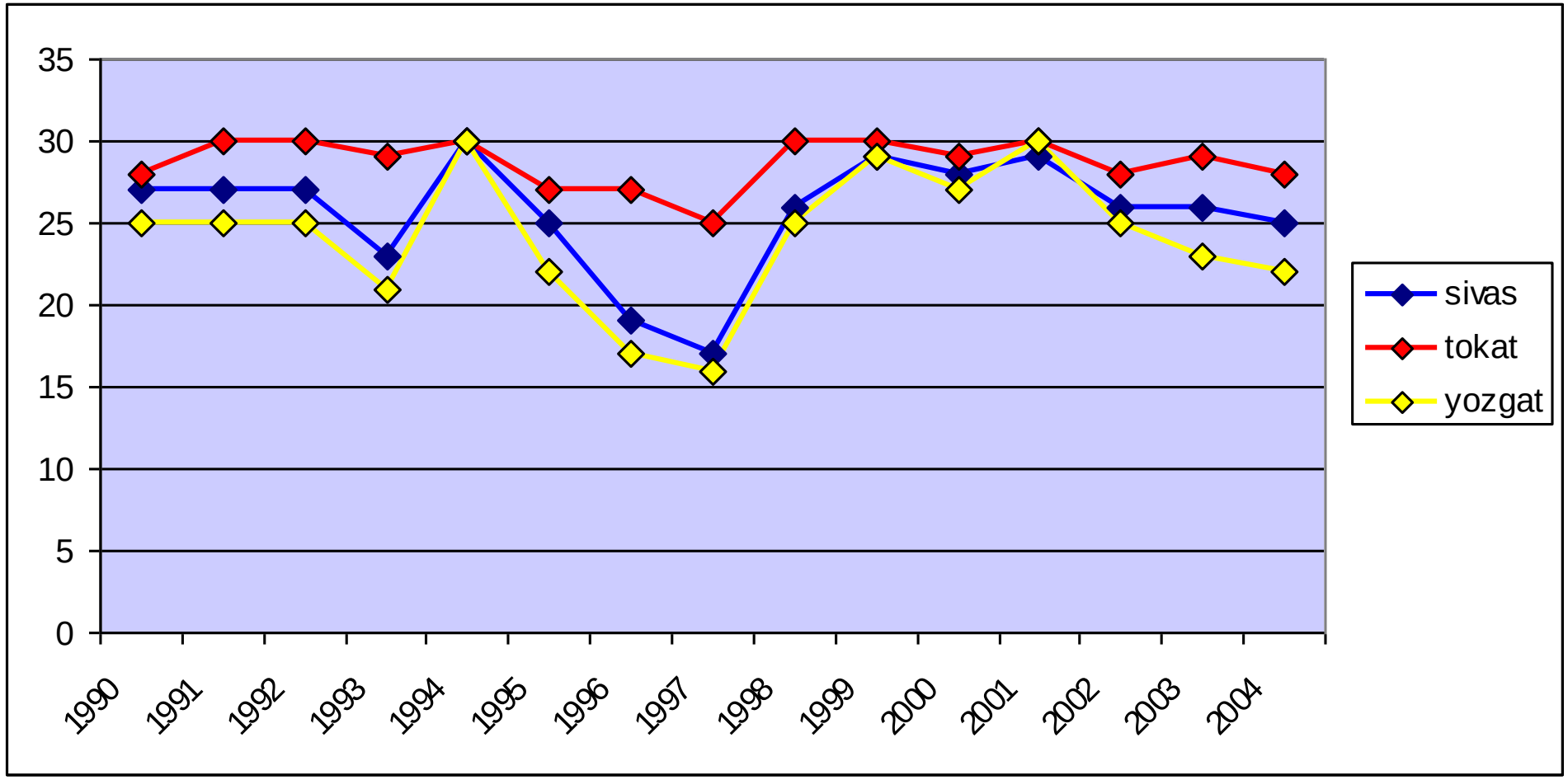
Mild clinical symptoms

- Described by Shepherd et al in 1980s.
- No striking notes in recent outbreaks, since 2000

Viremia

- Lasts for 7-10 days in mammals

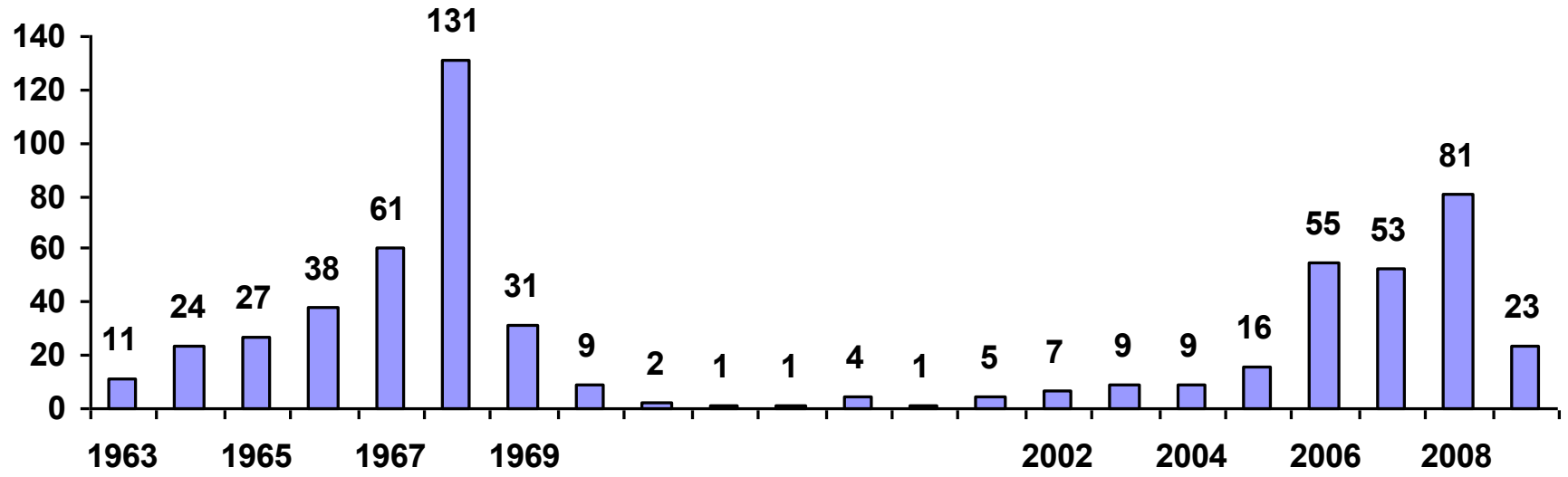




In April (1990-2004), number of days >5 ºC

Ergonul O, et al. *ECCMID 2005*, P 1147

CCHF cases in the Rostov region for 1963-2008



Cold winters in late 1960s; Hoogstral, 1979


Albania, 2006

Changes in Biotic Environment

De-population

İncrease in vectors and reservoirs

ПРАВДА

№ 10* (30)
Февраль
1942 г.

Новый порядок землепользования

Дар Адольфа Гитлера русскому народу

Крестьяне!

Германское правительство, освободившее вас от большевизма, решило дать крестьянам землю в единоличное пользование. В соответствии с этим объявляется новый порядок землепользования. Его цель:

Трудолюбивому крестьянину — своя земля

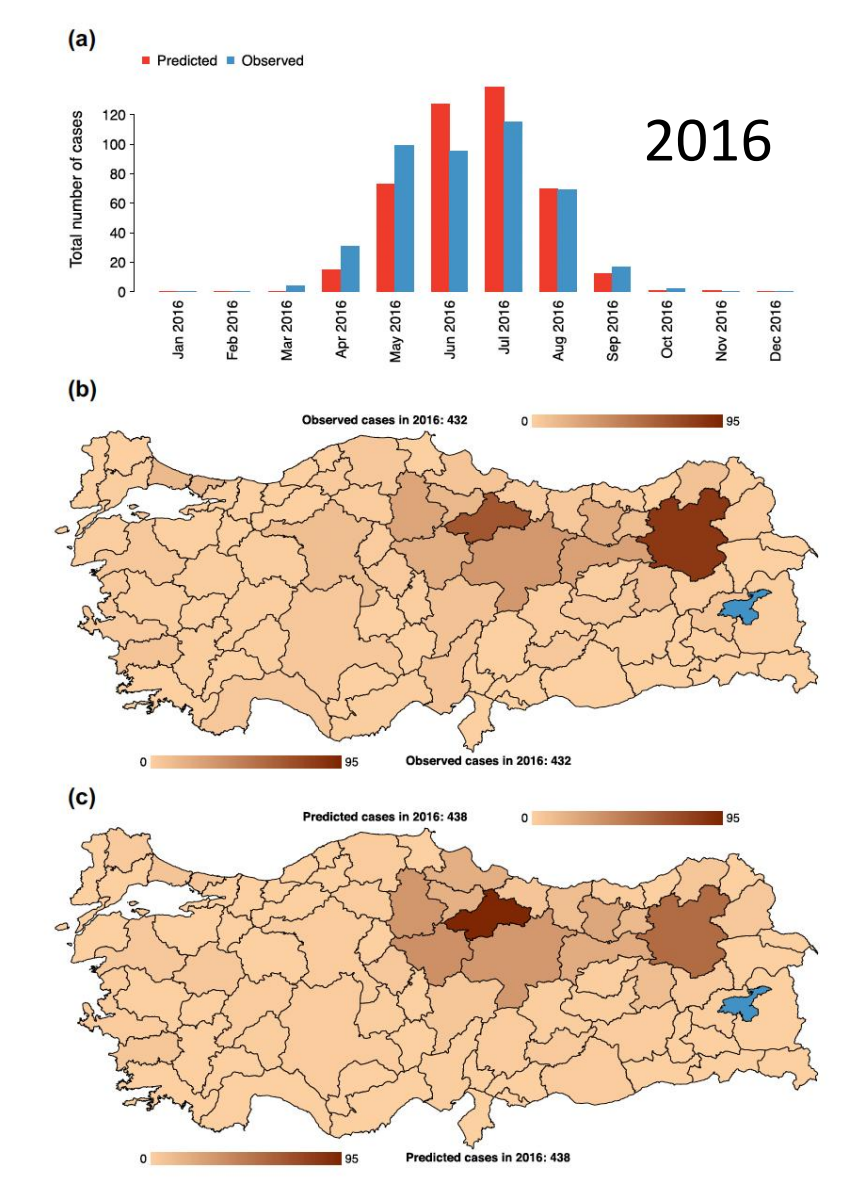
Свободные люди —

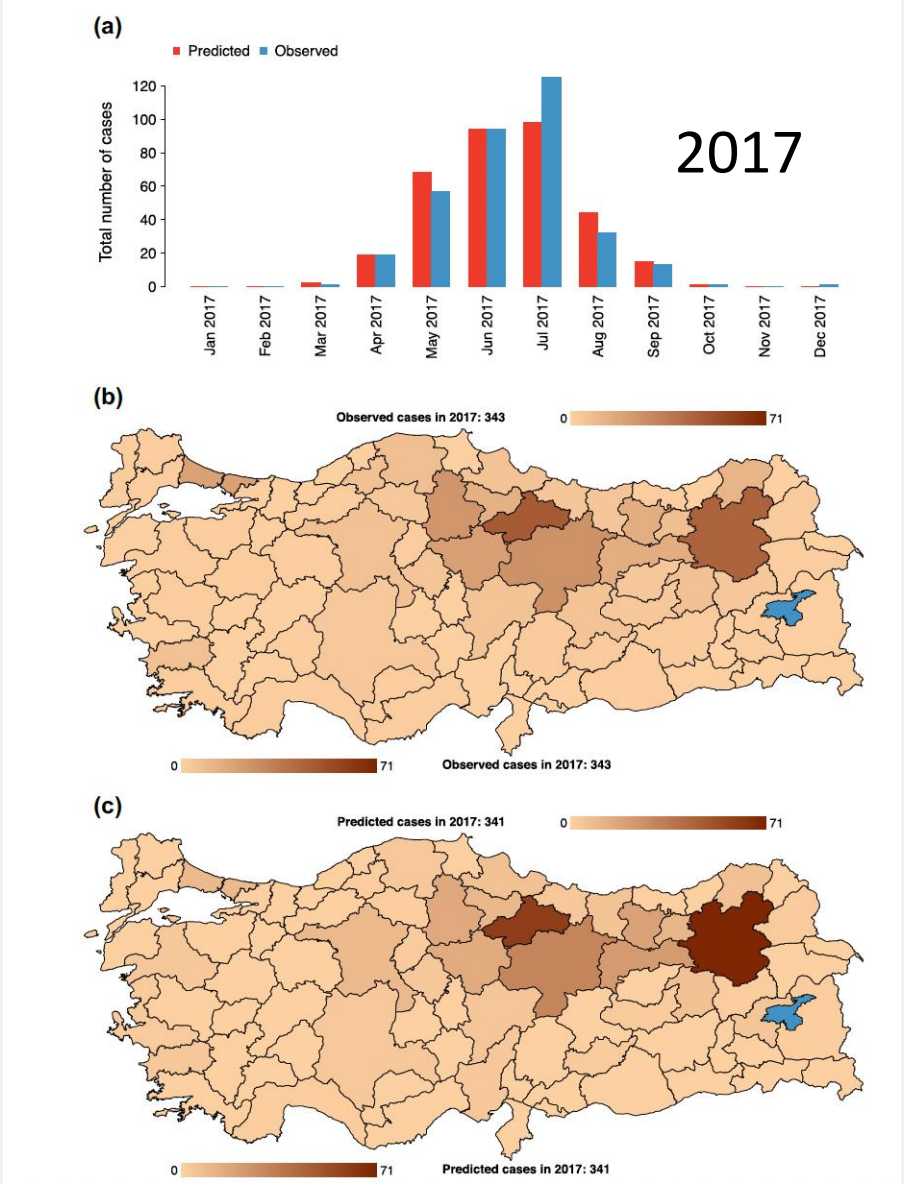
на свободной земле!

Re-population

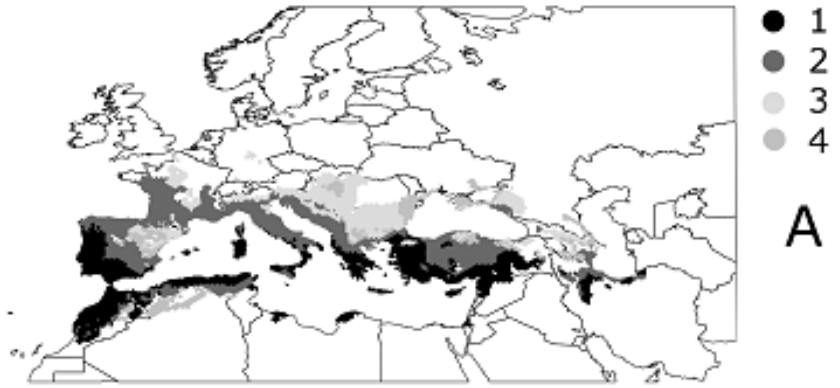
Sudden Exposure

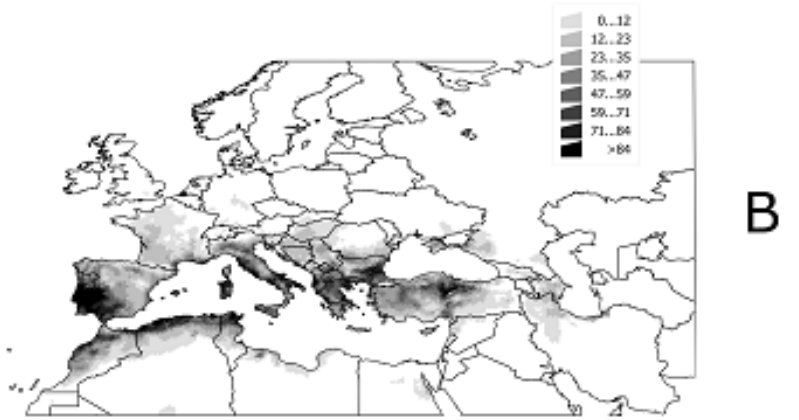
Prospective Prediction Tool for Turkey

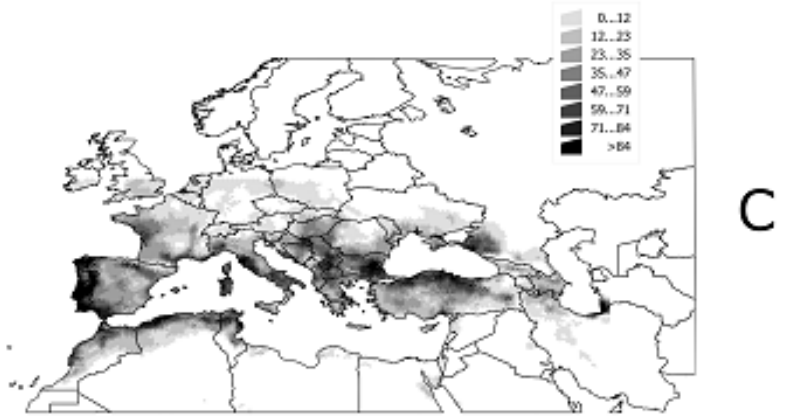




Ak, Ergönül, Gönen. *Clin Microbiol Infect* 2020







Known records of *Hyalomma marginatum*

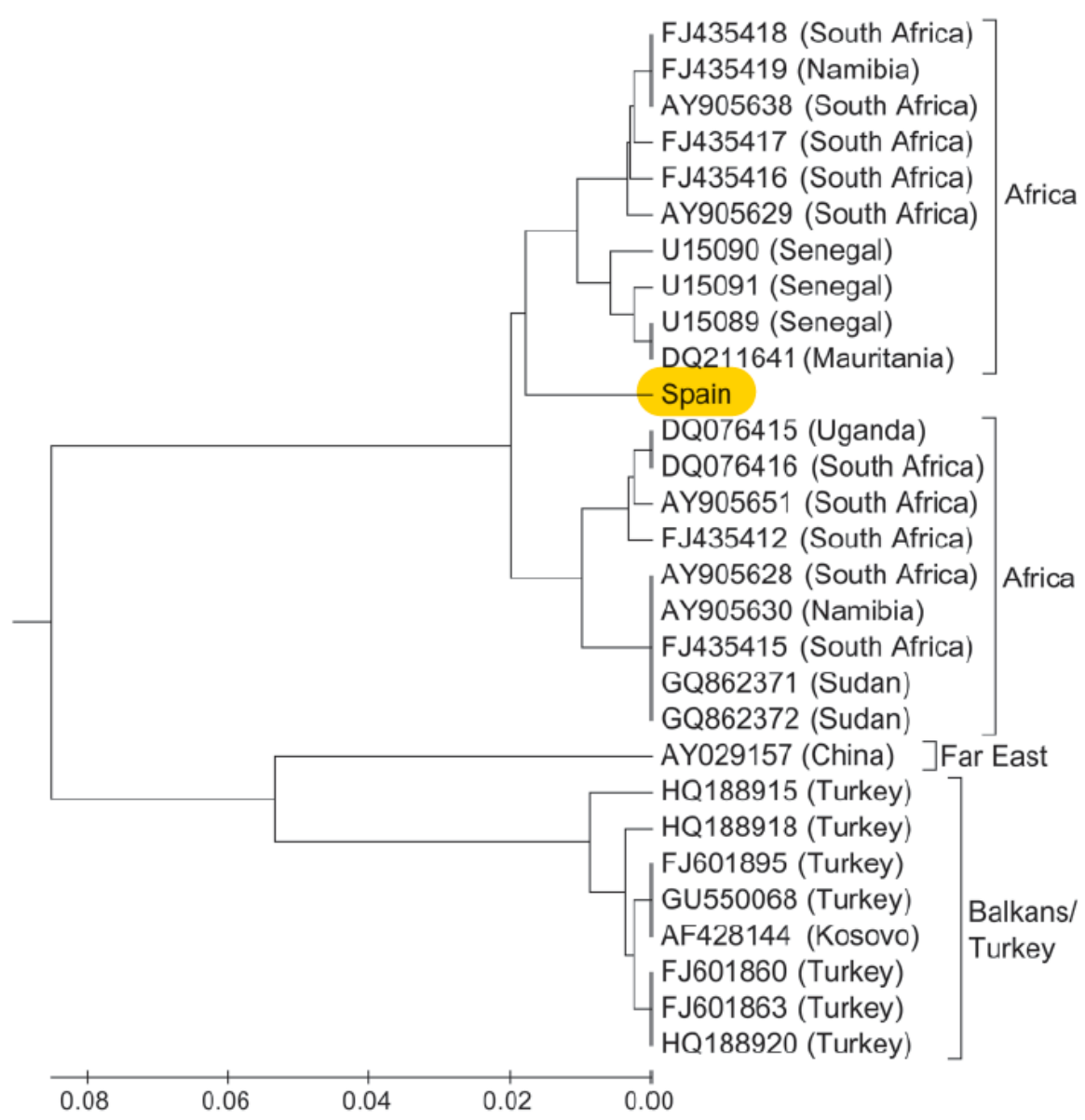
The predicted climate suitability for the tick *H. marginatum* in the area of analysis with current (1970-2000) climate conditions

The predicted climate suitability as projected for the year 2050

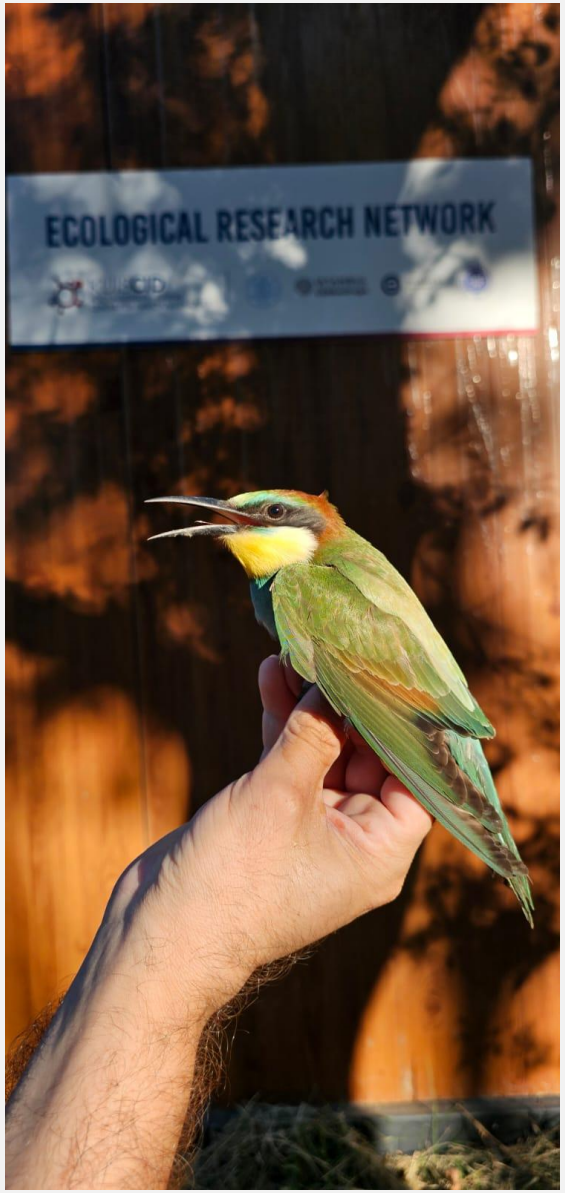
Estrada-Pena 2009

Crimean-Congo Hemorrhagic Fever Virus in Ticks, Southwestern Europe, 2010

This finding suggests the circulation of CCHFV in southwestern Europe. The close affinity of the strain from Spain with strains circulating in western Africa and the lack of similarity with isolates from eastern Europe suggest the introduction of this virus from nearby countries of northern Africa. Migratory movements of birds could explain the presence of the virus in southwestern Europe because birds are common hosts of immature *H. marginatum*, which was reportedly introduced into Europe through annual migratory flights along the western coast of Africa (*10*). Because

