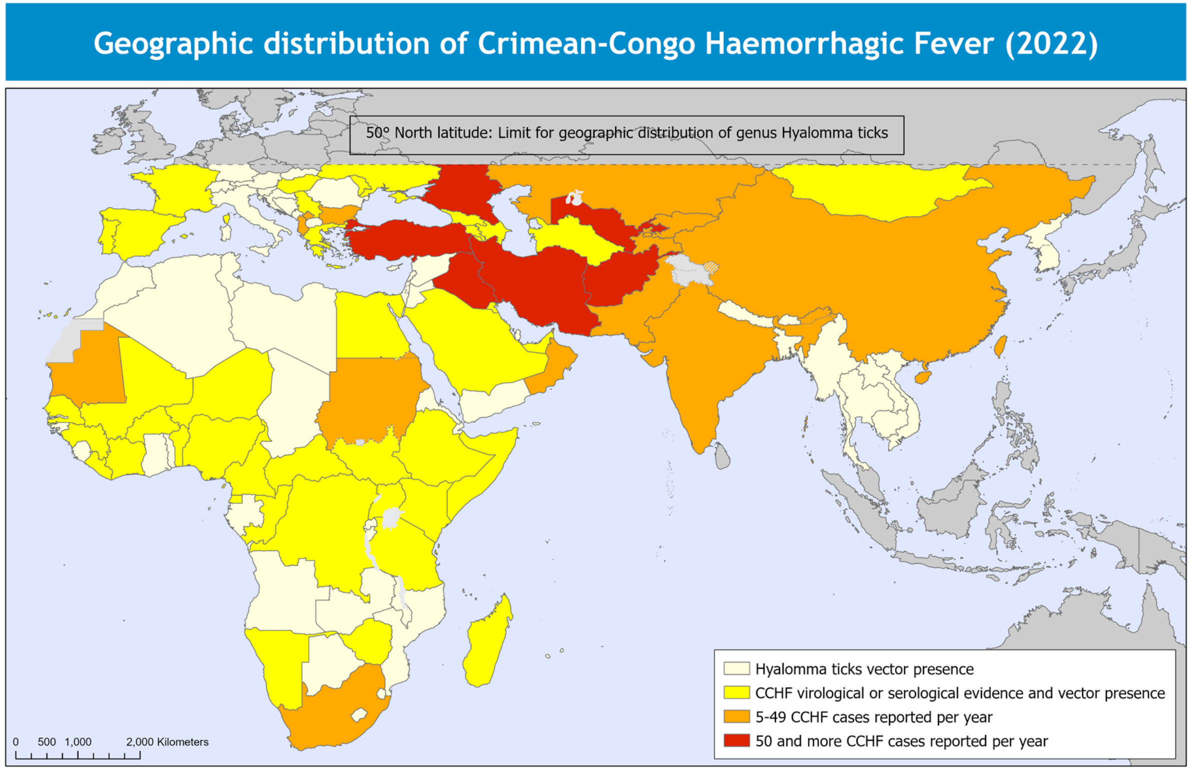
Funded by the European Union

CCHF STATUS IN BALKANS & BLACK SEA

Aykut Ozkul, DVM, PhD

Crimean Congo Hemorrhagic Fever

- An endemic disease in Africa, Asia, the Balkans and Russia.
- Several cases and virus detection in Western Europe.
- An arbovirus caused fatal disease in humans.
- Animals can get infected but no disease is reported.
- Classified in WHO's public health priority list, since the absence of therapeutic agents and licensed vaccine(s).



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Data Source: WHO - Viral Haemorrhagic Fevers (VHF)
Map Production: Jewgeni Bader, EYE Secretariat
Map Creation Date: 01