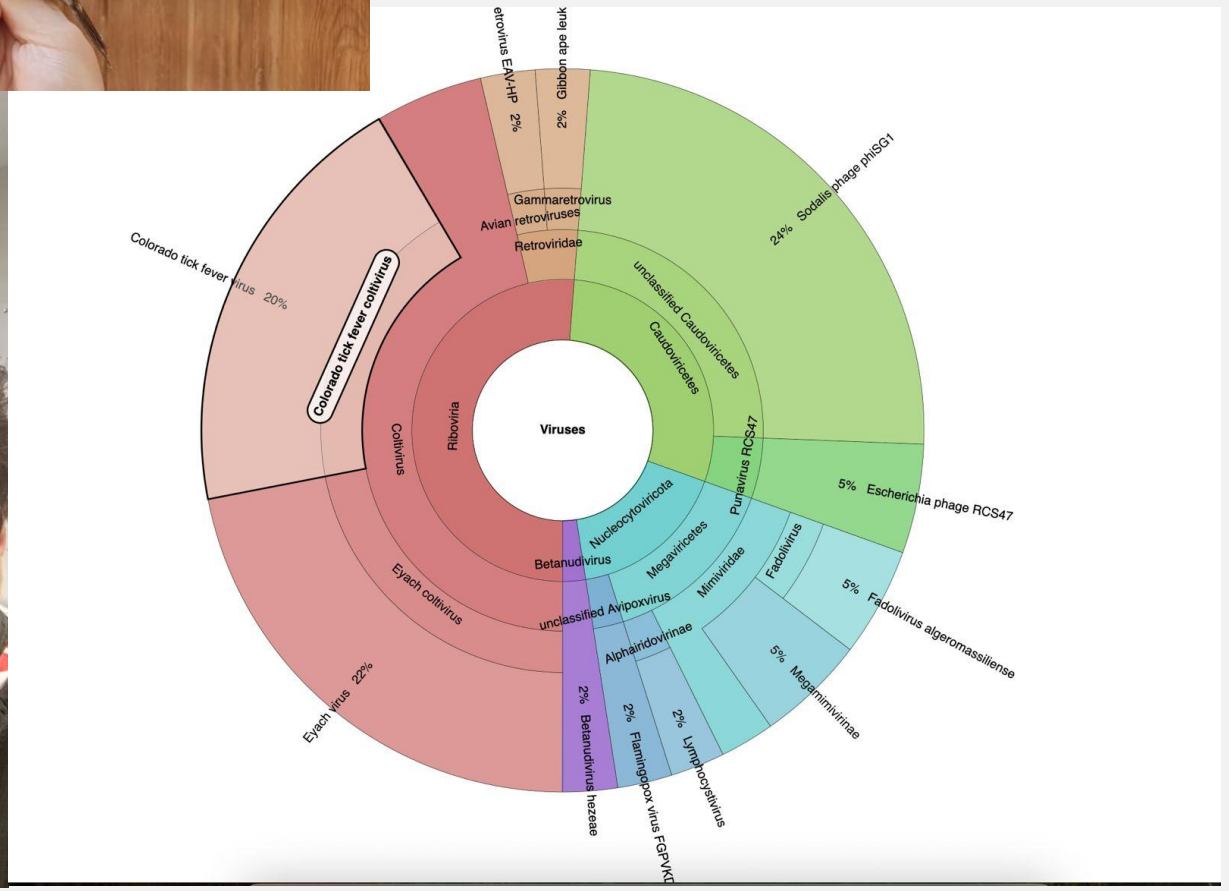


Estrada-Pena, *Emerg Infect Dis* 2010

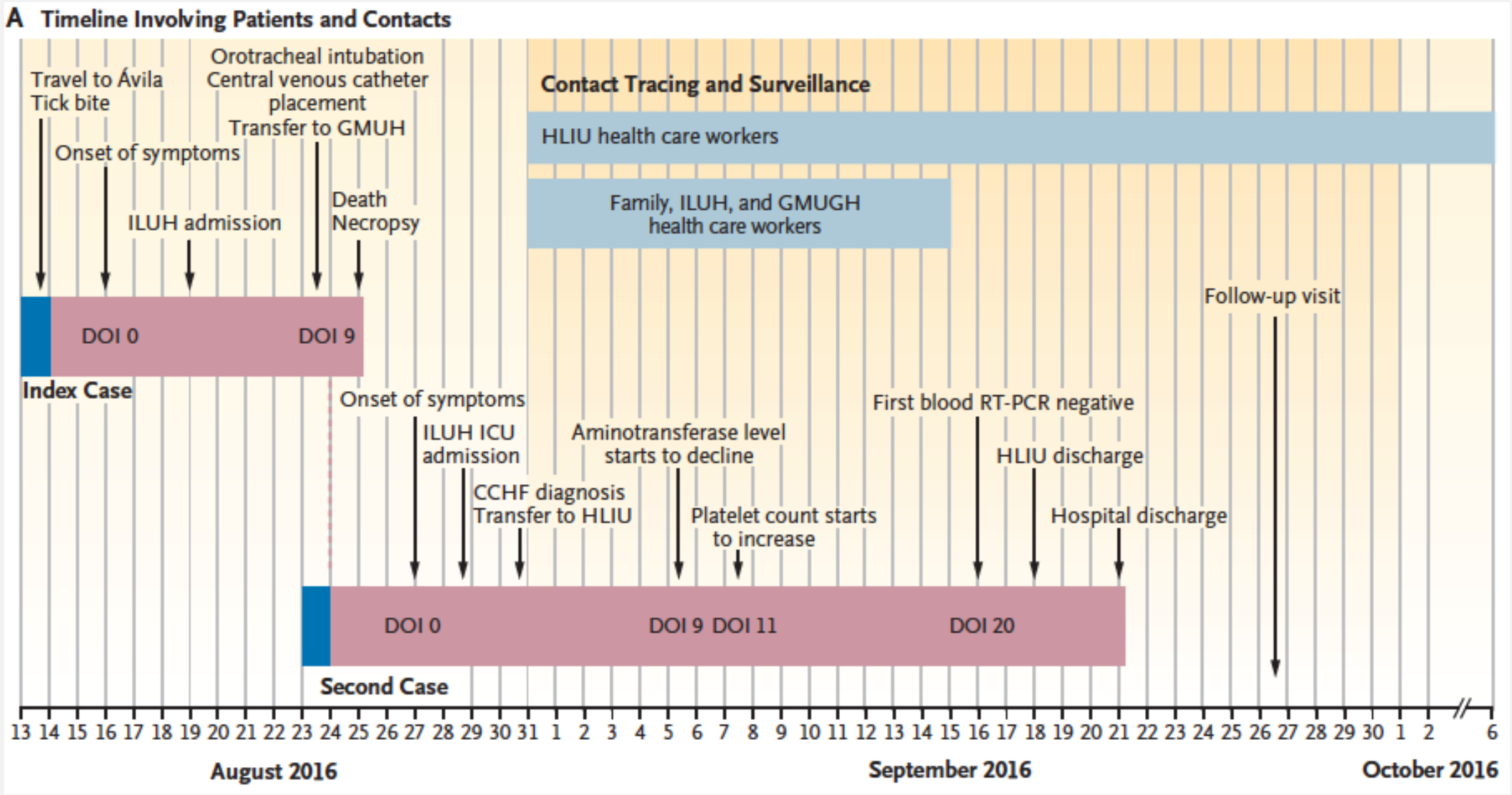

ECOLOGICAL RESEARCH NETWORK


Ficedula parva 1y
ringed: 13 sept
recaptured: 24 sept


ECOLOGICAL RESEARCH NETWORK
KUISCID
KOÇ UNIVERSITY - İŞBANK
CENTER FOR INFECTIOUS DISEASES
İSTANBUL
CERRAHPAŞA
MARMARA

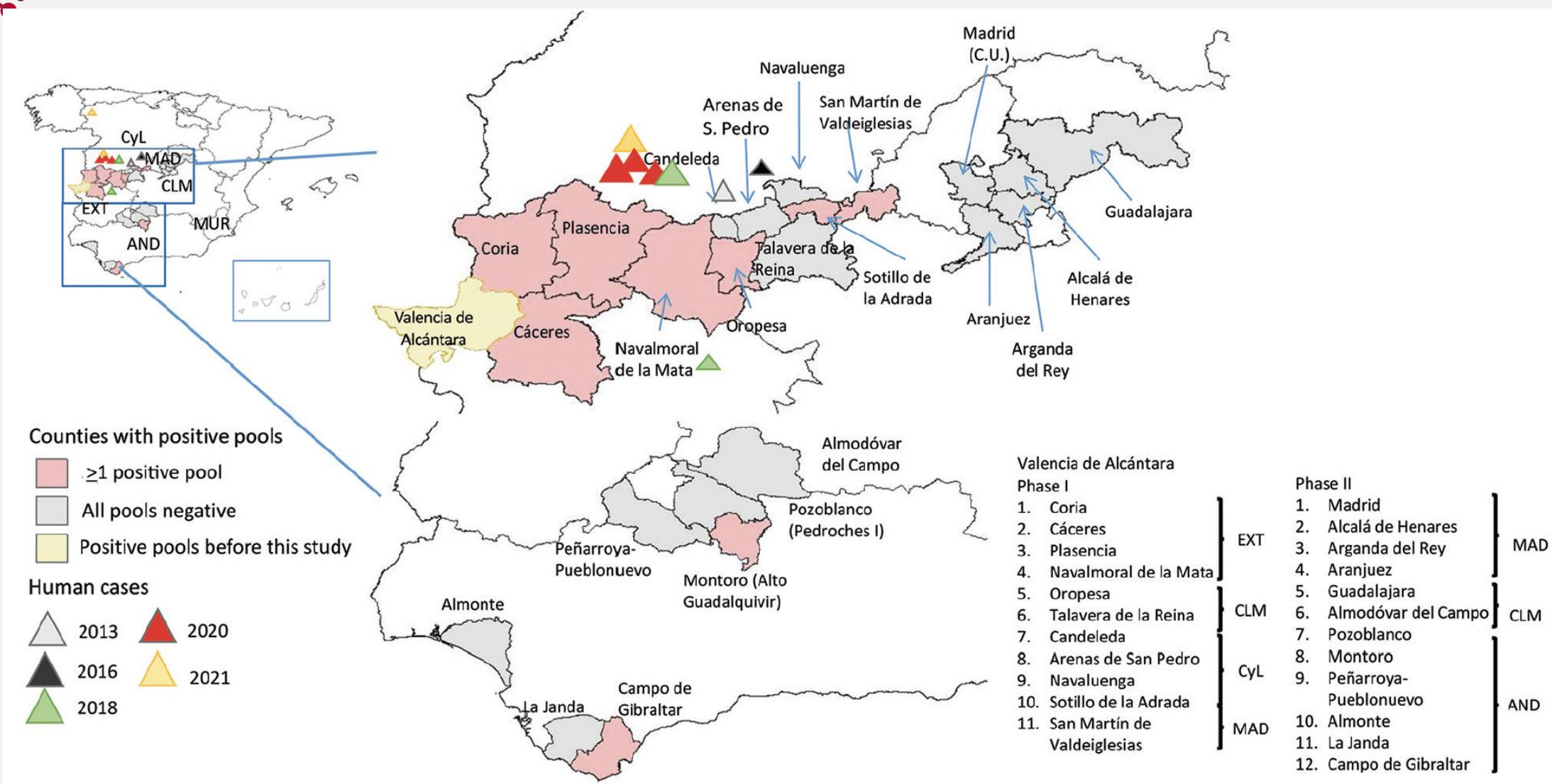

Viruses
Riboviria
Orthornavirae
Duplopiviricetes
Colorado tick fever coltivirus
Colorado tick fever virus 20%
Coltivirus
Eyach coltivirus
Eyach virus 22%
Retroviridae
Gammaretrovirus
Avian retrovirus EAV-HP 2%
Gibbon ape leuk
Caudoviricetes
unclassified Caudoviricetes
24% Sodalis phage phiSG1
Punavirus RCS47
5% Escherichia phage RCS47
Nucleocytoviricota
Megaviricetes
Betanudivirus
unclassified Avipoxvirus
Mimiviridae
Fadolivirus
5% Fadolivirus algeromassiliense
Alphairidovirinae
5% Megamimivirinae
2% Betanudivirus hezeae
2% Flamingopox virus FGPV
2% Lymphocystivirus

Autochthonous Crimean-Congo Hemorrhagic Fever in Spain



Negredo A, NEJM 2017

Widespread Detection of Multiple Strains of CCHF Virus in Ticks, Spain



Sánchez-Seco M, Sierra M, Estrada-Peña A, Valcárcel F, Molina R, de Arellano E, et al. Emerg Infect Dis. 2022

Widespread Detection of Multiple Strains of CCHF Virus in Ticks, Spain

Ticks were collected from animals and vegetation, samples pooled (12,584 ticks; 4,556 pools)

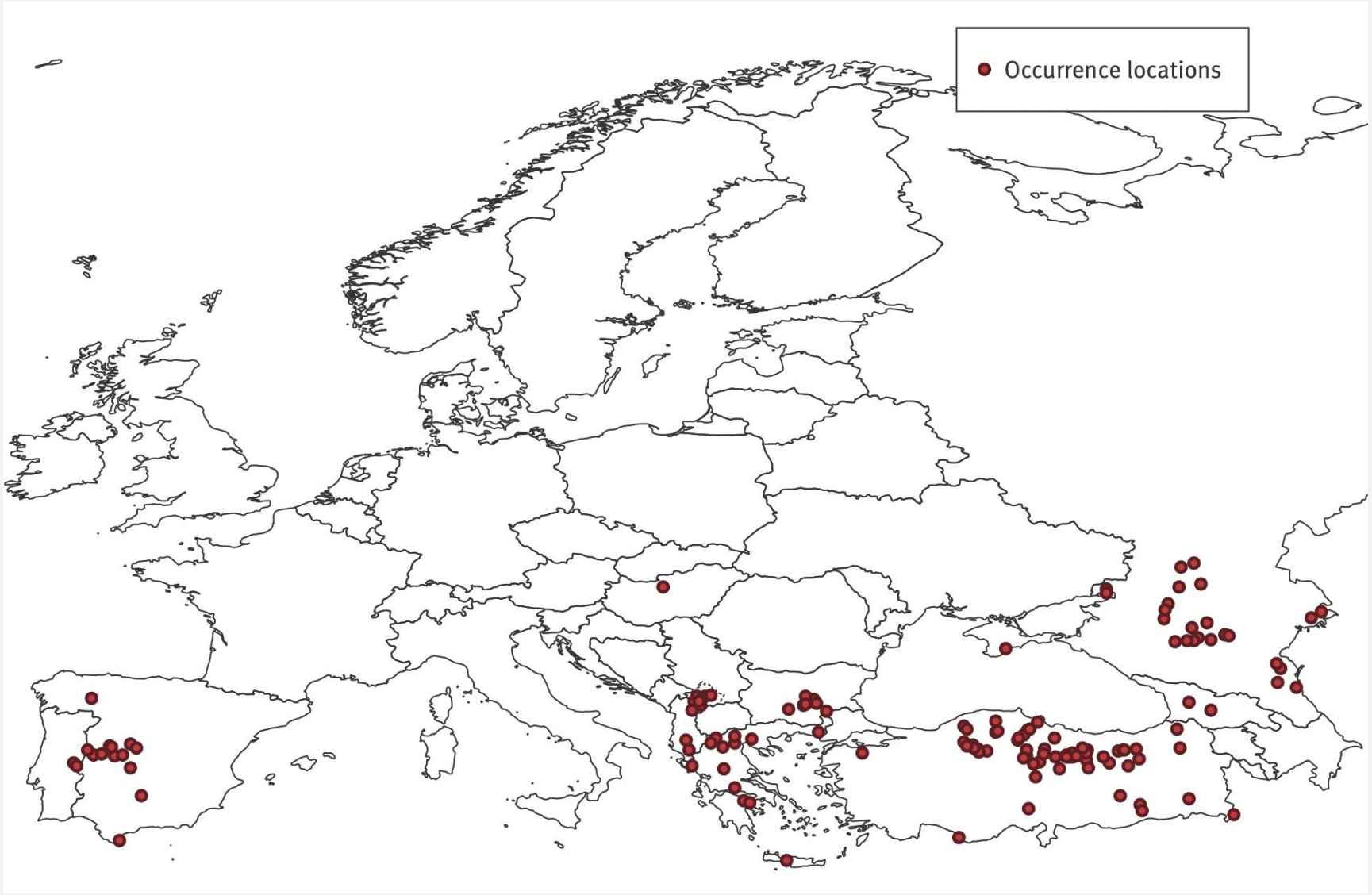
135 pools from most of the regions studied, indicating that it is widespread in Spain.

CCHF virus genotypes I, III, and IV in the tick species collected, most commonly in Hyalomma lusitanicum, suggesting this tick has a prominent role in the virus's natural cycle.

The red deer (Cervus elaphus) was the host that most frequently yielded positive ticks.

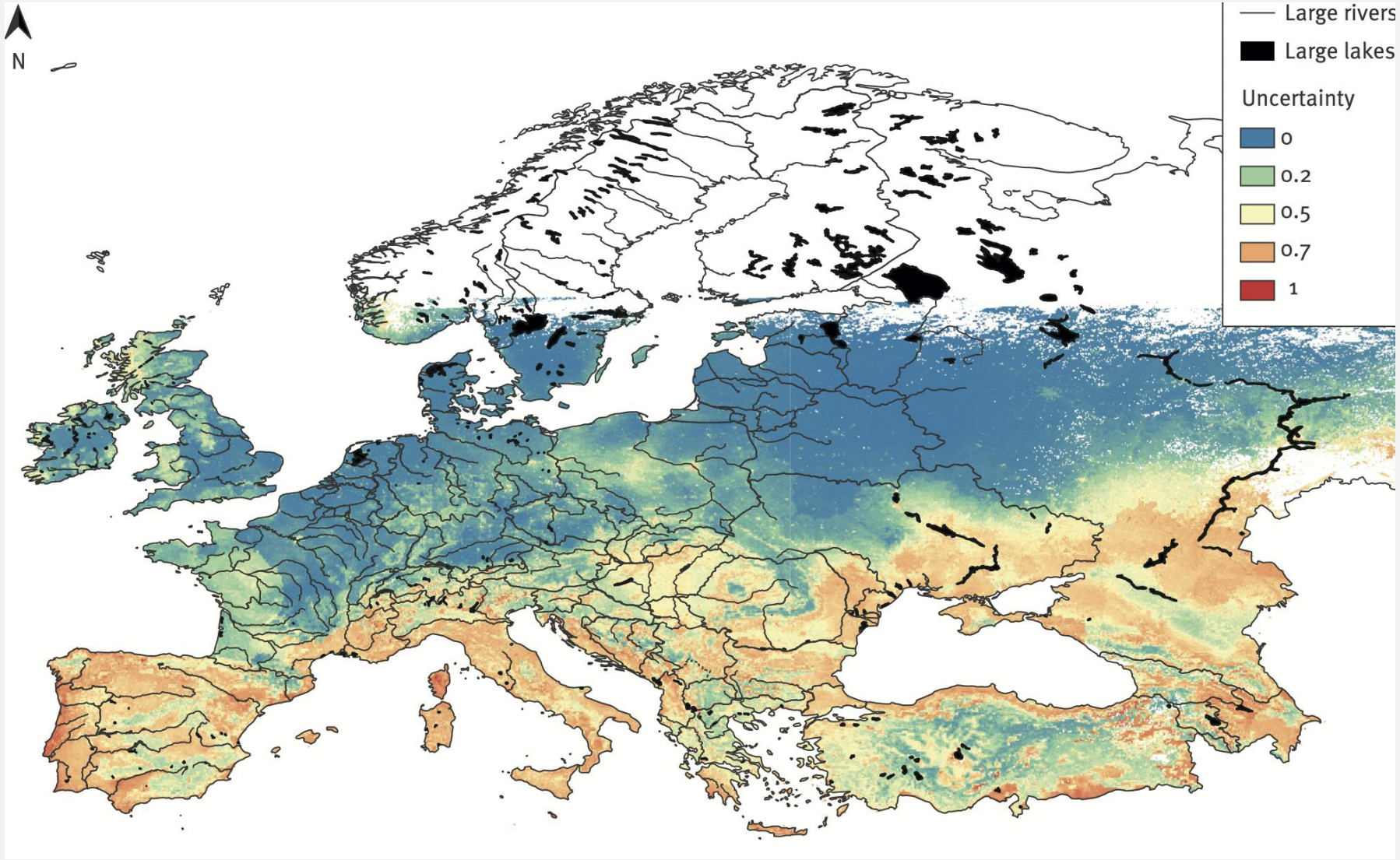
Sánchez-Seco M, Sierra M, Estrada-Peña A, Valcárcel F, Molina R, de Arellano E, et al. Emerg Infect Dis. 2022

Epidemic intelligence from Open Sources (EIOS) of CCHF in European Region, 2012 to 2022: a new opportunity for risk mapping of neglected diseases



Fanelli A, Schnitzler JC, De Nardi M, Donachie A, Capua I, Lanave G, Buonavoglia D, Caceres-Soto P, Tizzani P. Euro Surveill. 2023

Epidemic intelligence from Open Sources (EIOS) of CCHF in European Region, 2012 to 2022: a new opportunity for risk mapping of neglected diseases



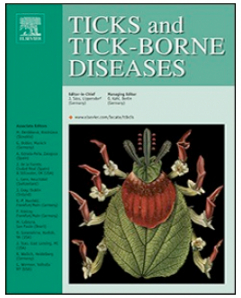
Fanelli A, Schnitzler JC, De Nardi M, Donachie A, Capua I, Lanave G, Buonavoglia D, Caceres-Soto P, Tizzani P. Euro Surveill. 2023

Ticks and Tick-borne Diseases 12 (2021) 101541

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis



First report of human exposure to *Hyalomma marginatum* in England: Further evidence of a *Hyalomma* moulting event in north-western Europe?

L. McGinley[a,*], K.M. Hansford[a,b], B. Cull[a], E.L. Gillingham[a,b], D.P. Carter[c], J.F. Chamberlain[d], L.M. Hernandez-Triana[e], L.P. Phipps[e], J.M. Medlock[a,b]

[a] *Medical Entomology and Zoonoses Ecology, Emergency Response Department, Public Health England, Porton Down, Salisbury, SP4 0JG, UK*
[b] *NIHR Health Protection Research Unit in Environmental Change and Health, UK*
[c] *Genomics of Rare and Emerging Human Pathogens, National Infection Service, Public Health England, Porton Down, Salisbury, SP4 0JG, UK*
[d] *Virology and Pathogenesis, National Infection Service, Public Health England, Porton Down, Salisbury, SP4 0JG, UK*
[e] *Wildlife Zoonoses and Vector-Borne Research Group, Department of Virology, Animal and Plant Health Agency, Addlestone, Surrey, KT15 3NB, UK*

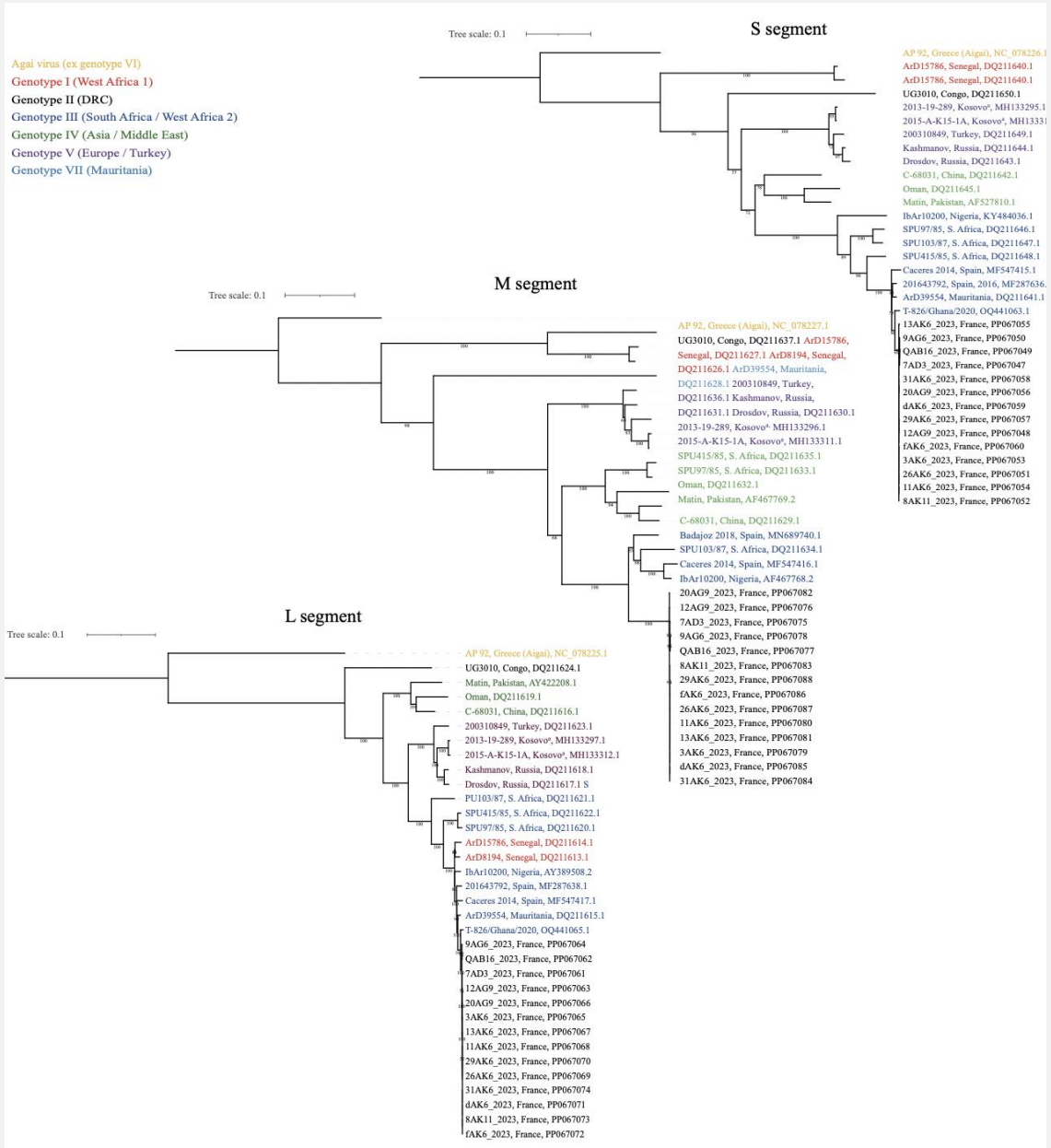
Prevalence of CCHFV in ticks in Western Europe

Table 1. Prevalence of Crimean-Congo hemorrhagic fever virus (CCHFV) in ticks.

Country	Dates	% of Infection Rate (No. of Positive Samples/No. of Analyzed Ticks) [1]		Source	Reference
		PI	MIR (No. of Pools)		
Austria	2018	0 (0/1) *H. marginatum*		Migratory bird (presumably)	[28]
Corsica (French island)	2014–2015		0 (0/1015) (332 pools) 0 (0/362) *H. marginatum* (89 pools) 0 (0/518) *R. bursa* (108 pools) 0 (0/135) *H. scupense* (135 pools)	Cattle, goat, sheep, horses, dogs, wild boards, mouflons	[29]
Germany	2015	0 (0/1) *H. rufipes*		Horse	[30]
Spain	2010		1.7 (2/117) *H. lusitanicum* (12 pools)	Deer	[31]
	2009–2015	0 (0/161) *H. marginatum*		Asymptomatic patients, birds	[32]
	2013–2015		0 (0/2053) (229 pools) 0 (0/1333) *H. marginatum* (151 pools) 0 (0/680) *H. lusitanicum* (74 pools) 0 (0/40) *R. bursa* (4 pools)	Vegetation, cattle, sheep	[33]
	2014–2015		0.5 (1/208) (45 pools) 0.5 (1/204) *H. lusitanicum* (NA) 0 (0/2) *Dermacentor* spp. (NA) 0 (0/4) *Rhipicephalus* spp. (NA)	Deer	[34]
	2016–2017		1.35 (128/>9500) (3959 pools) NA *H. lusitanicum* (NA) NA *D. marginatus* (NA) NA *Rhipicephalus* sp. (NA)	Wild or domestic animals [2]	[35]
	2011–2015	2.78 (44/1579) 4.0 (43/1079) *H. lusitanicum* 0.4 (1/238) *H. marginatum* 0 (0/46) *Rhipicephalus* spp. 0 (0/3) *I. ricinus* 0 (0/1) *Dermacentor* sp. 0 (0/212) not identified		Vegetation, deer, fallow deer, red fox, cattle, sheep, wild board [3]	[36]
	2017	21.0 (129/613) 20.2 (119/589) *H. lusitanicum* 41.7 (10/24) *D. marginatus*		Red deer, wild boar, fallow deer, roe deer	[37]
	2017		0.5 (7/1356) (452 pools) [4]	Vegetation	[38]
UK	2018	0 (0/1) *H. rufipes*		Horse	[39]
	2018	0 (0/1) *H. marginatum*		Vegetation [5]	[40]

H. marginatum: Hyalomma marginatum; R. bursa: Rhipicephalus bursa; H. scupense: Hyalomma scupense; H. rufipes: Hyalomma rufipes; H. lusitanicum: Hyalomma lusitanicum; D. marginatus: Dermacentor marginatus; I. ricinus: Ixodes ricinus; [1] Total infection rate [PI: Prevalence of infection (data from individual ticks), MIR: Minimum infectious rate (data from pools)], and corresponding of each tick species analyzed; [2] All positive samples corresponded to ticks collected from wildlife, mainly H. lusitanicum from deer; [3] Positive samples were collected from deer (n = 41) and cattle (n = 3); [4] The majority of them (80%) corresponded to H. lusitanicum; [5] The tick was crawling on the leg of a man; NA: Not available.

Portillo A, *Microorganisms* 2021



Agai virus (ex genotype VI)

Genotype I (West Africa 1)

Genotype II (DRC)

Genotype III (South Africa / West Africa 2)

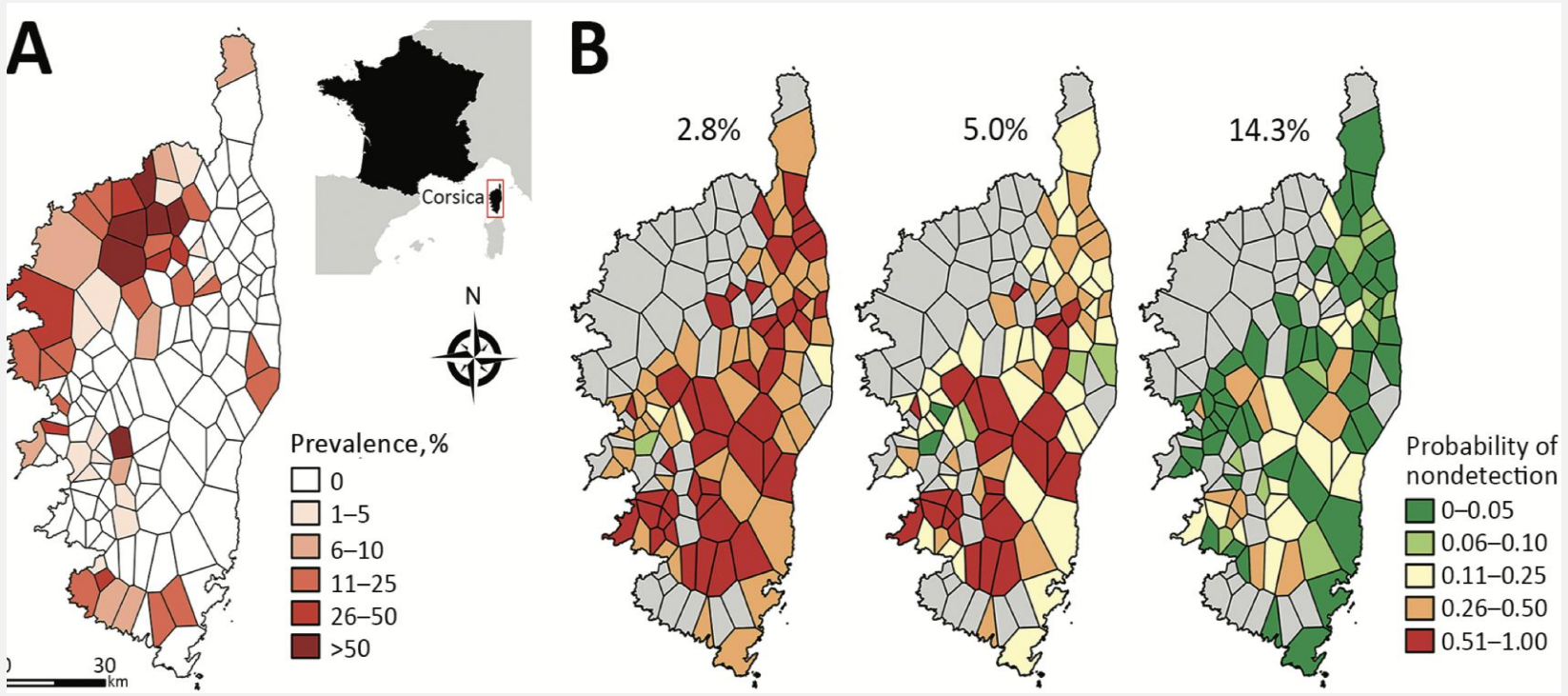
Genotype IV (Asia / Middle East)

Genotype V (Europe / Turkey)

Genotype VII (Mauritania)

Bernard C, et al.. Euro Surveill. 2024

CCHF Virus **Antibodies** among Livestock Corsica: 2014-2016



Antibodies in livestock

cattle, sheep, and goats

N = 3,890

Corsica

2014–2016

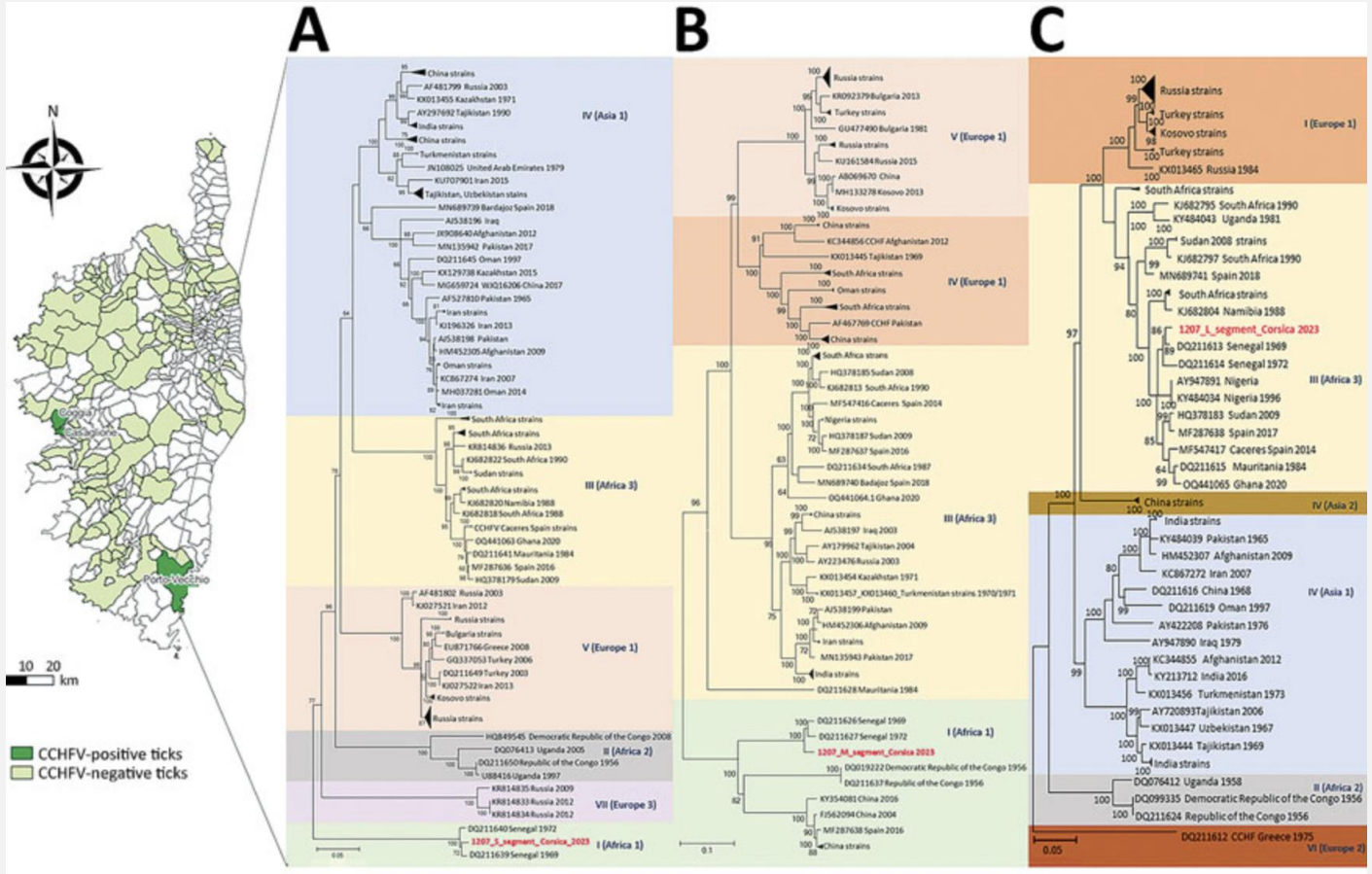
9.1% seropositivity

A: Spatial variability of CCHFV antibody prevalence

B: Probability of nondetection of CCHFV antibody in areas where estimated prevalence was null

Grech-Angelini S, et al. Emerg Infect Dis. 2020

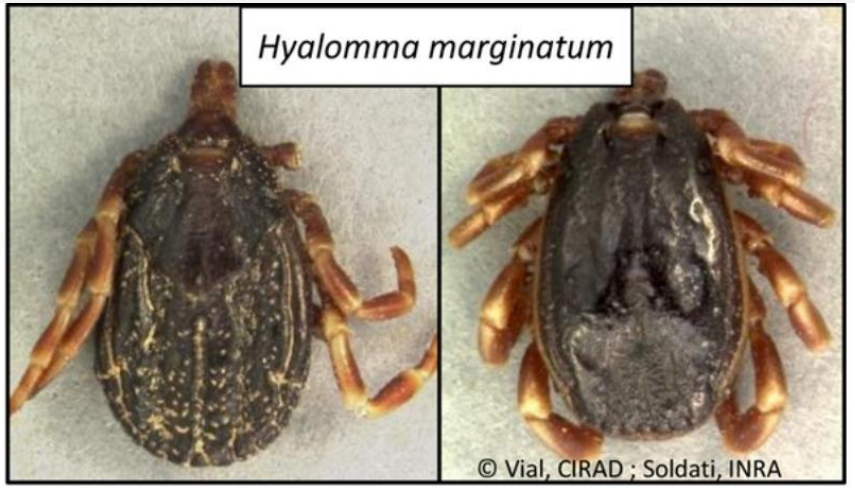
CCHF virus in ticks collected from cattle, Corsica, 2023



- *Hyalomma marginatum (most likely the source)* in Southeastern and central western parts of Corsica.
- CCHF virus African genotype I
- Multiple CCHFV-positive ticks were found on the same animal (cattles).
- CCHFV strains circulating in Corsica and Spain have distinct origins.
- Migratory birds via two different ways from Africa

Kiwan P, Masse S, Piorkowski G, Ayhan N, Gasparine M, Vial L, et al.. Emerg Infect Dis 2024

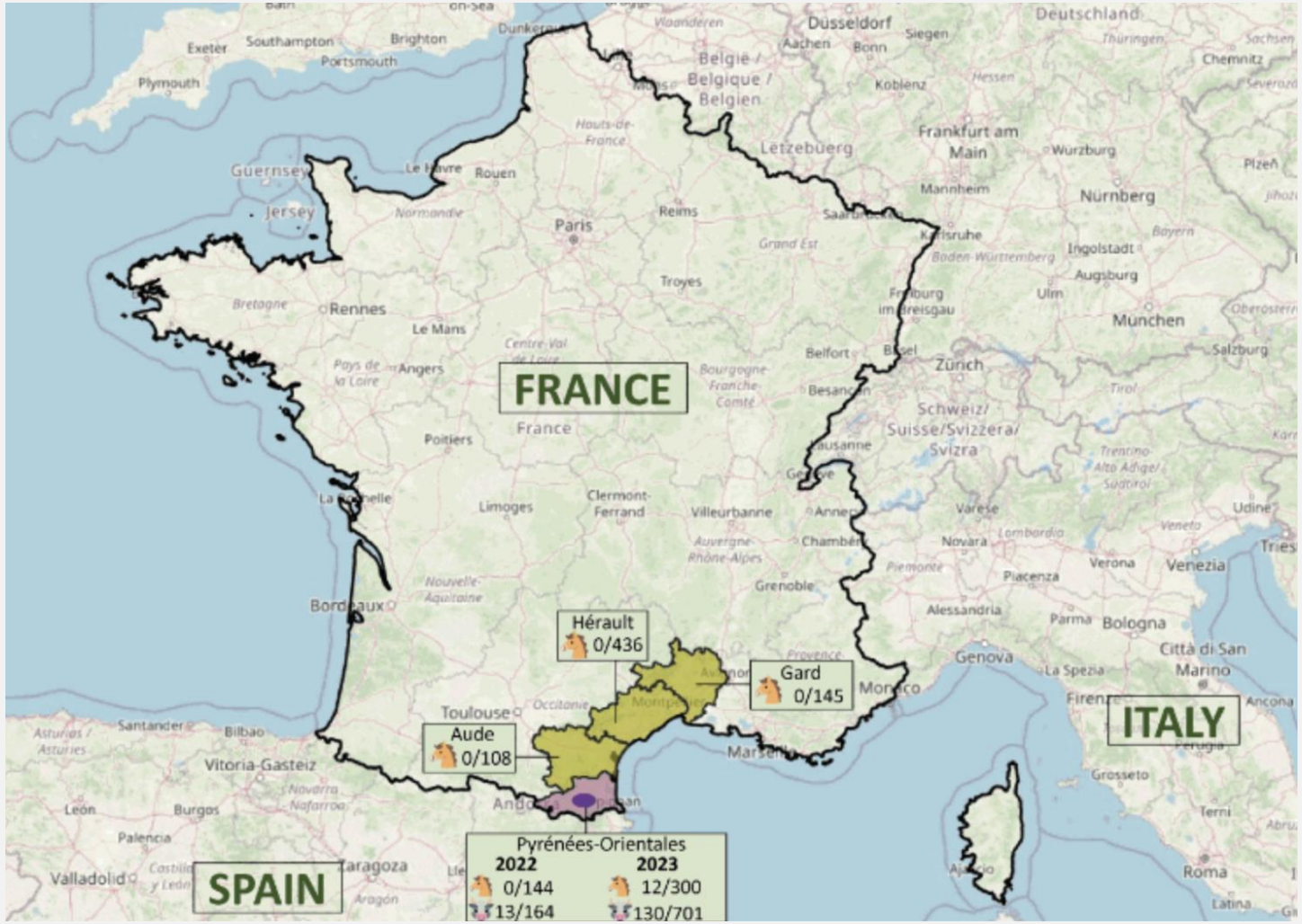
Strong evidence for the presence of the tick Hyalomma marginatum Koch, in southern France (2016)



Presence of reproducing populations in
Southern Continental France

Vial L, TTBD, 2016

CCHF virus in *Hyalomma marginatum* ticks in Southern France (2023)



2022: 13/997 (1.3%) ticks
All from the same cattle farm in Pyrénées-Orientales

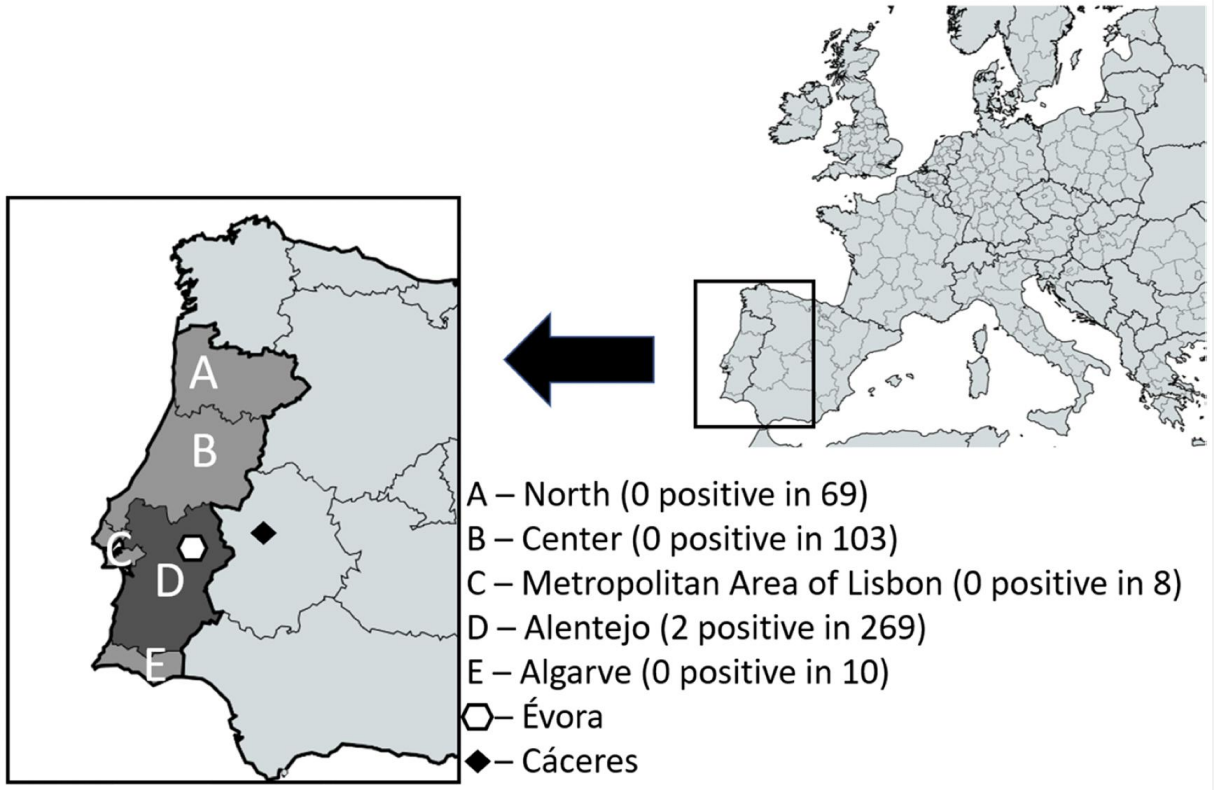
2023: 142/ 1,001 (14.2%)
H. marginatum ticks were positive for CCHFV.

in Pyrénées-Orientales, 15 cattle farms, 3 farms with cattle and horses 3 farms with horses.

Bernard C, et al.. Euro Surveill. 2024

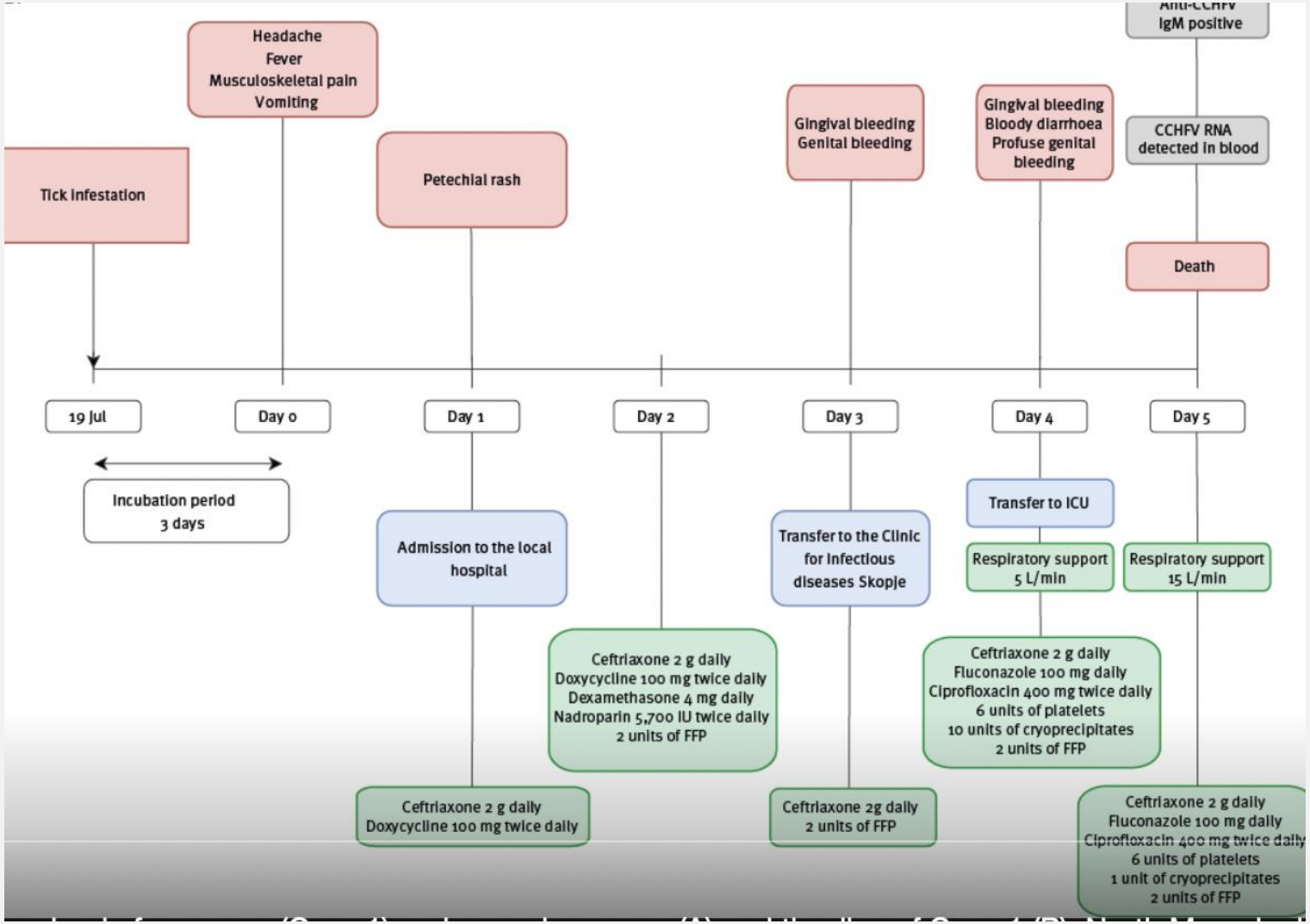
Crimean-Congo hemorrhagic fever virus circulating among sheep of Portugal: a nationwide serosurvey assessment

João R. Mesquita[1,2] · Rita Cruz[3,4] · Fernando Esteves[3,4] · Carla Santos[3,4] · Humberto Pousa[1] · Catarina Coelho[3,5,6] · Ana Cristina Mega[3] · Carmen Nóbrega[3,5] · Helena Vala[3,5] · Christophe Nicolas Peyrefitte[7,8,9] · Maria São José Nascimento[10] · Patrícia Ferreira Barradas[2,11,12]



Mesquita, J.R., Cruz, R., Esteves, F. *et al. Trop Anim Health Prod* 2022

Cases of Crimean-Congo haemorrhagic fever in North Macedonia, 2023



Case 1 in a rural area of the eastern part of North Macedonia, died.

Case 2: healthcare worker.

Contact monitoring 1/67 +

(PPE) including gloves, mask, apron and face shield were used. The exposure could have occurred during possible improper removal of the PPE.

Case 3: from another region of the country, with no epidemiological link to the confirmed cases or identified contacts from contact tracing, was admitted to our clinic.

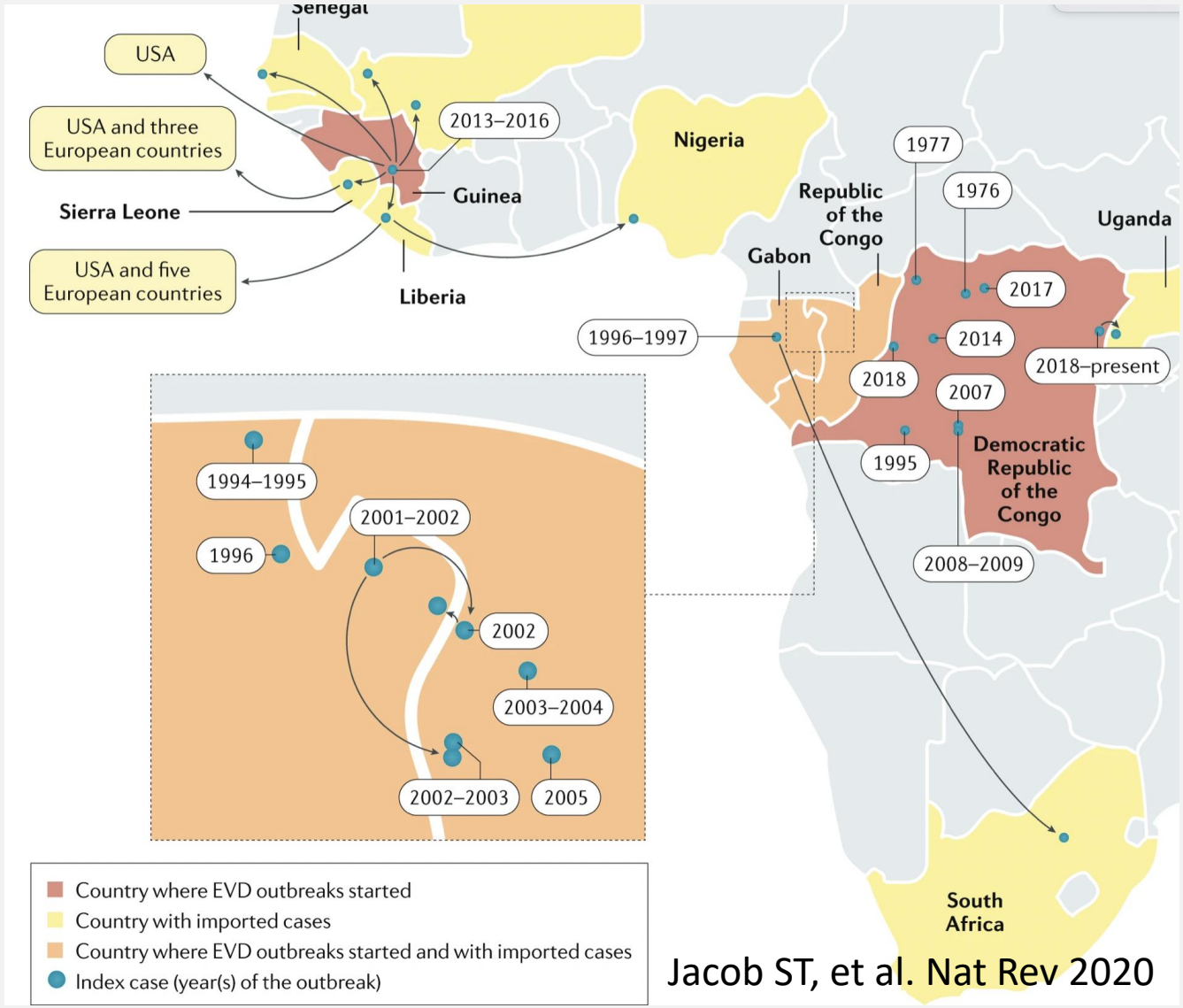
Jakimovski D, et al. Euro Surveill. 2023

CCHF in Europe: Total cases since 2013

	Bulgaria	Spain	Portugal	Macedonia	Greece	Total
2013	2/8	1				2/9
2014	1/8 + 1 (UK)					1/9
2015	2/4					2/4
2016	4	1/2				1/6
2017	2					2
2018	1/6 + 1 (GR)	1/2				2/9
2019	2					2
2020	1	1/3				1/4
2021		2				2
2022	1/2	1/2				2/4
2023	3	1		1/3		1/7
2024	1	2/4	1/1			2/6
2025		3			1/2	1/5
Total	7/43 (18%)	6/17(30%)	1/1	1/3 (33%)	1/2 (50)	13/63 (23%)

ECDC: by 23 October 2024

The Multiple Origins of Ebola Disease Outbreaks



Jacob ST, et al. Nat Rev 2020

1976 to 2022: 35 EVD outbreaks with 48 primary/index cases.

- Wildlife spillover
- Resurgence of human-to-human transmission could account for roughly a quarter of outbreaks
- Nosocomial transmission was associated with the majority of outbreaks.

Improving access to diagnostics as well as identifying groups at risk for resurgence of ebolaviruses will be crucial to preventing future outbreaks.

Judson SD, Munster VJ. J Infect Dis. 2023

The Presentation of a Case

37 years old male came to the outpatient clinic.

He has myalgia, sometimes high fever.

The first step is CBC

Platelet count	78,000/ml
Leukocyte count	3800/ml
CRP	30
Procalcitonin	0.8

The History of tick bite, location

Differential Diagnosis

- COVID-19
- CCHF
- West Nile
- Chikungunya
- Zika
- Sandfly
- Hanta virus
- Influenza
- Dengue
- EBV

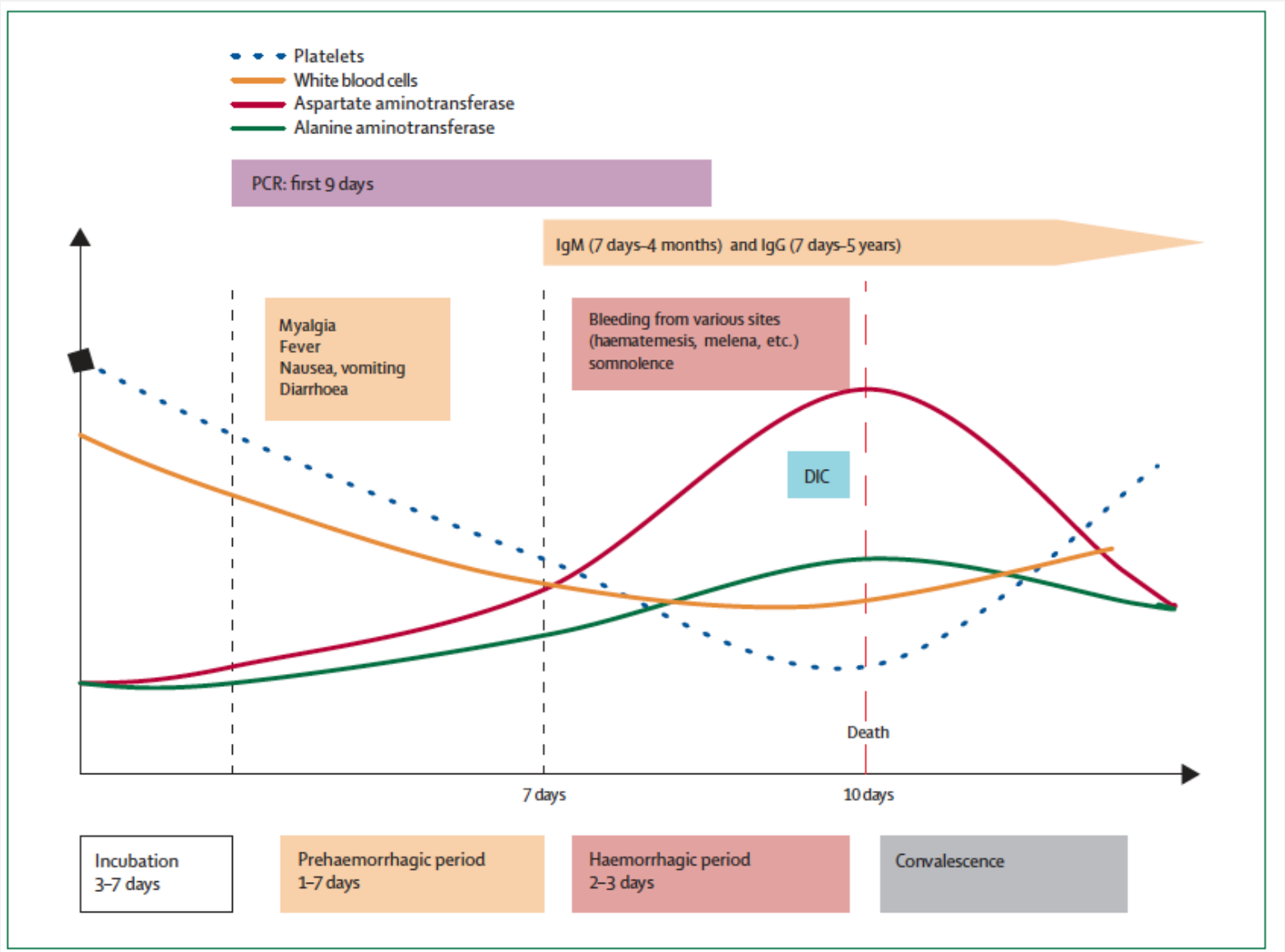


Figure 3: **Clinical and laboratory course of CCHF**
DIC=disseminated intravascular coagulation.

Ergonul O, Lancet ID, 2006

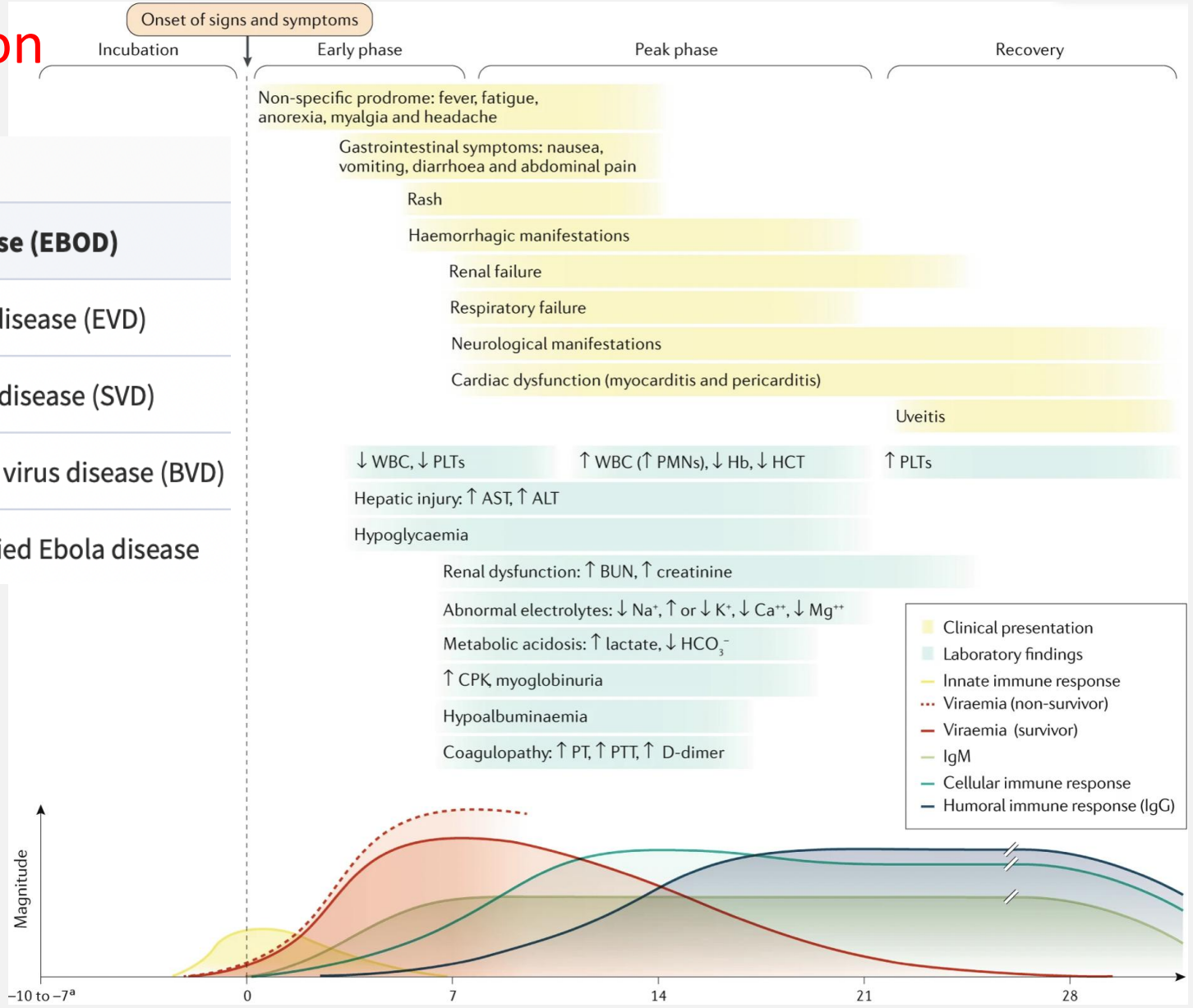
The Course of the Infection

Ebolaviruses Known to Cause Disease in Humans

Ebolavirus	Ebolavirus Species	Ebola Disease (EBOD)
Ebola virus (EBOV)	*Zaire ebolavirus*	Ebola virus disease (EVD)
Sudan virus (SUDV)	*Sudan ebolavirus*	Sudan virus disease (SVD)
Bundibugyo virus (BDBV)	*Bundibugyo ebolavirus*	Bundibugyo virus disease (BVD)
Taï Forest virus (TAFV)	*Taï Forest ebolavirus*	Other specified Ebola disease

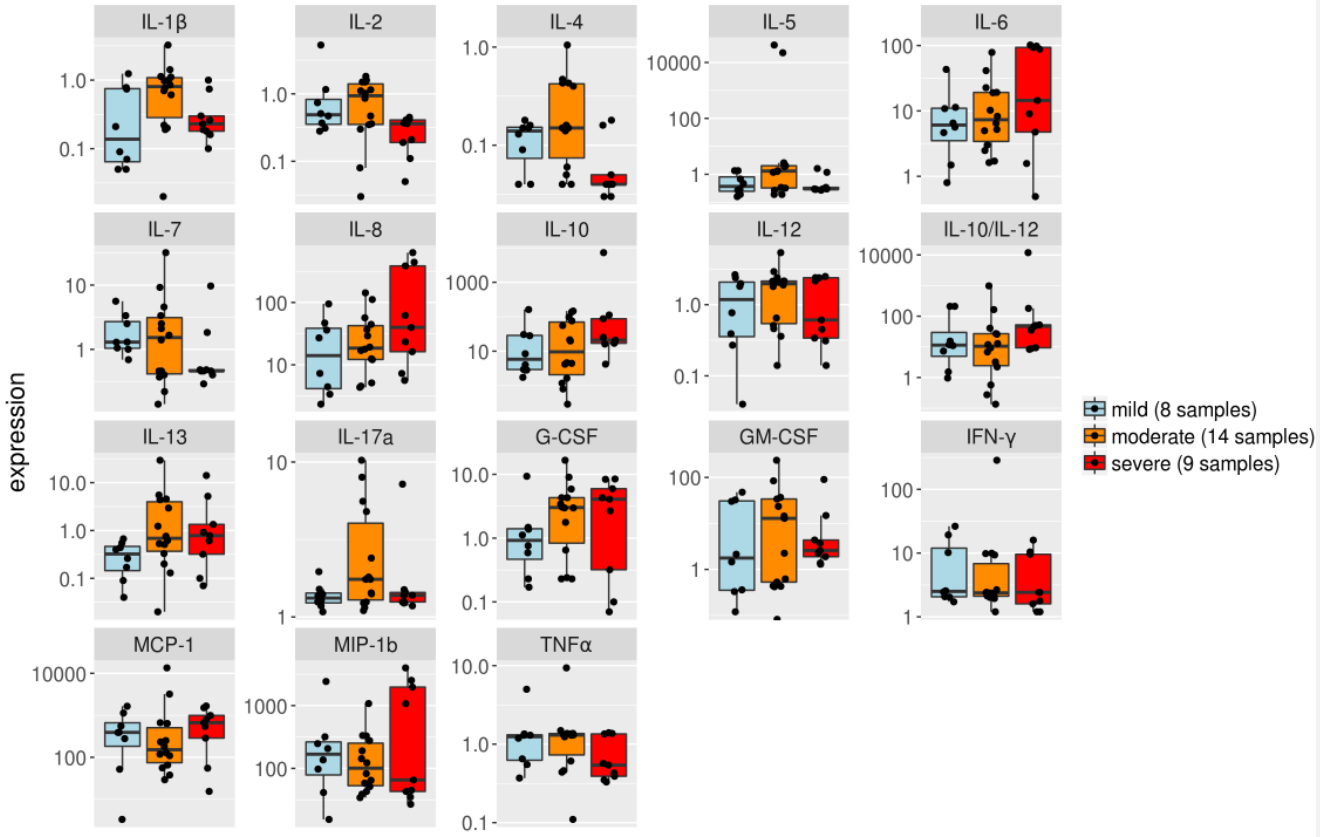
About 27.1% (95% CI, 14.5%–39.6%) of Ebola infections are asymptomatic.

Dean NE, et al. Clin Infect Dis 2016

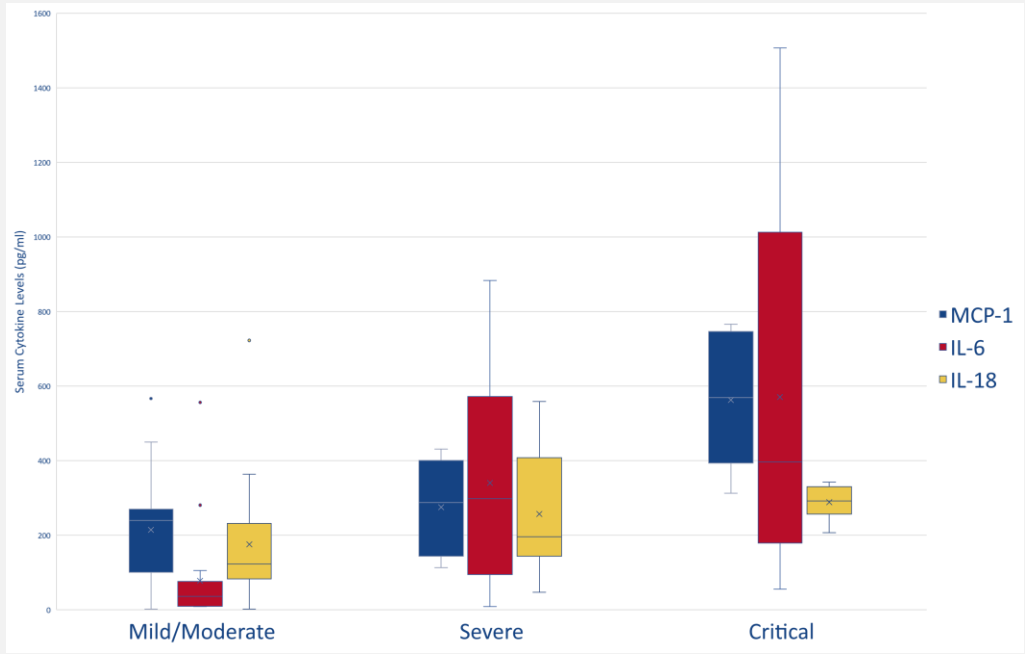


Jacob ST, et al. Nat Rev 2020

Cytokine Levels of Different Severity Groups for First Five Days

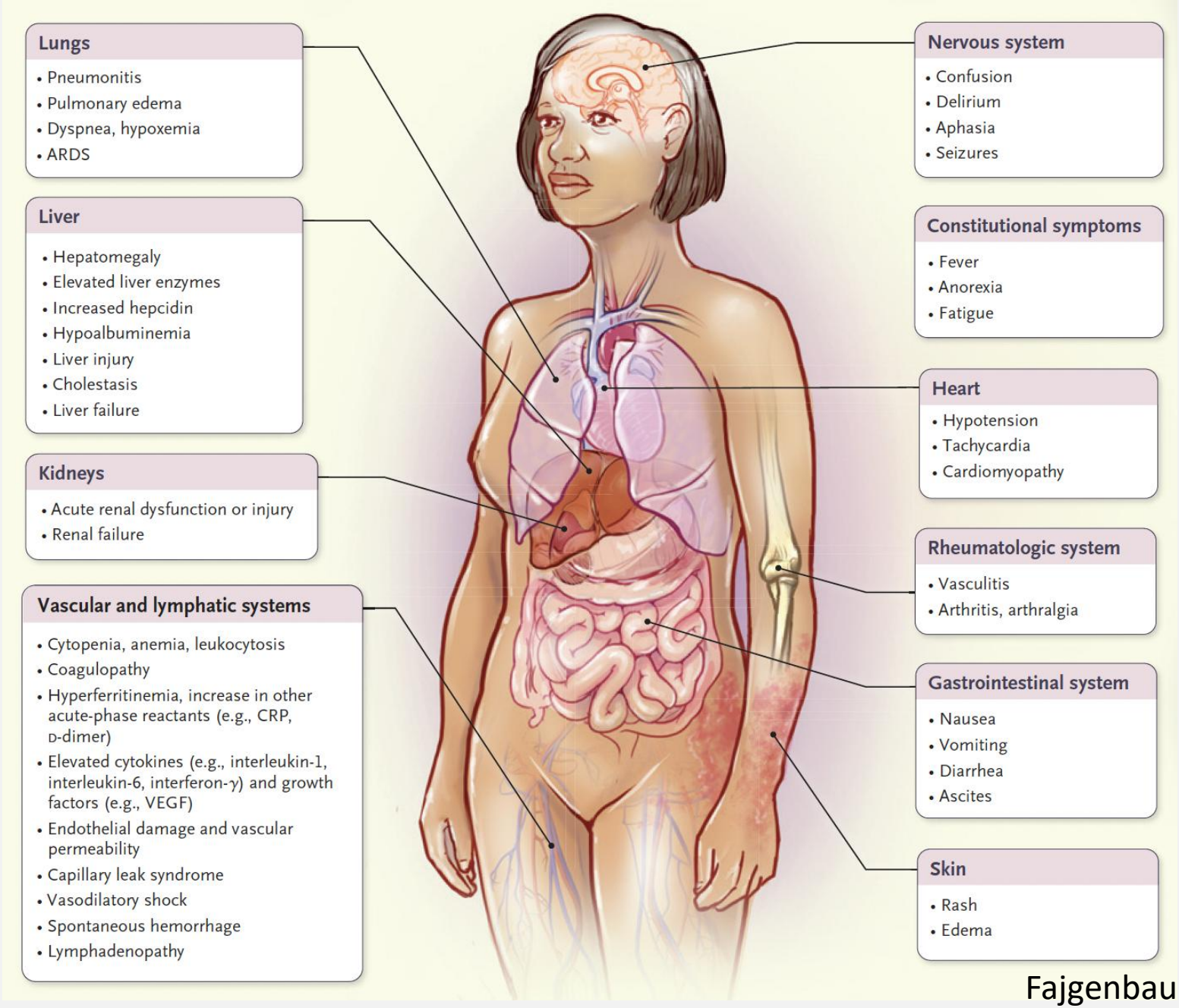


CCHF: J Med Virol 2017



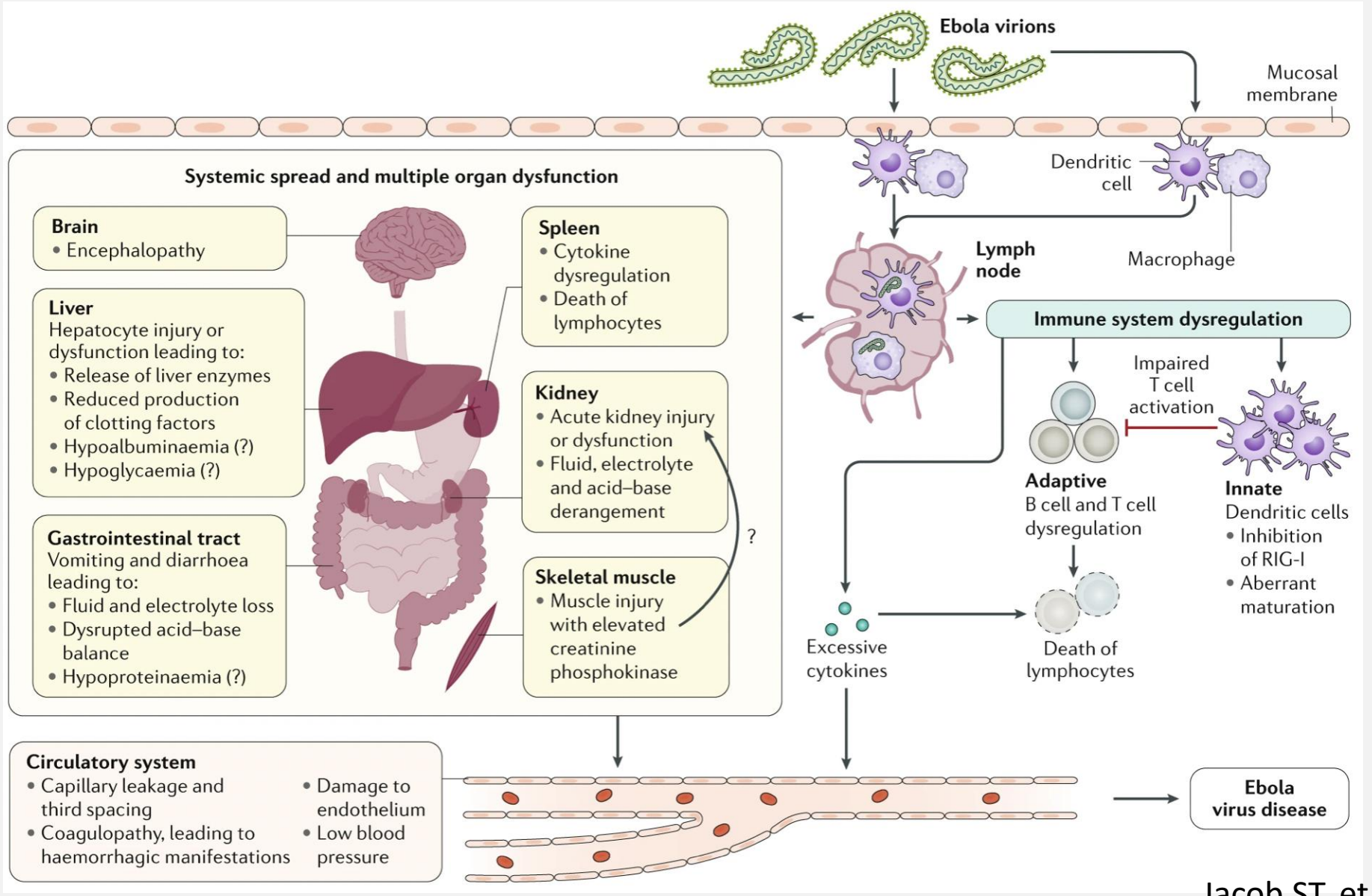
COVID-19: ECCMID 2022

Cytokine Storm



Fajgenbaum, et al. NEJM 2020

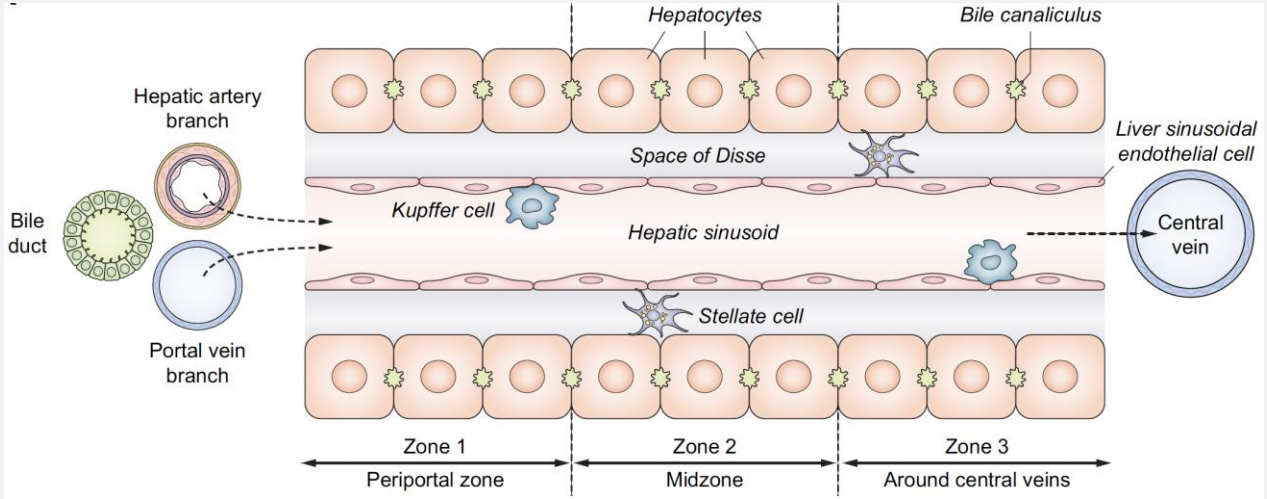
Pathogenesis of Ebola

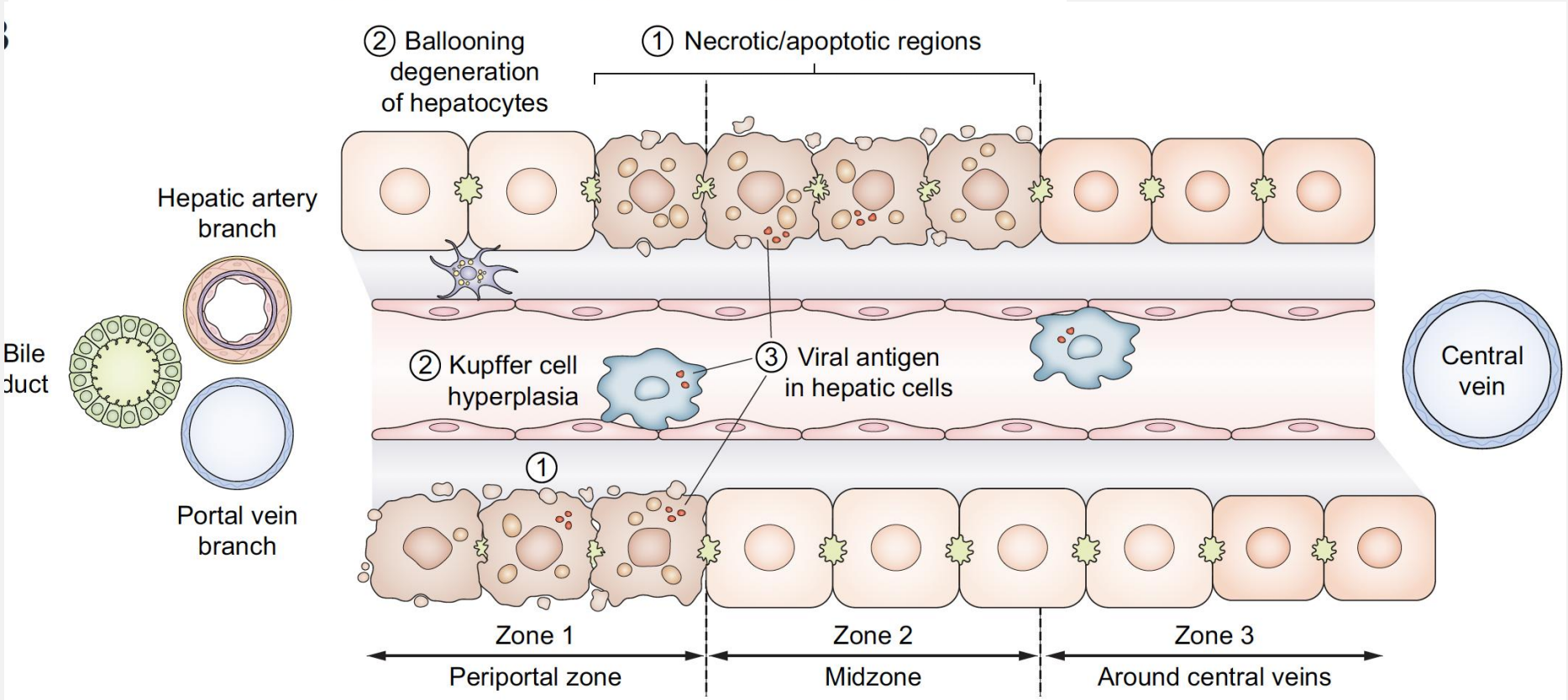


Jacob ST, et al. Nat Rev 2020

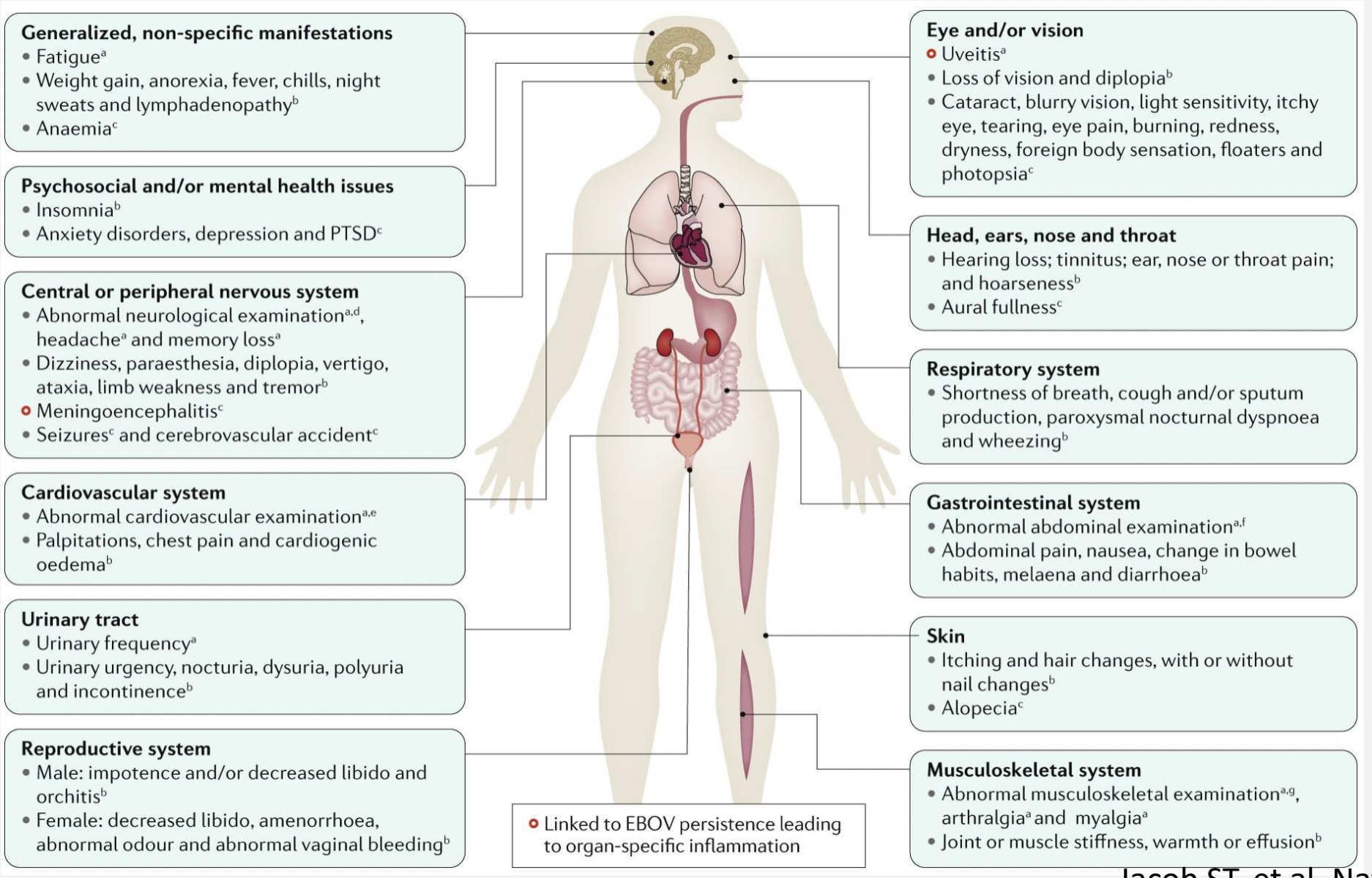
Exotic Viral Hepatitis: Pathogenesis in Liver

van Leeuwen LPM, et al. J Hepatol. 2022





Clinical Sequela of **Ebola Virus Disease** Survivors



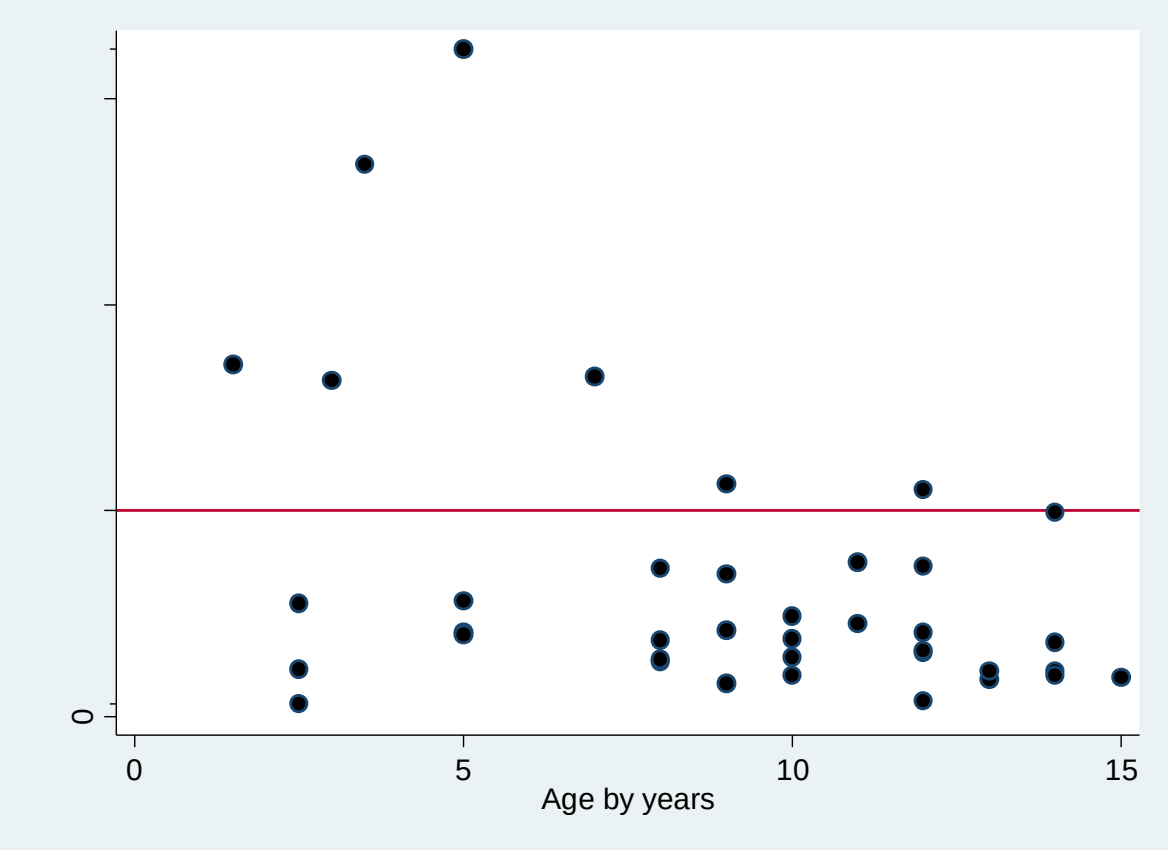
Jacob ST, et al. Nat Rev 2020

Fatality Among Hospitalized Children

33 children in İran: 24% (Sharifi-Mood, et al. Ped Infect Dis J 2008)

31 children in Turkey: 0% (Tezer H, et al. J Clin Virol 2010)

50 children in Turkey; 0% (Tuygun N, et al. Pediatr Int 2011)



Ebola Virus in Body Fluids: West Africa: 2014 to 2016

Aqueous humor

A patient with uveitis 14 weeks after the onset of Ebola symptoms and 9 weeks after viremia
(*Varkey JB, et al. NEJM 2015*).

Cerebrospinal fluid

Meningitis approximately 10 months after her initial diagnosis, and infectious virus was recovered from the cerebrospinal fluid
(*Jacobs M, et al. Lancet 2016*)

Urine

Ebola virus was cultured from a patient's urine 26 days after the onset of symptoms, which was nine days after the plasma RNA level became negative
(*Kreuels et al. NEJM 2014*)

Ebola Virus in Semen: West Africa: 2014 to 2016

267 male survivors, viral RNA in the semen of 30% of survivors, mean 19 months, max 40 months. (Longitidunal study in Liberia, NEJM 2019).

The concentration of viral RNA in semen during early recovery was 4 logs higher than in blood during peak infection (Barnes KG, et al. CID 2017)

Risk factors for persistence of EBOV in semen:

- Older age,
- decreased illness severity,
- elevated total serum IgG3 and HLA-C*03:04 allele expression

(Dyal J, et al. CID 2023).

CCHF: sexual transmission

Ergonul O, et al. Potential sexual transmission of CCHF infection. Jpn J Infect Dis 2014

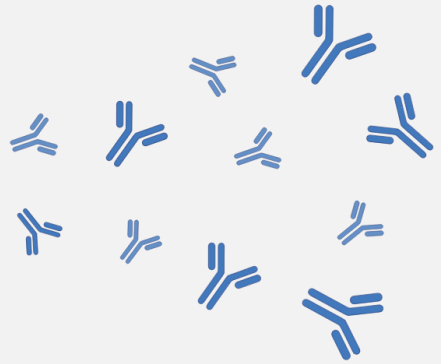
Pshenichnaya NY, et al. Possible sexual transmission of CCHF. Int J Infect Dis 2016

CCHF Survivors Project

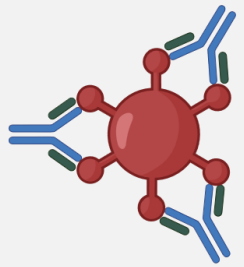
CCHF Survivors called by researchers
n = 2132

CCHF Survivors volunteered for the study
n = 104

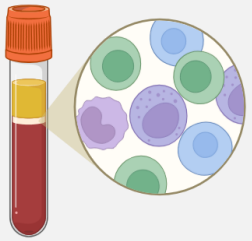
Serum Collection



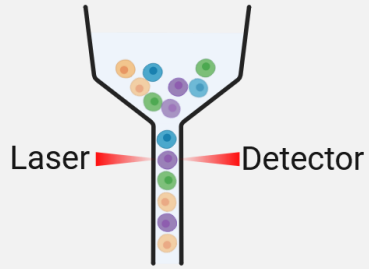
Investigation of anti-CCHFV antibodies by ELISA



Investigation of neutralizing antibodies by plaque assay



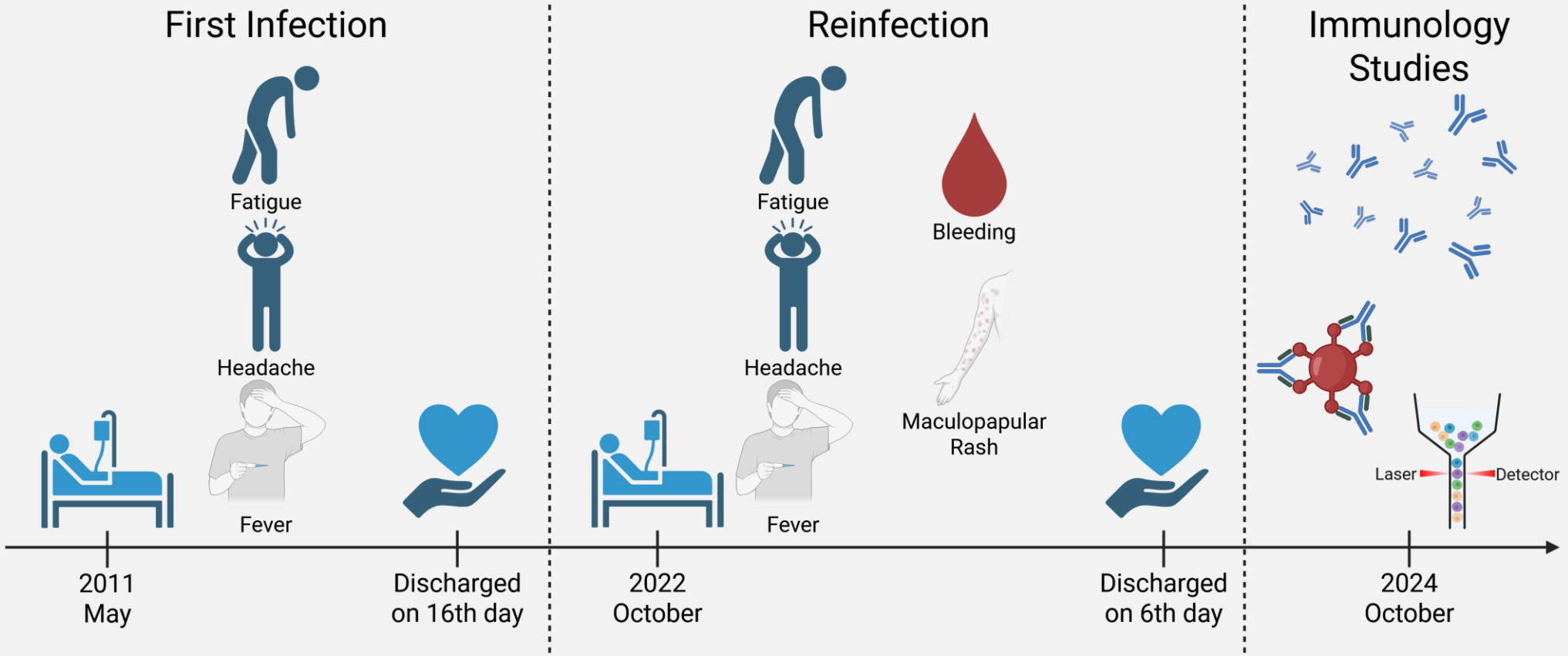
PBMC Collection



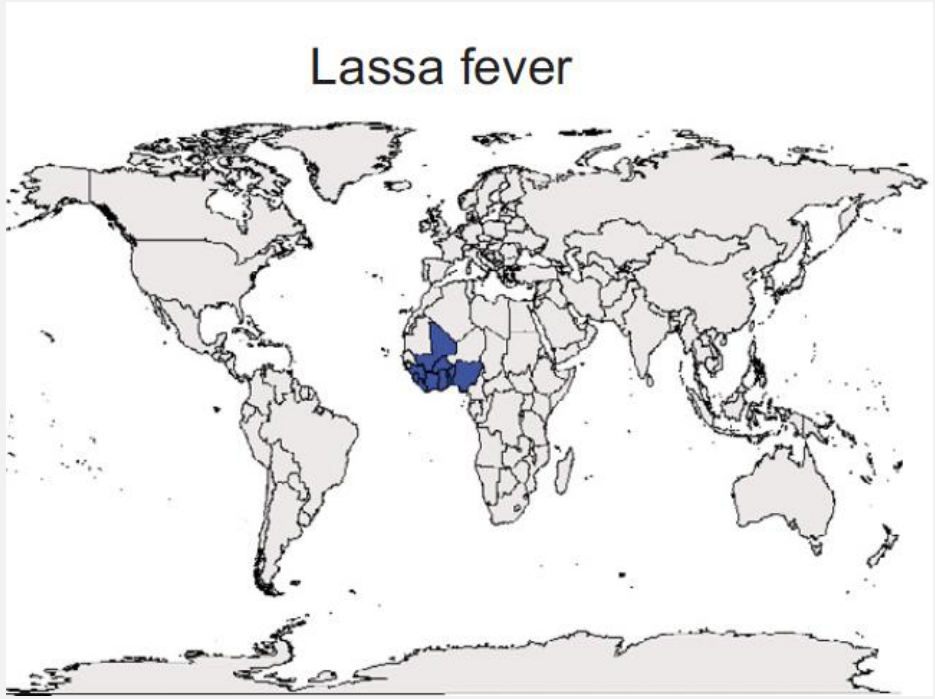
Investigation of antigen specific memory T cells by flow cytometry

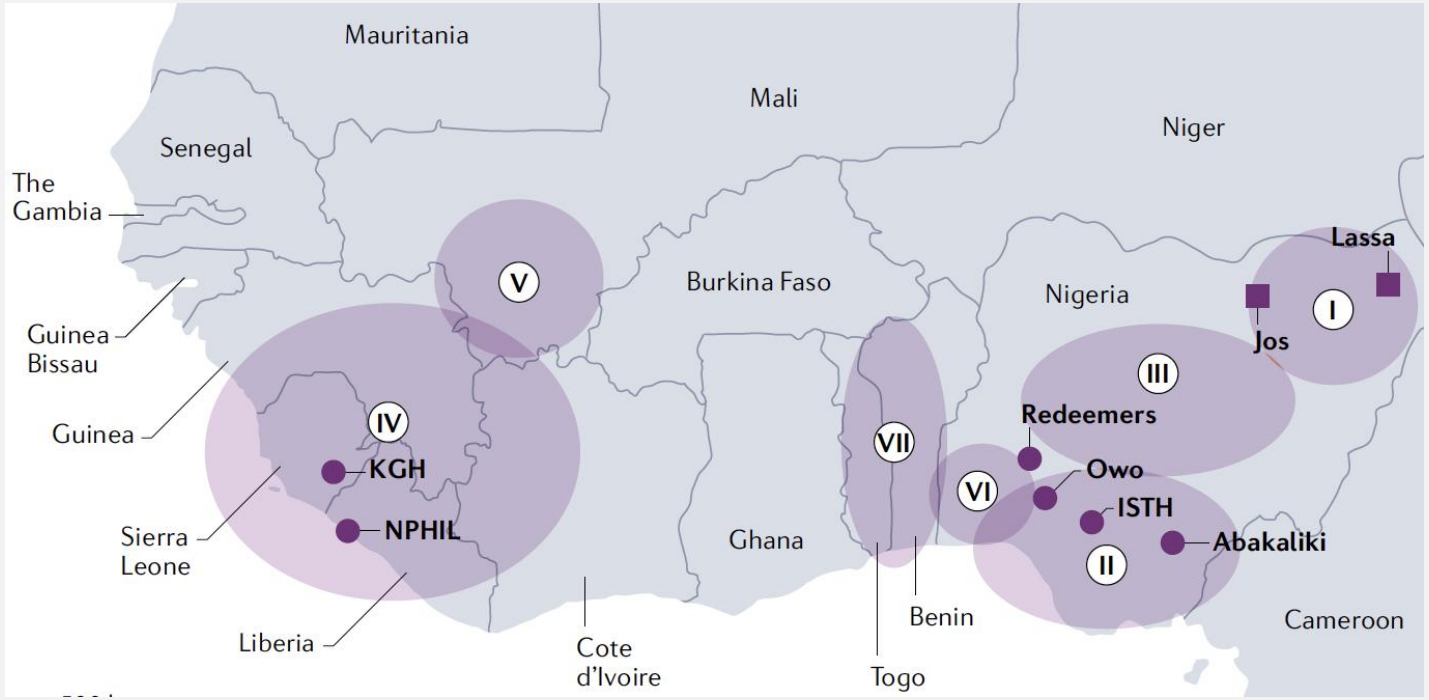
CCHF Survivors Project

- Current information: CCHFV infection provides lifelong immunity
- We detected a case reinfected with CCHF virus 11 years after first infection



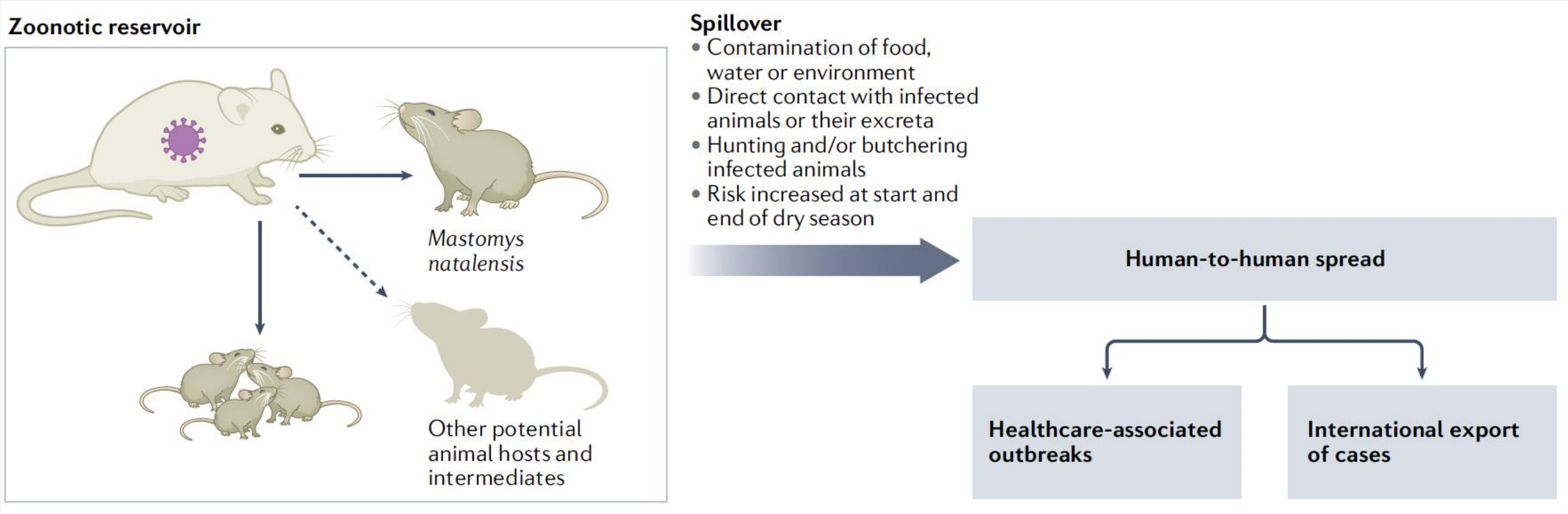
Lassa Fever





Garry RF. Nat Rev 2023

Lassa Fever



Garry RF. Nat Rev 2023

Dengue Fever

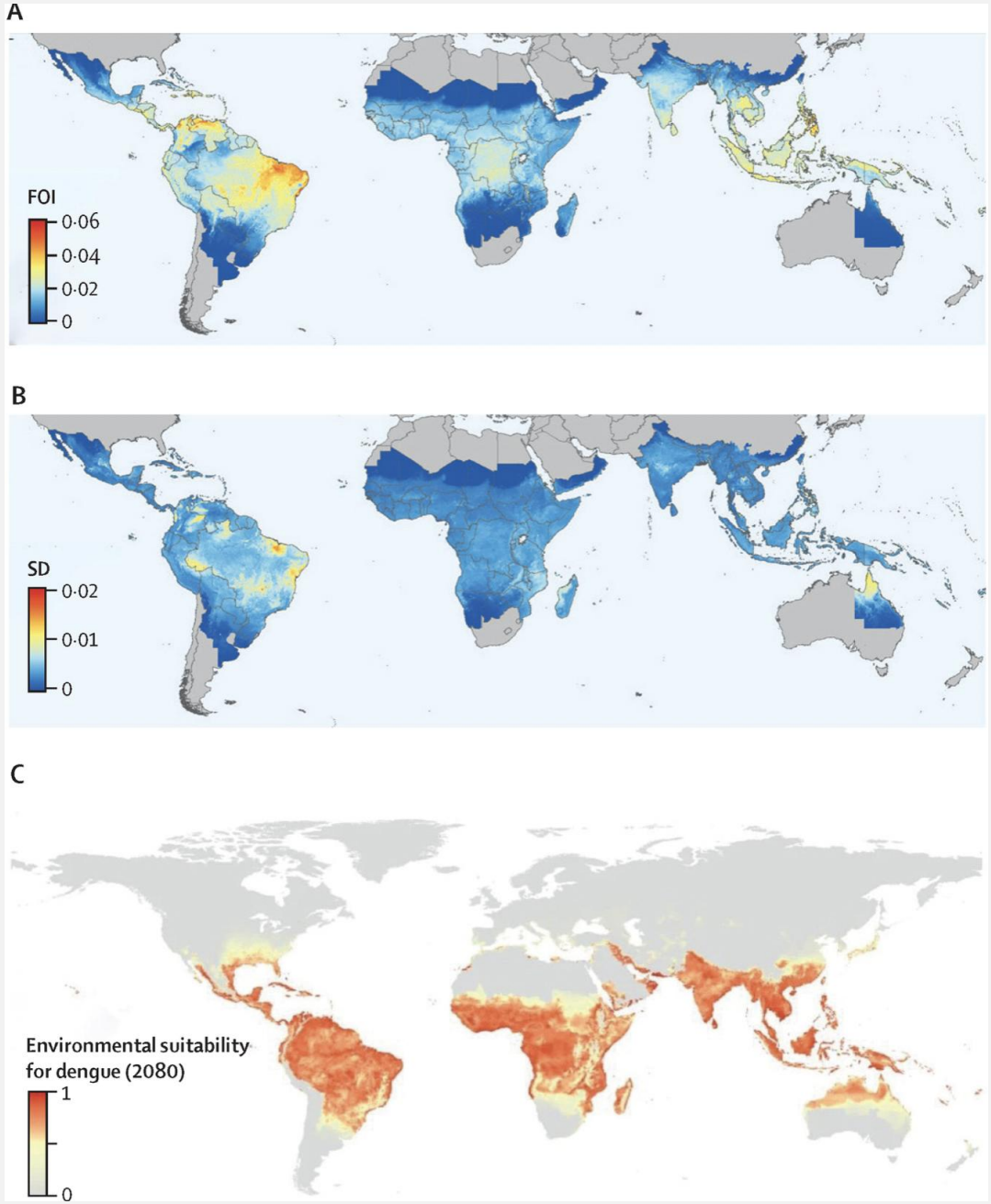
WHO:

Dengue is spreading to new areas in Europe, the Eastern Mediterranean and South America.

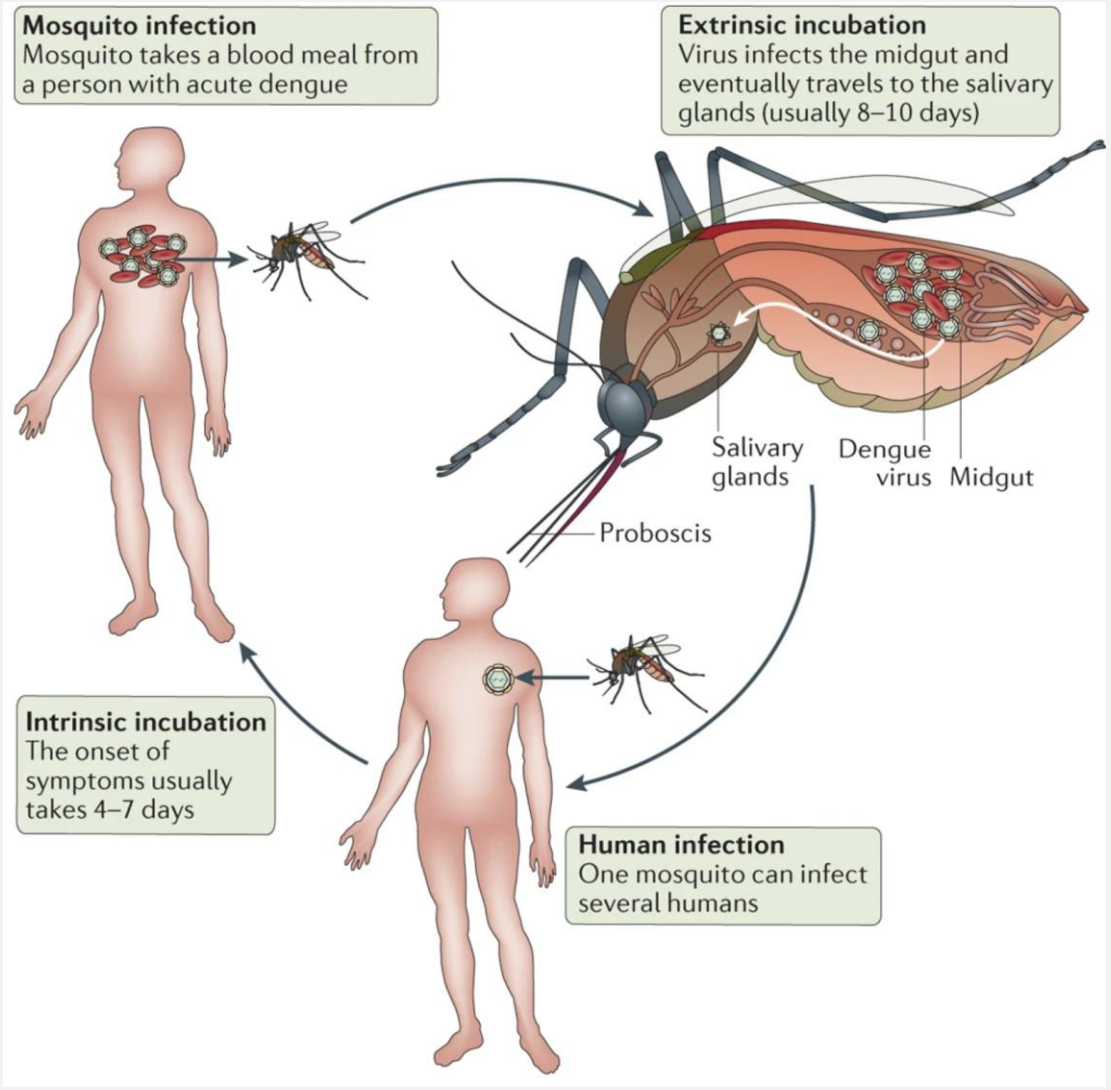
The largest number of dengue cases in 2023.

The WHO Region of the Americas reported 4.5 million cases, with 2300 deaths.

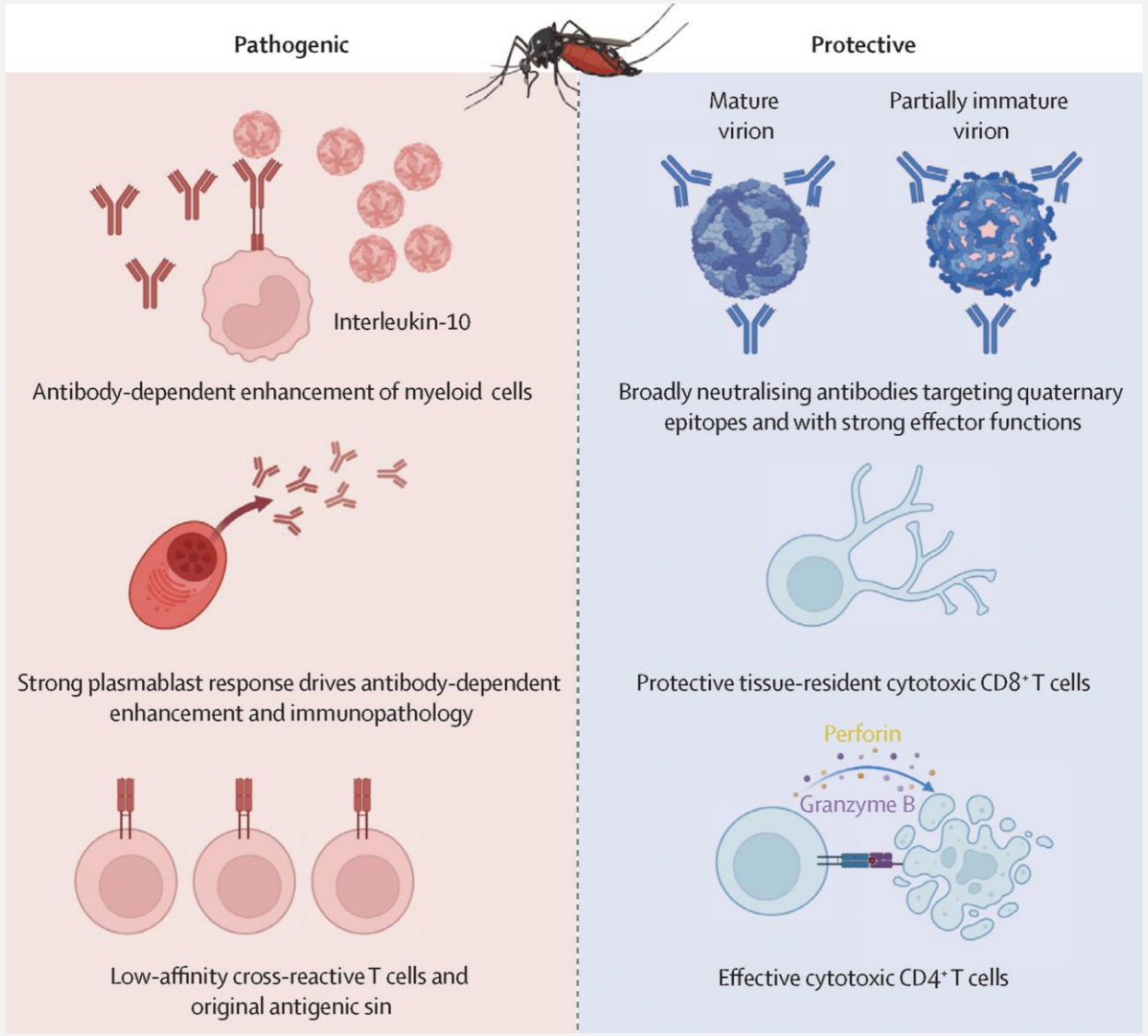
A high number of cases were reported in Asia: Bangladesh (321 000), Malaysia (111 400), Thailand (150 000), and VietNam (369 000).



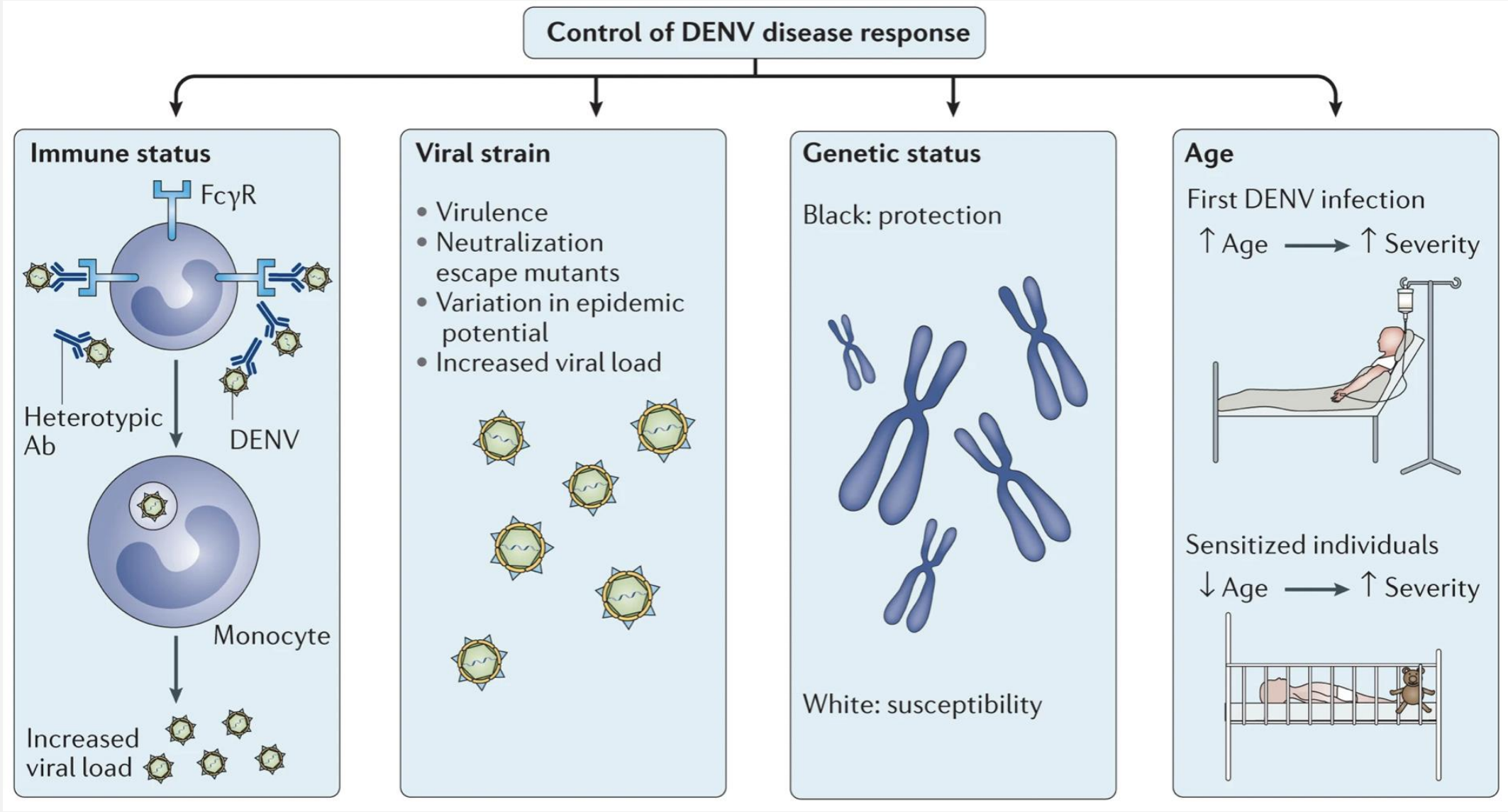
Paz-Bailey G, et al. Dengue. Lancet. 2024



Guzman M, et al. Nat Rev Dis Primers 2016

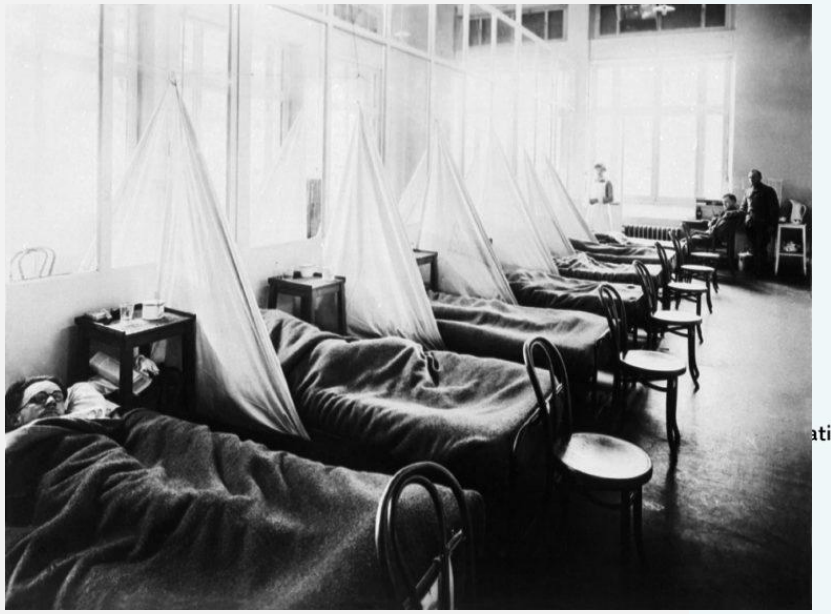


Paz-Bailey G, et al. Dengue. Lancet. 2024

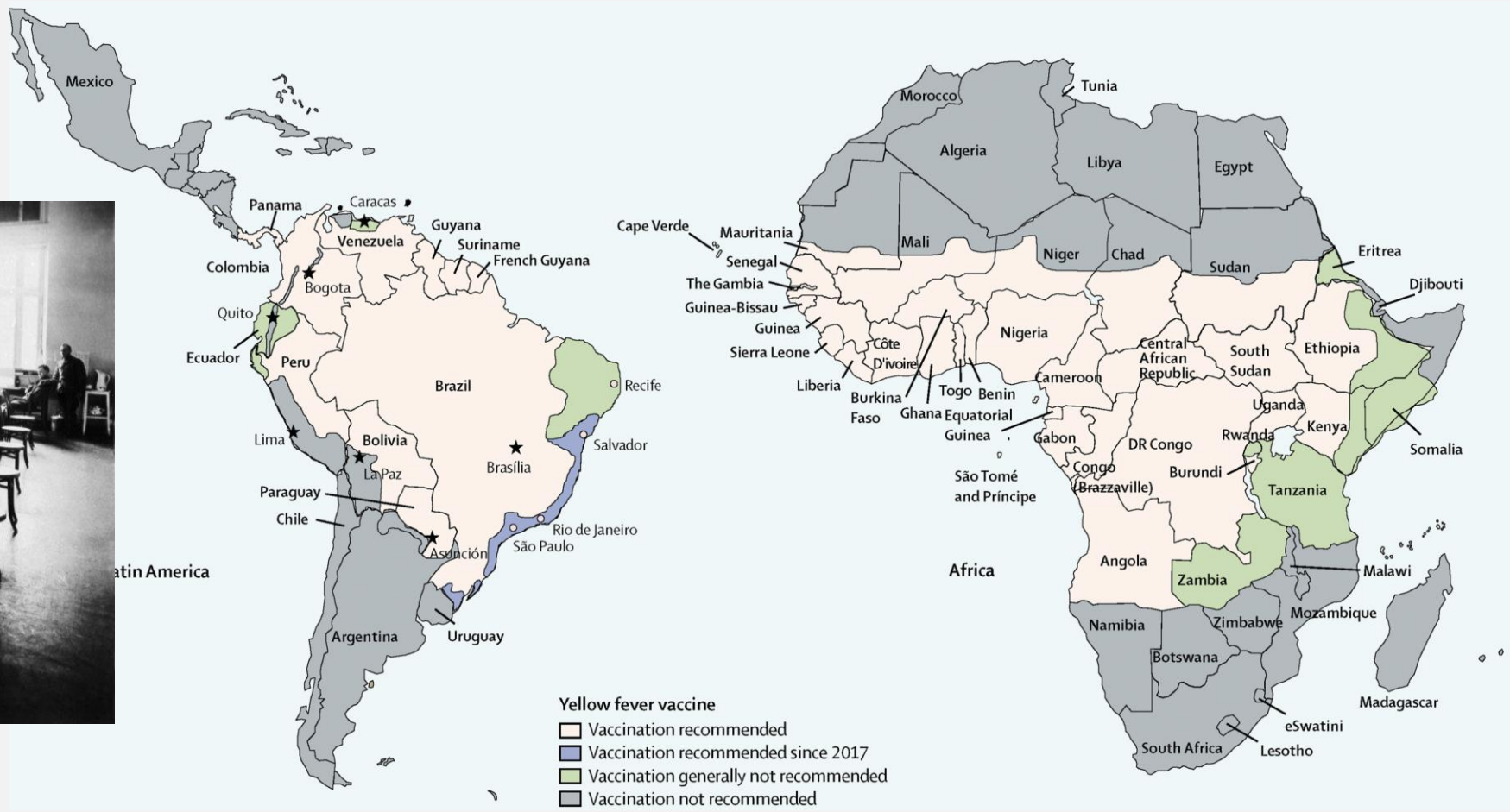


Guzman M, et al. Nat Rev Dis Primers 2016

Yellow Fever



Early 20th cc, Brasil

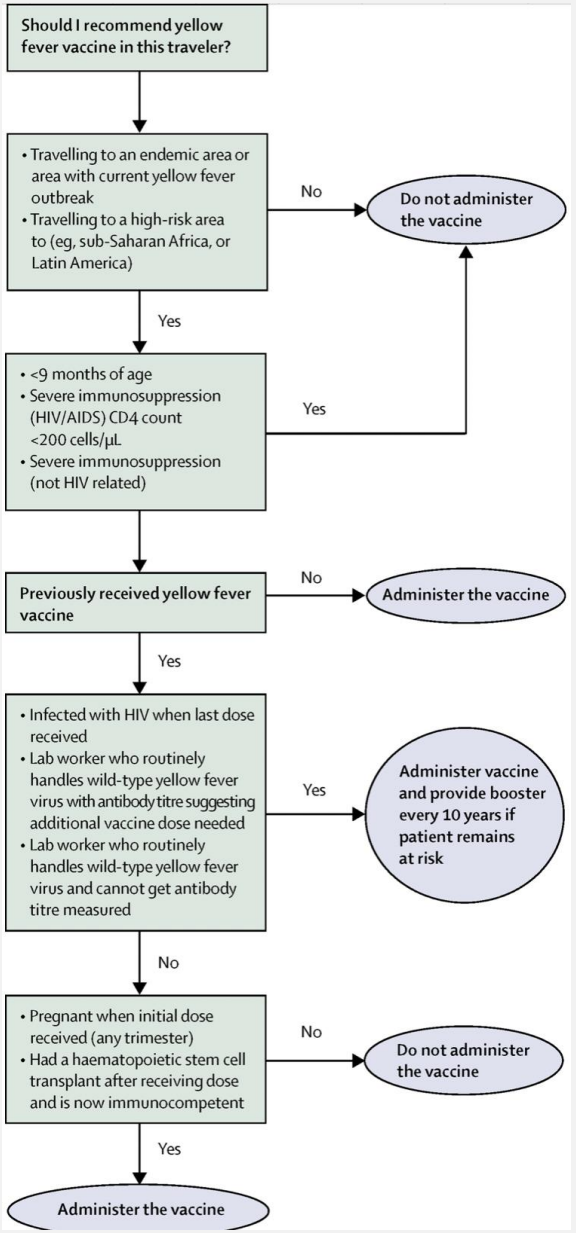


Reno E, et al. Prevention of yellow fever in travellers: an update. Lancet Infect Dis 2020

Yellow Fever

Max Theiler
1899-1972

Nobel Prize, 1951



No treatment
vaccination available since 1937

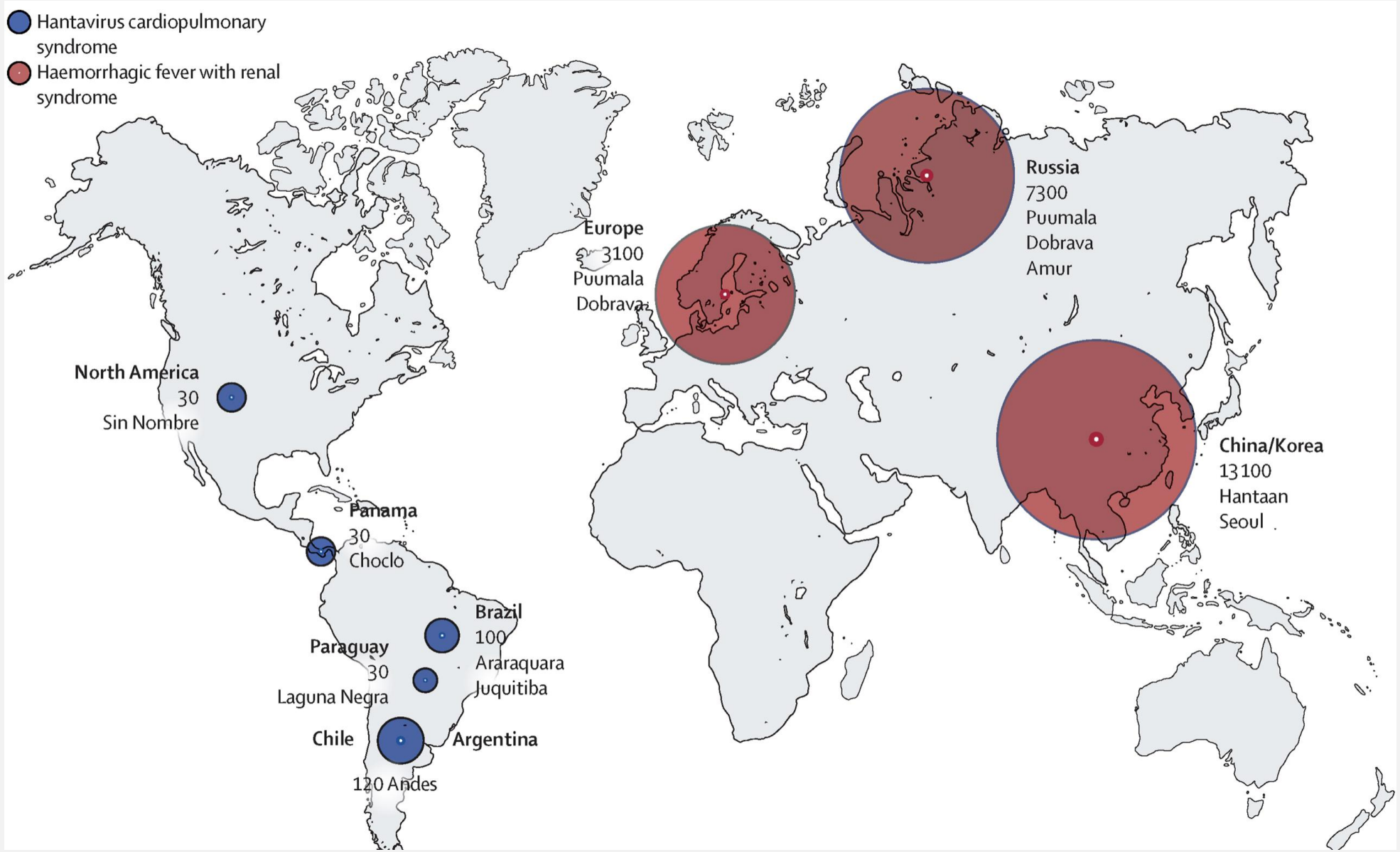
Every year, an increasing number of individuals are travelling to yellow fever endemic areas, many of whom have complex medical conditions.

Travel health practitioners should do individualised assessments of the risks and benefits of yellow fever vaccination to identify potential contraindications.

The most relevant contraindications
Thymoma
AIDS
Receiving immunosuppressive drugs

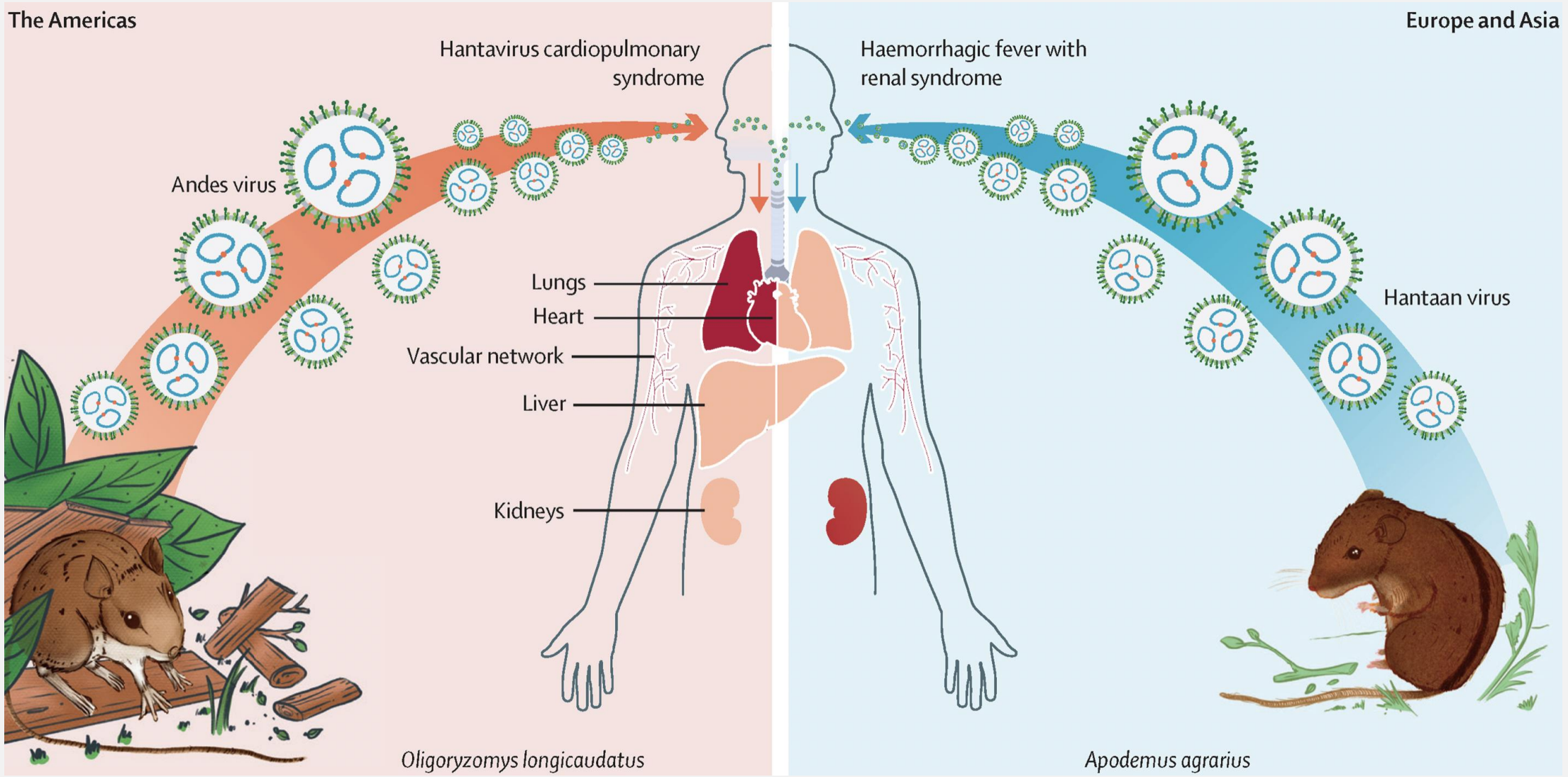
Reno E, et al. Prevention of yellow fever in travellers: an update. Lancet Infect Dis 2020

Hantavirus in Humans



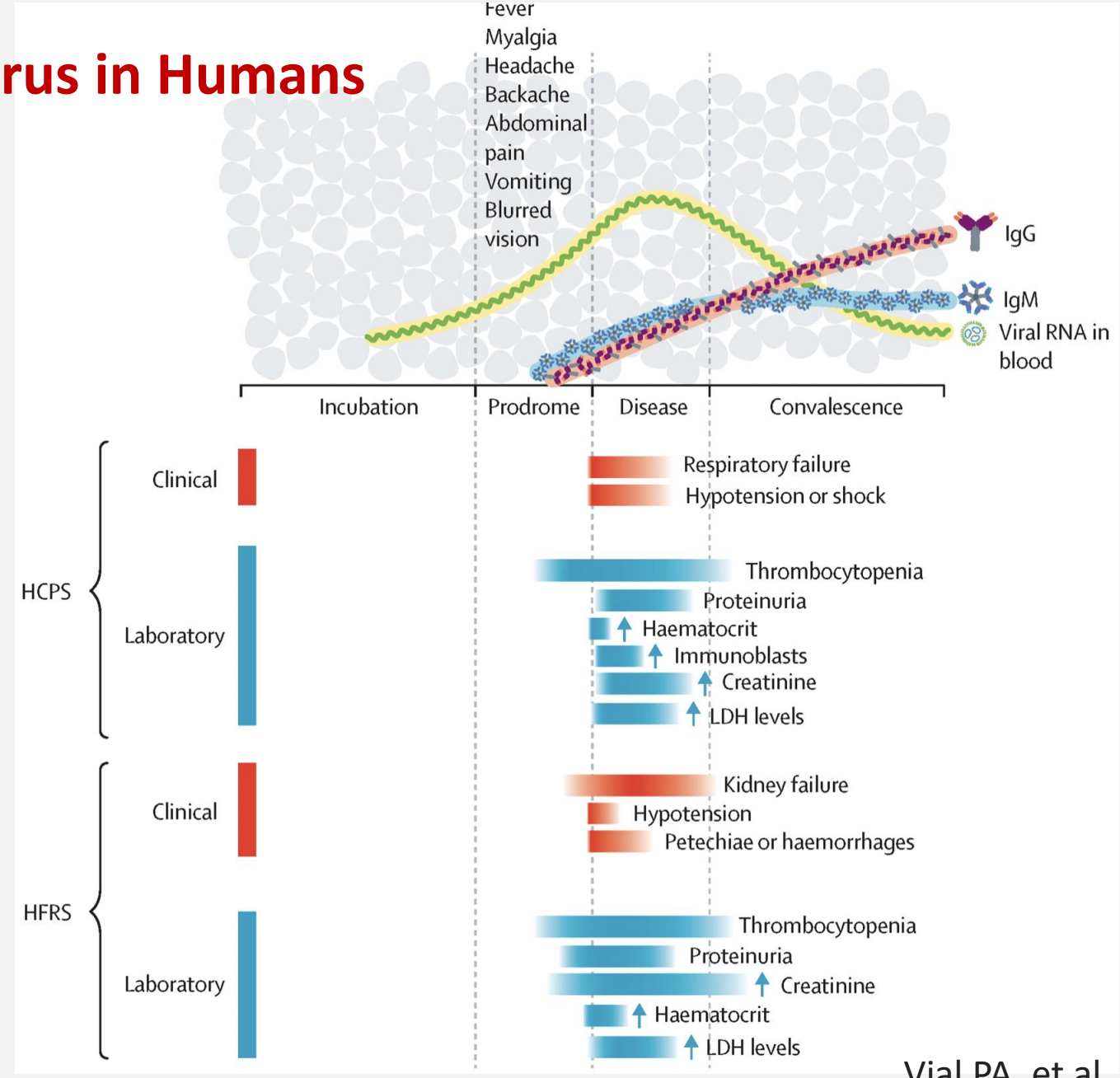
Vial PA, et al. Lancet Infect Dis. 2023

Hantavirus in Humans



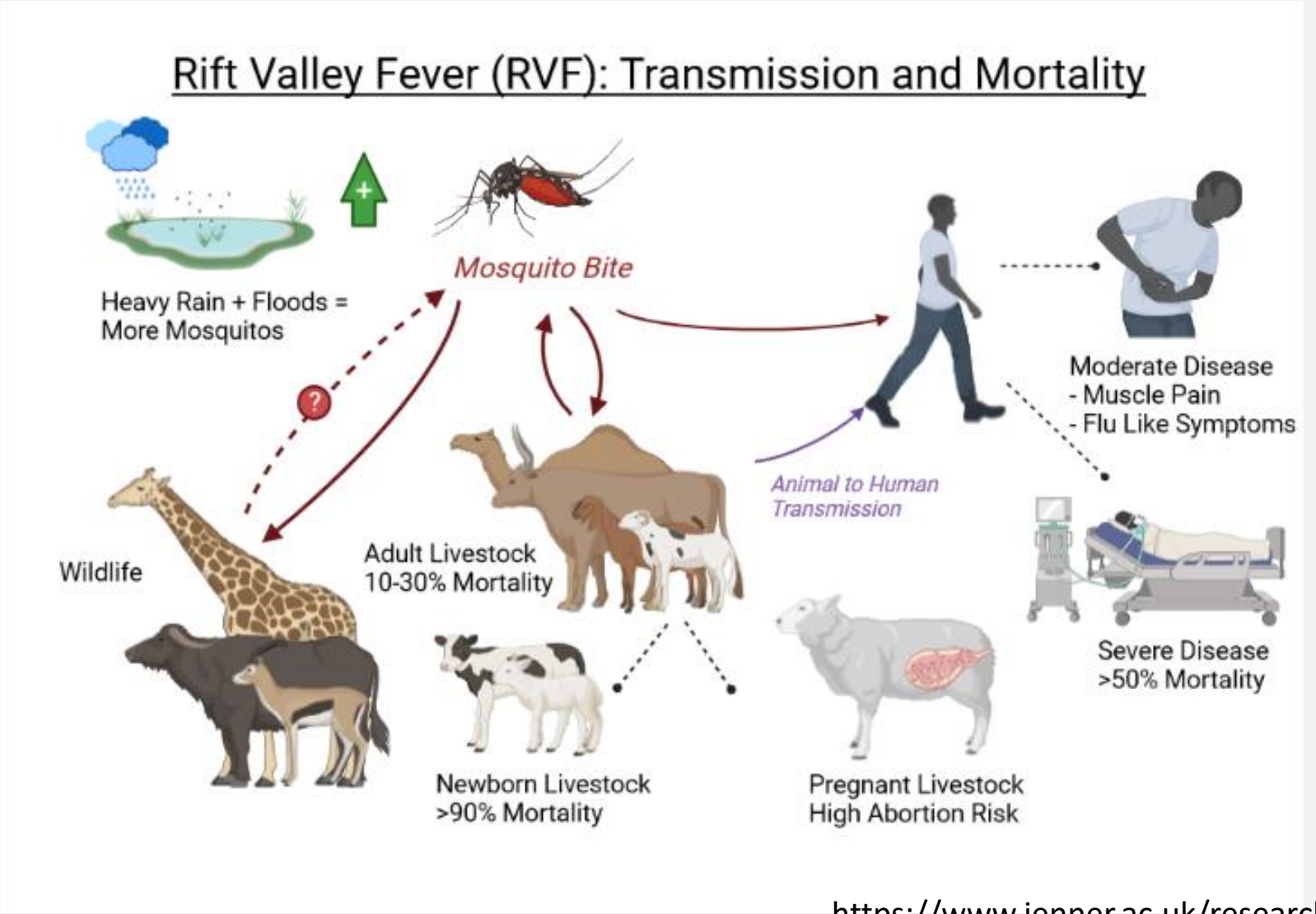
Vial PA, et al. Lancet Infect Dis. 2023

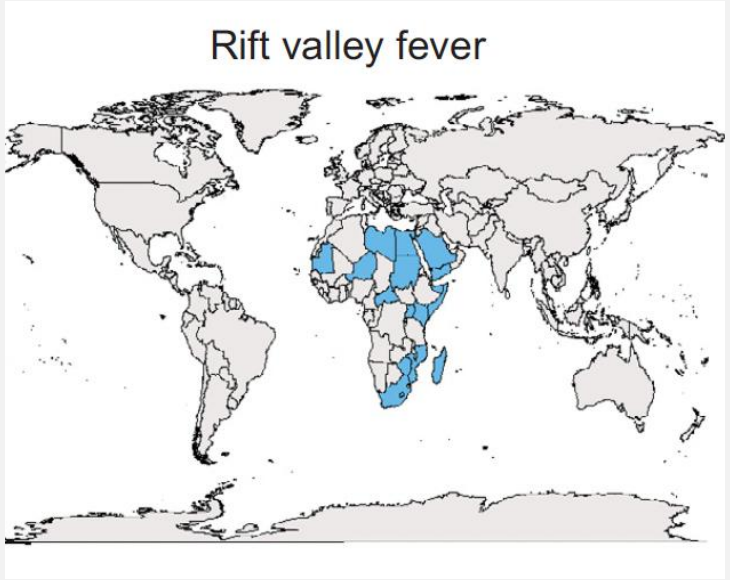
Hantavirus in Humans



Vial PA, et al. Lancet Infect Dis. 2023

Rift Valley Fever





https://www.jenner.ac.uk/research/emerging-pathogens/rift-valley-fever-rvf

Re-purposed Drugs

Ebola

- Favipiravir
- Brinsidofovir
- Remdesivir

CCHF

- Favipiravir
- Remdesivir
- Molnupiravir
- Nirmetralvir
- Monoclonal antibodies

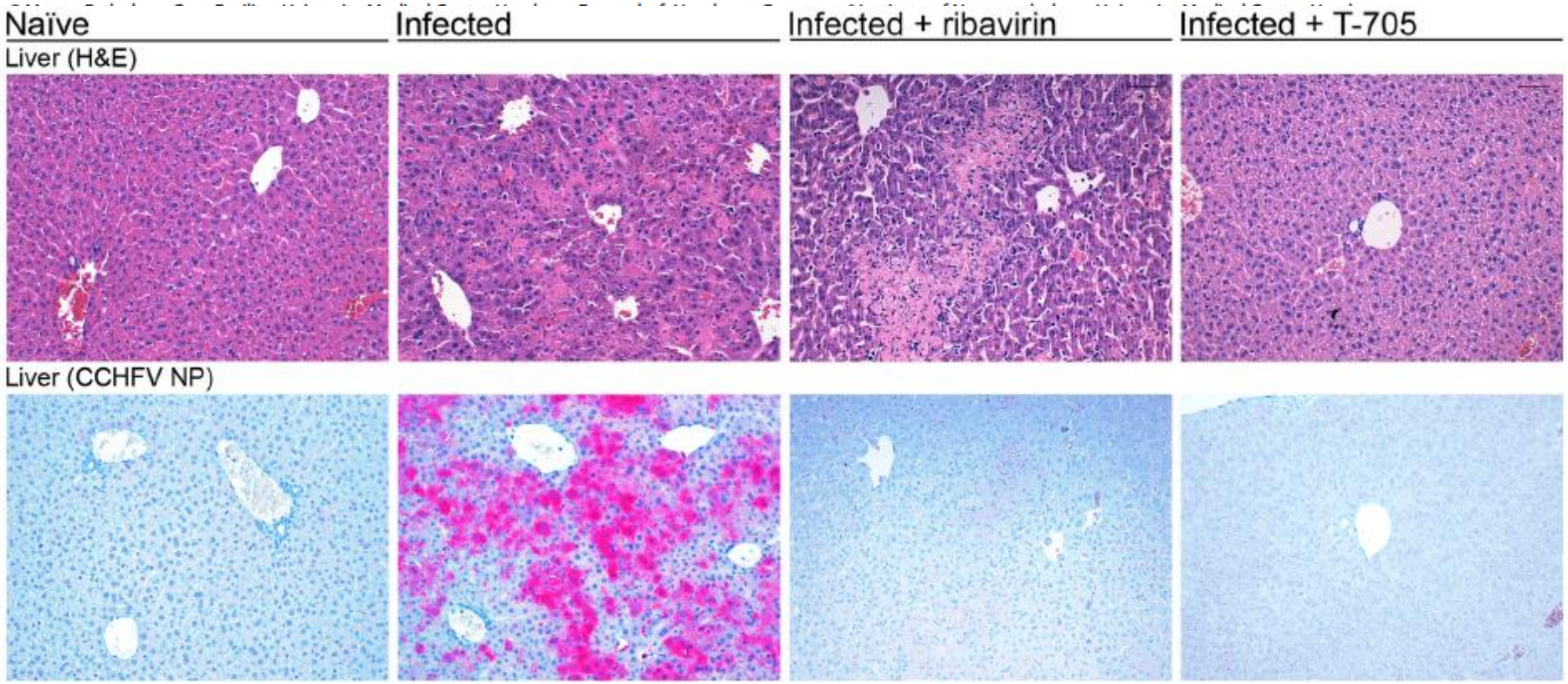
OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Evaluation of Antiviral Efficacy of Ribavirin, Arbidol, and T-705 (Favipiravir) in a Mouse Model for Crimean-Congo Hemorrhagic Fever

Lisa Oestereich[1,2☯], Toni Rieger[1,2☯], Melanie Neumann[3], Christian Bernreuther[4], Maria Lehmann[1,2], Susanne Krasemann[3], Stephanie Wurr[1,2], Petra Emmerich[1,2], Xavier de Lamballerie[5], Stephan Ölschläger[1¶¤], Stephan Günther[1,2¶*]

1 Department of Virology, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Germany, **2** German Centre for Infection Research (DZIF), Hamburg, Germany,



Ostereich L, et al. Plos One, 2014

Research paper

Efficacy of favipiravir (T-705) against Crimean-Congo hemorrhagic fever virus infection in cynomolgus macaques

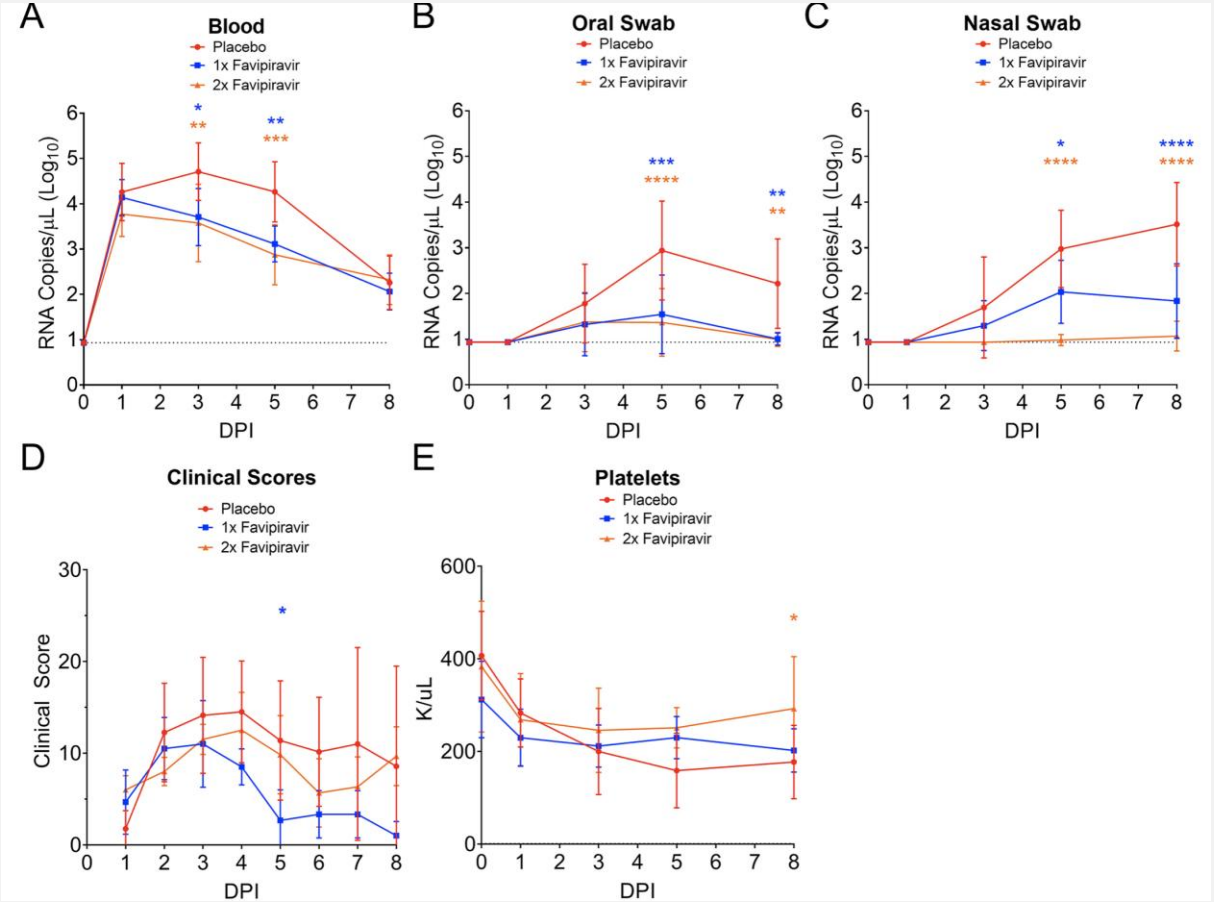
David W. Hawman [a], Elaine Haddock [a], Kimberly Meade-White [a], Glenn Nardone [b], Friederike Feldmann [a], Patrick W. Hanley [a], Jamie Lovaglio [a], Dana Scott [a], Takashi Komeno [c], Nozomi Nakajima [c], Yousuke Furuta [c], Brian B. Gowen [d], Heinz Feldmann [a]

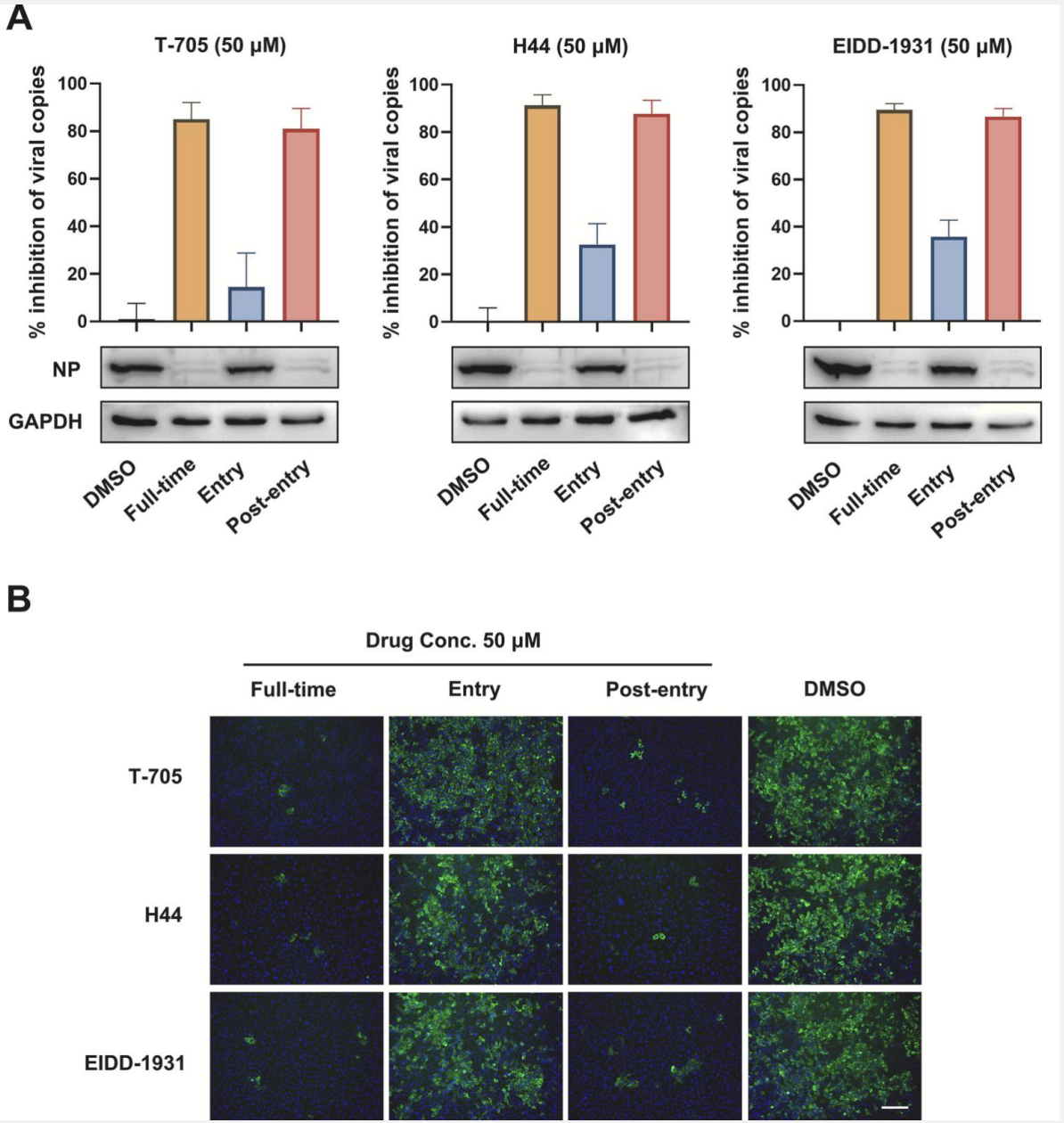
Once- or twice-daily favipiravir suppressed viremia and viral shedding in CCHFV infected macaques.

Viral loads within key tissues of favipiravir-treated animals trended lower than in placebo-treated animals.

Study highlights the importance of the macaque model of CCHF in evaluating antivirals for human CCHF cases.

Antivir Res 2020





ELSEVIER

Antiviral Research

Volume 199, March 2022, 105273

In vitro and *in vivo* efficacy of a novel nucleoside analog H44 against Crimean–Congo hemorrhagic fever virus

Qianran Wang [a, d, 1], Ruiyuan Cao [b, 1], Liushuai Li [a, d], Jia Liu [a], Jingjing Yang [b], Wei Li [b], Linjie Yan [b], Yanming Wang [b], Yunzheng Yan [b], Jiang Li [a], Fei Deng [a], Yiwu Zhou [c], Manli Wang [a] ✉, Wu Zhong [b] ✉, Zhihong Hu [a] ✉

H44: modified Favipiravir
T-705: Favipiravir
EIDD-1931: Remdesivir
EIDD-2081: Molnupiravir

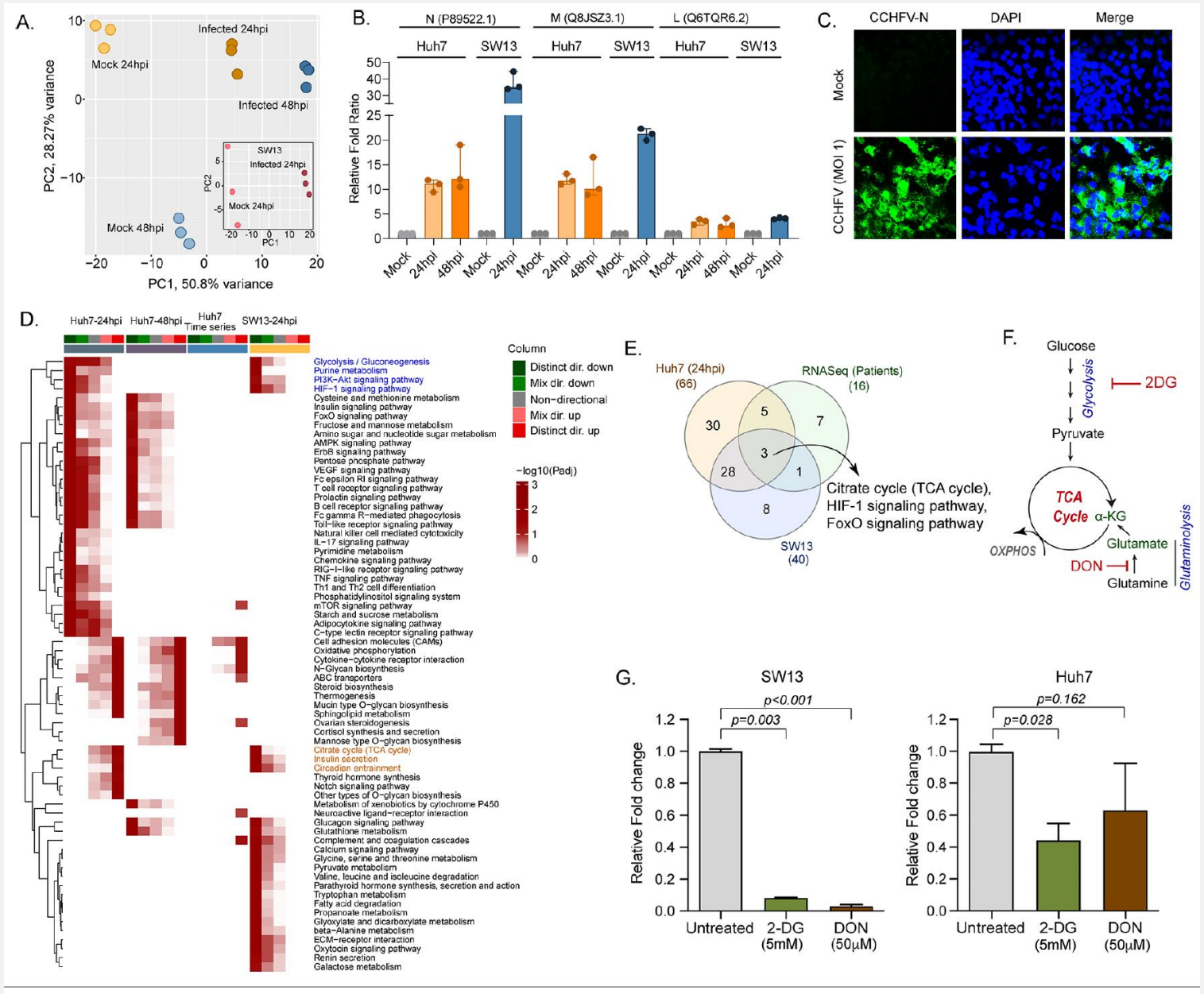
- H44, T-705, and EIDD-1931 inhibited CCHFV infection at the “post-entry” stage.

- EIDD-2081, the EIDD-1931 prodrug, did not protect IFNAR$^{-/-}$ mice from CCHFV infection.

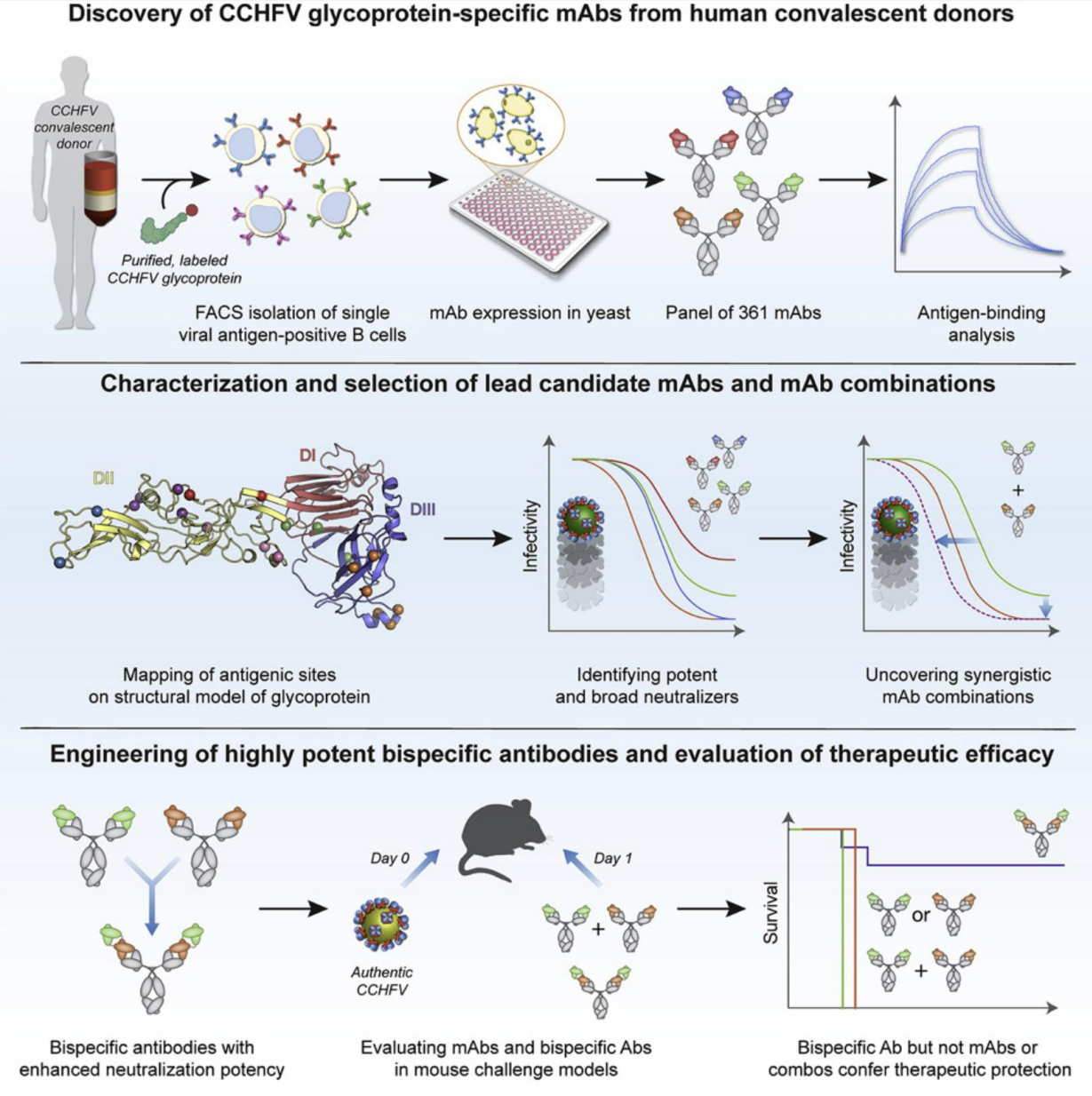
- **H44 protected IFNAR$^{-/-}$ mice from lethal CCHFV challenge as efficiently as T-705.**

Multi-omics insights into host-viral response and pathogenesis in Crimean-Congo hemorrhagic fever viruses for novel therapeutic target

By blocking the two key CCEM pathways, glycolysis and glutaminolysis,
viral replication was inhibited in vitro.
Activation of key interferon stimulating genes during infection suggested the role of type I and II interferon-mediated antiviral mechanisms both at the system level and during progressive replication.



Neogi U, Et al. eLife 2022



Cell

Volume 184, Issue 13, 24 June 2021, Pages 3486-3501.e21

CellPress

Article

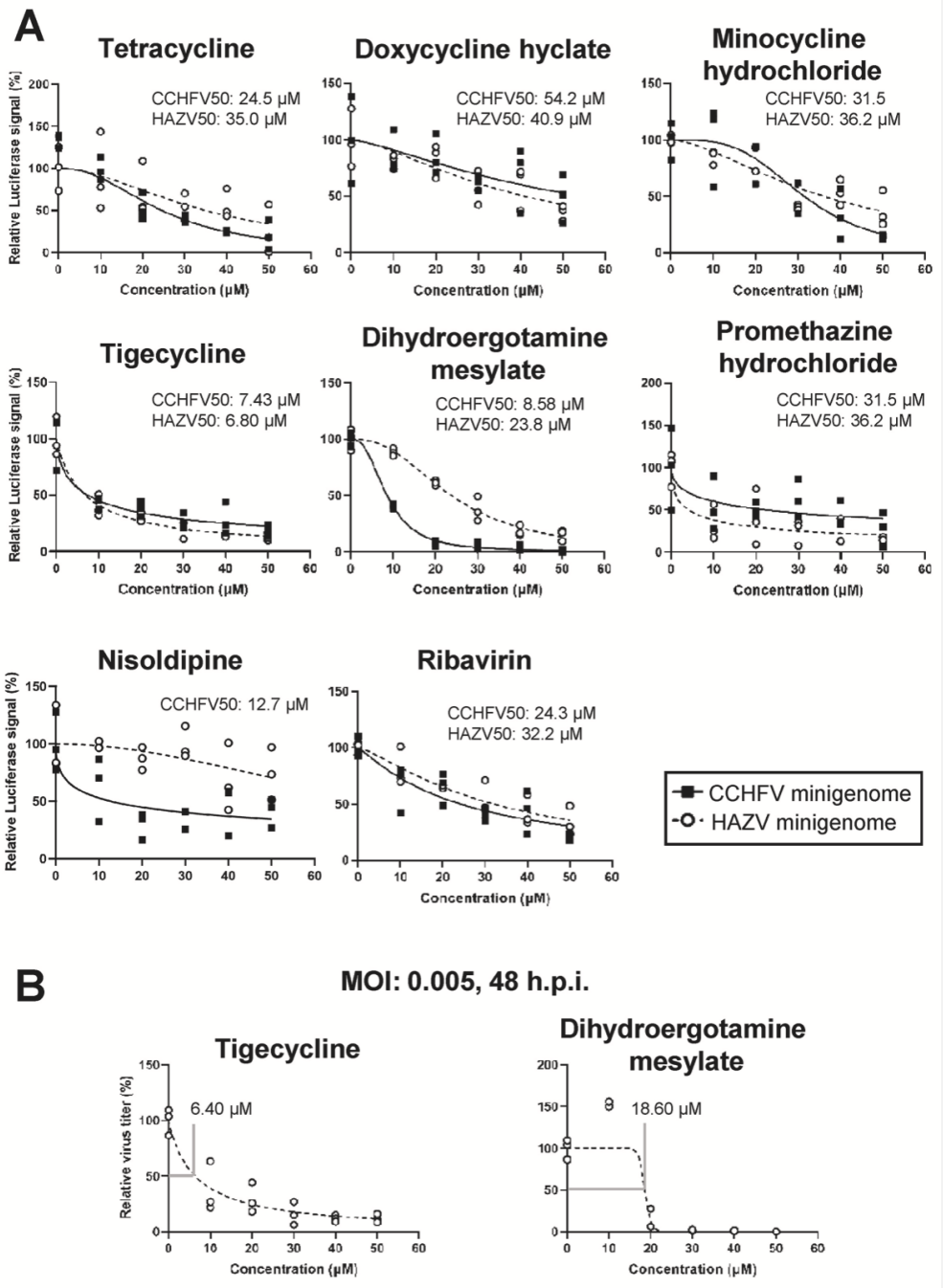
Protective neutralizing antibodies from human survivors of Crimean-Congo hemorrhagic fever

J. Maximilian Fels [1, 15], Daniel P. Maurer [2, 15], Andrew S. Herbert [3, 14, 15], Ariel S. Wirchnianski [1, 4], Olivia Vergnolle [4, 16], Robert W. Cross [5, 6], Dafna M. Abelson [7], Crystal L. Moyer [7], Akaash K. Mishra [8], Jennifer T. Aguilan [12], Ana I. Kuehne [3], Noel T. Pauli [2], Russell R. Bakken [3], Elisabeth K. Nyakatura [4, 16], Jan Hellert [9, 17], Gregory Quevedo [4], Leslie Lobel [10, 18], Stephen Balinandi [11] ... Kartik Chandran [1, 19, 20]

361 monoclonal antibodies against CCHFV glycoproteins isolated from human survivors

- Potent and broad neutralizers targeting six antigenic sites in Gc identified
- Specific combinations of noncompeting antibodies afford synergistic neutralization
- Bispecific antibody combining synergistic antibodies confers therapeutic protection

Cell 2021



Antiviral Research
Volume 200, April 2022, 105276

A screen of FDA-approved drugs with minigenome identified tigecycline as an antiviral targeting nucleoprotein of Crimean-Congo hemorrhagic fever virus

Minato Hirano [a], Yasuteru Sakurai [a, b], Shuzo Urata [a, b], Yohei Kurosaki [a, b], Jiro Yasuda [a, b], Kentaro Yoshii [a, b]

Library screening of FDA-approved compounds identified ten candidate compounds.

tigecycline showed inhibition at 10 μM concentration.

Tigecycline treatment dissociated the interaction between CCHFV N protein and RNA: a new target of antiviral development.

Antivir Res 2022

Ribavirin

Arenaviridae
Lassa Fever
South America HF
Bunyavirales
Hanta
Rift Valley
CCHF

PAPER

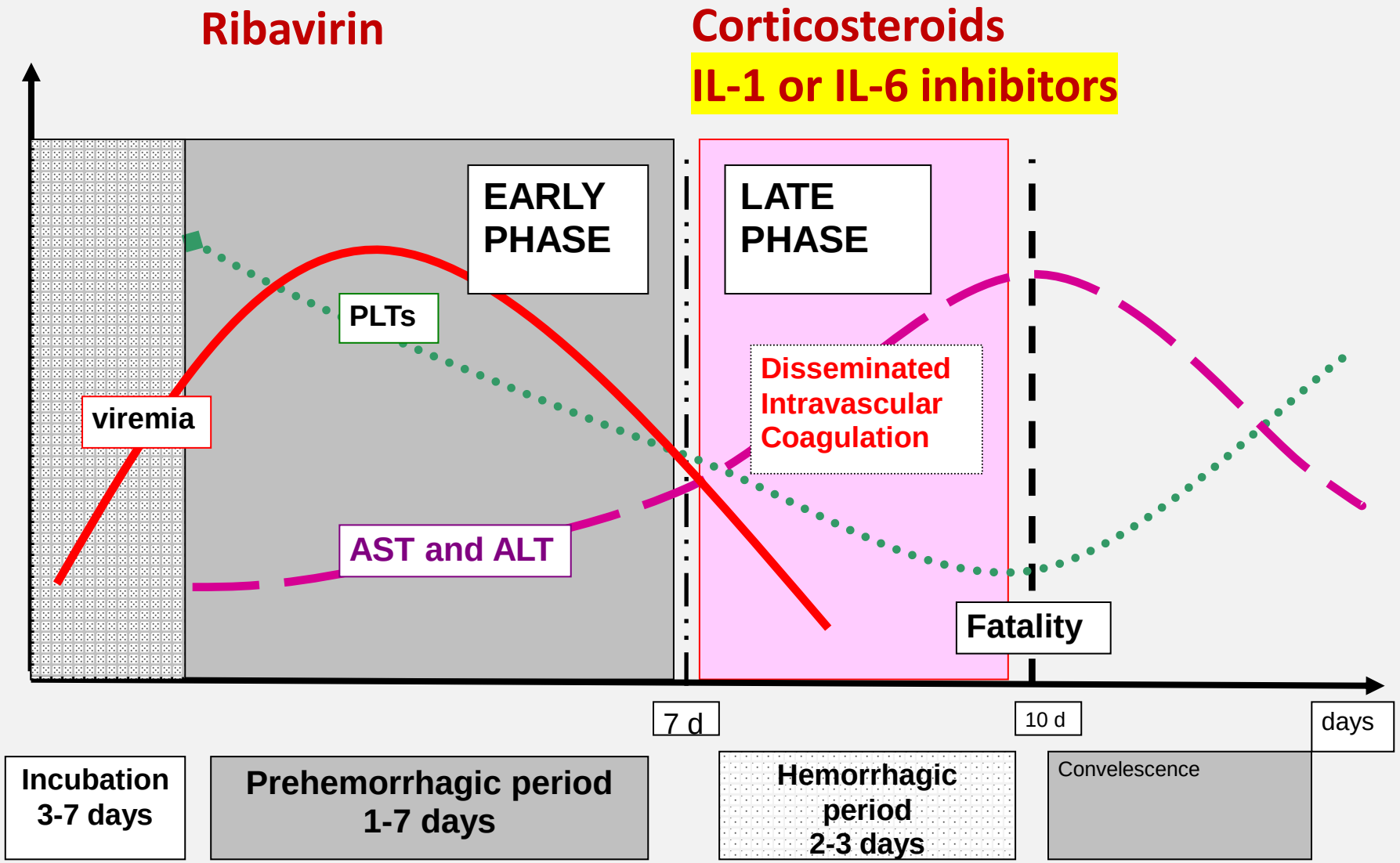
A randomised controlled trial of ribavirin in Crimean Congo haemorrhagic fever: ethical considerations

B Arda,[1] A Aciduman,[1] J C Johnston[2,3]

CONCLUSION

There is universal agreement that placebo-controlled trials should be prohibited in life-threatening conditions if an existing treatment is effective at prolonging or preserving life. The available literature provides convincing evidence that CCHF may be effectively treated with prompt administration of ribavirin. It is the standard of care in several nations, and ratified by the Centers for Disease Control and WHO. Therefore, it would be decidedly unethical to conduct an RCT of ribavirin in patients harbouring this life-threatening disease.

J Med Ethics 2011



Ergonul O. Treatment of CCHF, Antivir Res 2008

Problems in Study Design: What We Learned?

A. Study Design

1. Inclusion criteria
    1. Severity (Confounding by indication)
    2. Number of days from onset of symptoms
        1. Prehemorhagic
        2. Hemorhagic
2. Ineffective application:

    GIS symptoms in oral use (hematemesis)
3. Duration of treatment

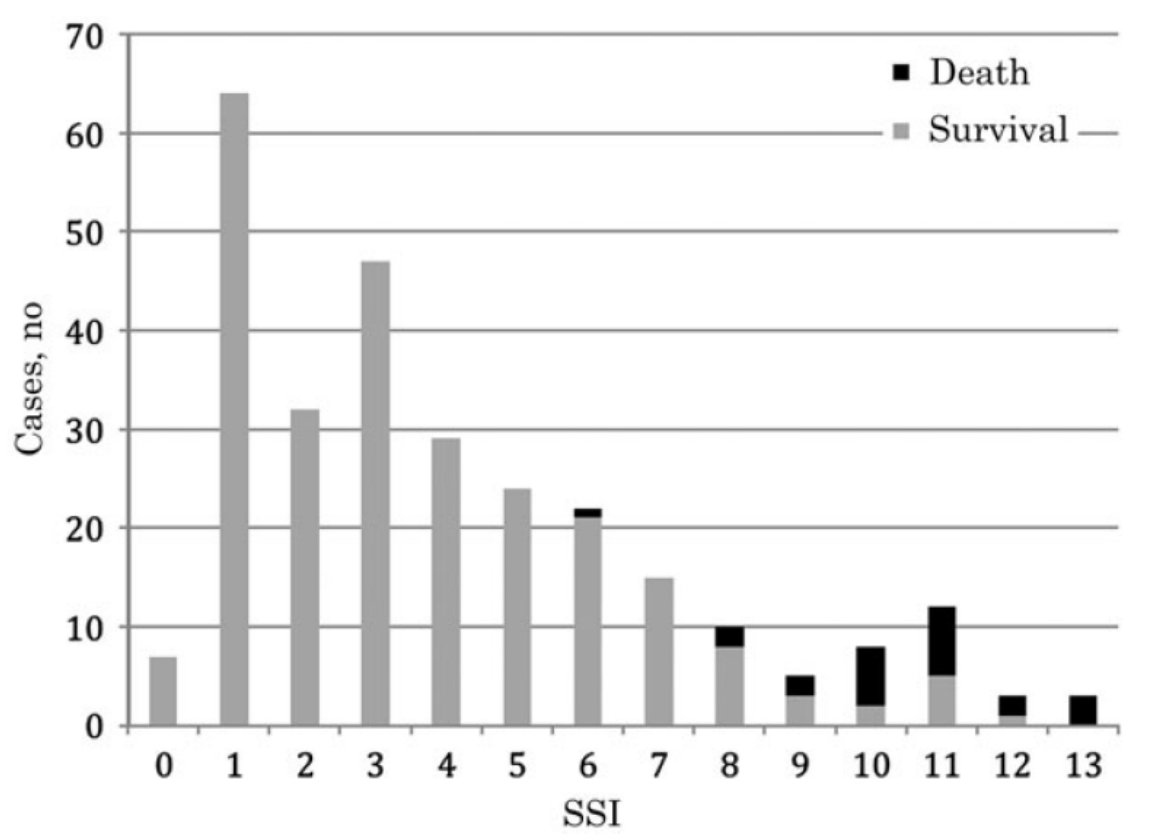
B. Statistical Analysis

1. P value is not everything; sample size is important
2. Meta-analysis: oranges & apples; early vs late

Severity Scoring Index for Crimean-Congo Hemorrhagic Fever and the Impact of Ribavirin and Corticosteroids on Fatality

Başak Dokuzoguz,[1] Aysel Kocagül Celikbas,[1] Şebnem Eren Gök,[1] Nurcan Baykam,[1] Mustafa Necati Eroglu,[1] and Önder Ergönül[2]

[1]Clinical Microbiology and Infectious Diseases Clinic, Ankara Numune Education and Research Hospital, Ankara, and [2]Infectious Diseases and Clinical Microbiology, Koç University, School of Medicine, Istanbul, Turkey



Clin Infect Dis 2013

Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

SSI Parameter	Score
Platelet count, $\times 10^3$ platelets/mm^3	
>150	0
150–50	1
49–20	2
<20	3
aPTT, sec	
≤34	0
35–45	1
46–59	2
>60	3
Fibrinogen level, mg/dL	
≥180	0
179–160	1
159–120	2
<120	3
Bleeding	
No	0
Petechia	1
Ecchymosis	2
Bleeding	3
Somnolence	
No	0
Yes	1

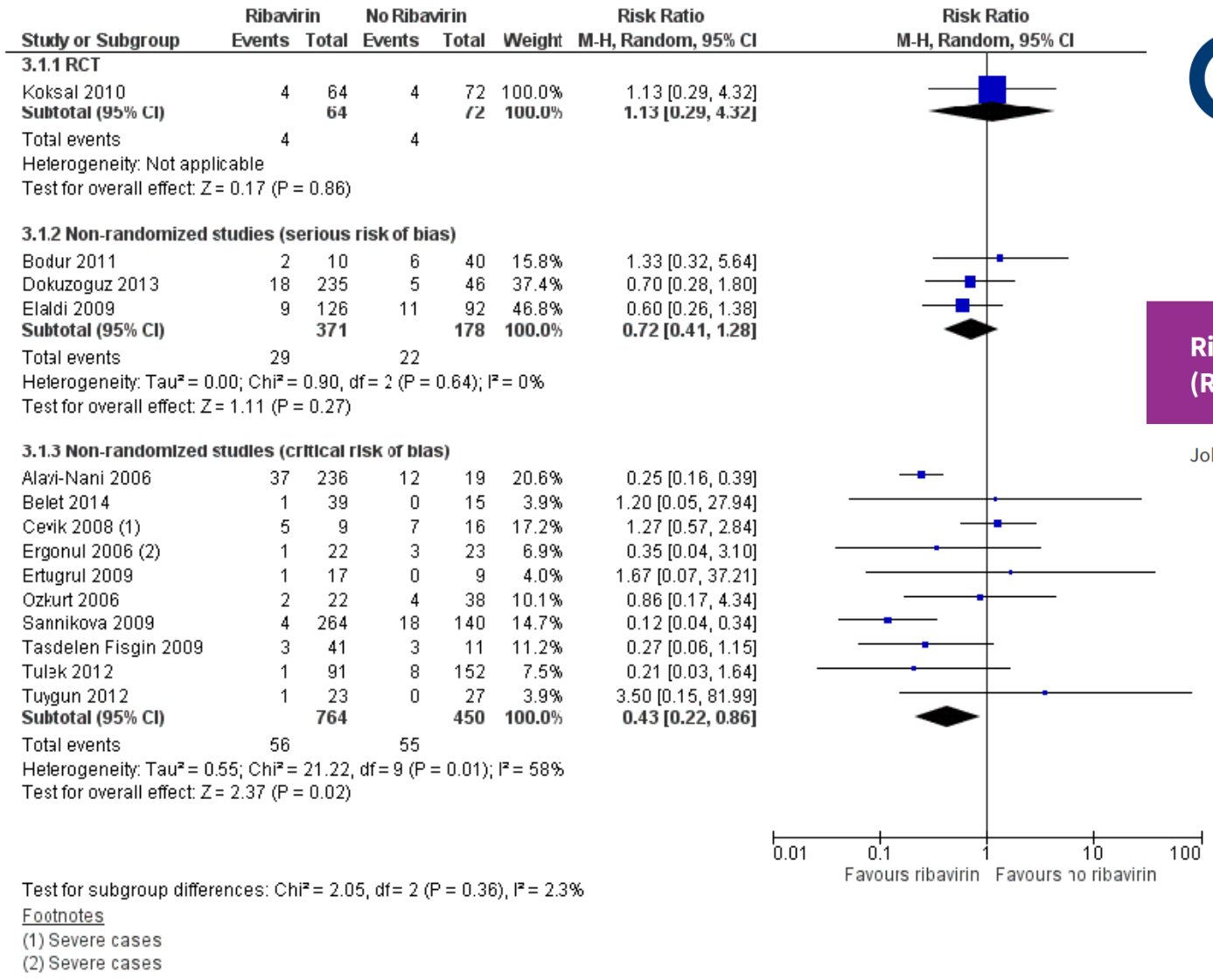
Table 3. Univariate and Adjusted Analysis for Prediction of Death

	Univariate Analysis		Adjusted Analysis	
Factor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
SSI	2.49 (1.82–3.41)	<.001	3.27 (2.09–5.13)	<.001
Ribavirin use	0.68 (.23–1.93)	.470	0.04 (.004–.48)	.01
Corticosteroid use	5.65 (2.31–13.77)	<.001	0.22 (.039–1.27)	.092

Abbreviations: CI, confidence interval; OR, odds ratio; SSI, severity scoring index.

Dokuzoğuz B, et al. Clin Infect Dis 2013

Figure 7. Forest plot of subsidiary descriptive analysis: ribavirin versus no ribavirin, outcome: mortali



Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.3%

Footnotes

(1) Severe cases

(2) Severe cases

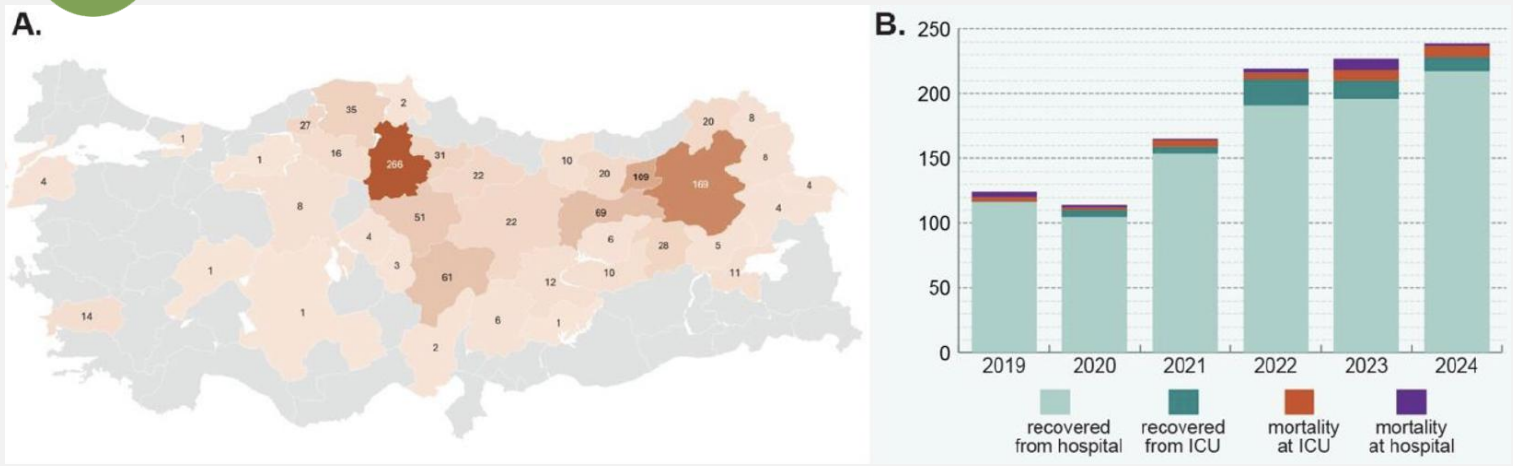
Cochrane Library

Cochrane Database of Systematic Reviews

Ribavirin for treating Crimean Congo haemorrhagic fever (Review)

Johnson S, Henschke N, Maayan N, Mills I, Buckley BS, Kakourou A, Marshall R

Predictors of ICU Admission



- 18 centers, 1103 lab confirmed cases (2019-2024)
- ICU Admission 8%
- Case fatality rate 5.1%

Table 3

Time-dependent Cox regression model evaluating the effect of early ribavirin administration on in-hospital mortality truncated at 30 days

Variables	aHR	95% CI	p value
Being a female	0.611	0.323–1.153	0.128
Age (≥50 y)	2.565	1.241–5.301	**0.011**
Being a farmer	0.604	0.328–1.114	0.106
Diabetes mellitus	2.708	1.278–5.739	**0.009**
Chronic heart disease	1.242	0.481–3.208	0.654
Hypertension	0.951	0.404–2.239	0.909
Ribavirin initiation within ≤96 h	0.214	0.066–0.694	**0.010**

Güllü D, Yigci D, Baykam N, Çelikbaş AK, Yapar D, Akdoğan Ö, Özden K, Sarıkaya Rİ, Hasanoğlu İ, Güner R, Doğan E, Karakeçili F, Alay H, Yüce ZT, Eren EE, Erbay A, Gök ŞE, Kader Ç, Kalın GÜ, Yetişgen A, Özgüler M, Şenol A, Gündağ Ö, Özer MÇ, Soyak F, Tanır B, Alıravcı ID, Çınar G, Öztürk B, Gürbüz E, Özbay BO, Pınarlık F, Kuşkucu M, Ergönül Ö. Key predictors of mortality in Crimean-Congo haemorrhagic fever: a retrospective multicentre cohort study. *Clin Microbiol Infect. 2025*

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Probable Crimean-Congo hemorrhagic fever virus transmission occurred after aerosol-generating medical procedures in Russia: nosocomial cluster

Natalia Yurievna Pshenichnaya *, Svetlana Alexeevna Nenadskaya

Rostov State Medical University, Rostov-on-Don, Russia

This case of airborne transmission of CCHF demonstrates that during performance of any AGMPs for any CCHF patient, airborne precautions should always be added to standard precautions (particulate respirator protective to N95 or equivalent standard, eye protection, single airborne precaution room or well-ventilated setting, etc.) according to WHO guidelines[16] for all HCWs who are in a patient's room. Access to any room where the aerosol-generating procedures are performed should be extremely limited.

IJID, 2015

Jpn. J. Infect. Dis., 64, 439-443, 2011

Short Communication

Prompt Administration of Crimean-Congo Hemorrhagic Fever (CCHF) Virus Hyperimmunoglobulin in Patients Diagnosed with CCHF and Viral Load Monitorization by Reverse Transcriptase-PCR

Ayhan Kubar*, Mustafa Haciomeroglu[1], Aykut Ozkul[2], Umit Bagriacik[3], Esragul Akinci[4], Kenan Sener, and Hurrem Bodur[4]

Gulhane Military School of Medicine, Ankara; [1]Refik Saydam Hygiene Center, Ankara; [2]Ankara University, Ankara; [3]Gazi University, Ankara; and [4]Ankara Numune Training and Research Hospital, Ankara, Turkey

No difference in fatality

Specific Immunoglobulin
Bulgarian Experience

Passive simultaneous transfer of two different specific immunoglobulin preparations,

“CCHF-bulin” (for intramuscular use)
“CCHF-venin” (for intravenous use),

prepared from the plasma of CCHF survivor donors; applied among 7 patients
(Vassilenko et al., 1990).

Poor data, recently summarized;

Keshtar Jahromi M, et al. Antiviral Res 2011

Ebola Treatment

Atoltivimab, maftivimab, and odesivimab (REGN-EB3)

October 2020, the FDA approved the triple-monoclonal antibody (mAb). This combination of three mAbs targets three nonoverlapping epitopes on the *Zaire Ebolavirus* virus surface glycoprotein, providing potent virus neutralization. Trade name: Inmazeb

Ansumivab(mAb114)

December 2020, the FDA approved the monoclonal antibody ansuvimab (sold as Ebanga). This mAb was isolated from a survivor of Ebola virus disease and neutralizes the virus.

Ebola Vaccines

ERVEBO® (Ebola Zaire Vaccine,, rVSVΔG-ZEBOV-GP or rVSV-ZEBOV) is approved by the FDA

live, attenuated recombinant vesicular stomatitis virus (rVSV) vaccine manufactured by Merck.

Clinical trials have shown that the vaccine elicits rapid antibody response in 14 days after a single dose.

The Ad26.ZEBOV/MVA-BN-Filo vaccination strategy

The Ad26.ZEBOV/MVA-BN-Filo vaccination strategy uses two different vaccines separated by eight weeks.

The European Medicines Agency granted marketing authorization for the individual components of the vaccine series (recombinant adenovirus AD26.ZEBOV; sold as Zabdeno) and modified vaccinia Ankara (MVA-BN-Filo; sold as Mvabea) for individuals aged one year and older.

Ebola outbreak in the DRC: why is it so deadly?

"It's not identical to previous strains that have been identified, which strongly suggests that it's a new spillover event,"

(Peter Horby at the Pandemic Sciences Institute at the University of Oxford, UK)

Nature 25 Sept 2025

Dengue Vaccines

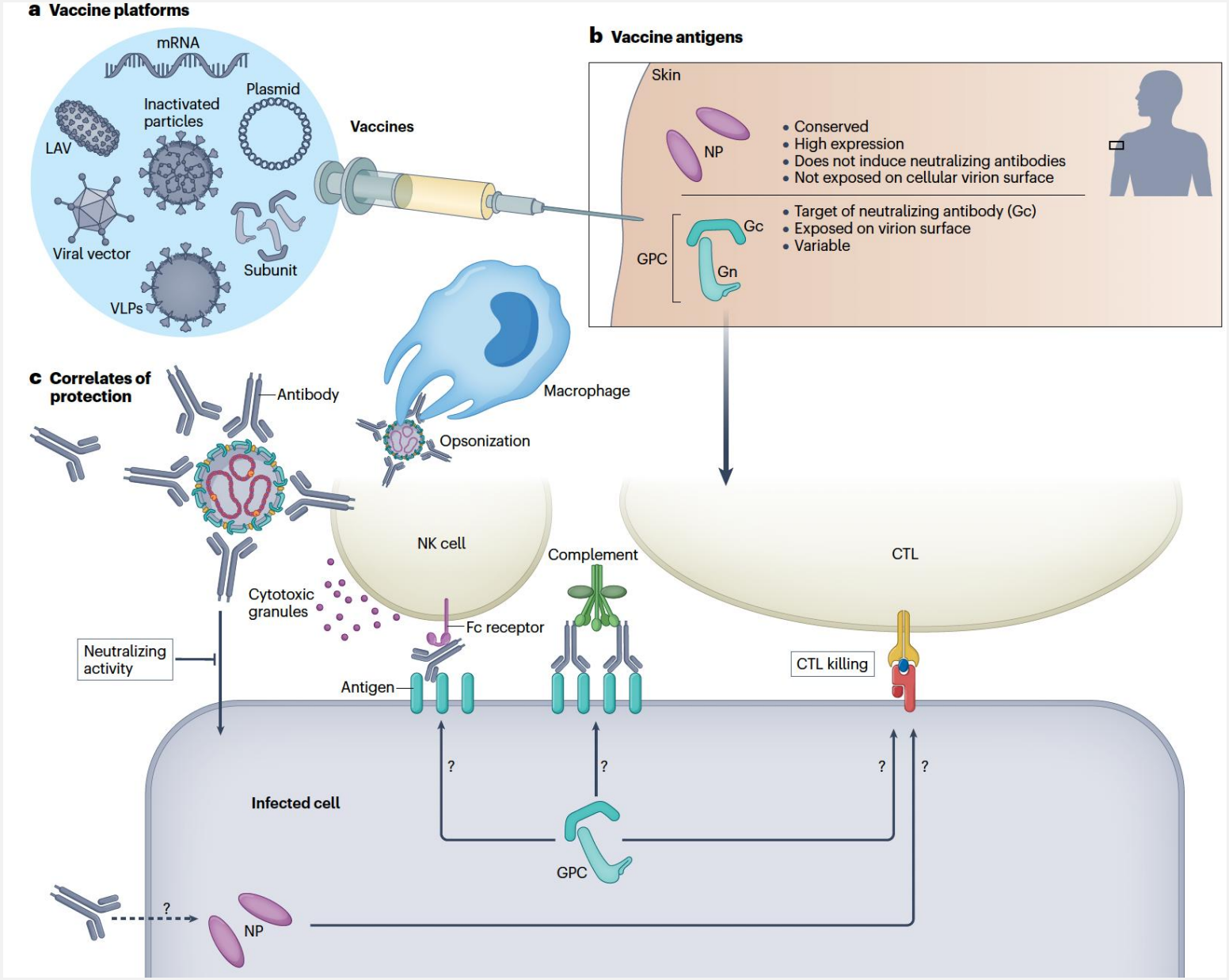
Dengvaxia® (Sanofi) was approved for use in patients aged 9 years and above in Mexico, the Philippines, and Brazil in 2015 and in El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand, and Singapore in 2016; it was also approved for use in Europe in 2018.

QDENGA® (Takeda) was approved for use in Europe, Brazil, Argentina, Indonesia, and Thailand in 2022.

Individuals who were vaccinated and then acquired a natural dengue infection had higher risk of severe disease.

WHO advises pre-vaccination screening be conducted, and to only vaccinate individuals who have evidence of a previous natural dengue infection.

Vaccine Studies for CCHF



Hawman DW & Feldmann H.
Nature Rev Microbiol

Summary

In diagnosis, nucleic acid based technology is the most sensitive diagnostic method.

The determination of IgM/IgG antibodies is a reasonable alternative, but cross-reactivity can be a problem in the case of flaviviruses.

Licensed vaccines are available for Yellow Fever, Dengue, and Ebola

Therapy is predominantly supportive.

- Corticosteoids and IL inhibitors are in use
- Monoclonal antibodies
- New antivirals

To ensure that preventive measures can be introduced to control possible outbreaks, the timely detection of these viruses is very important.

- Widely used rapid diagnostic tests are needed.

Thank you

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https://kuiscid.ku.edu.tr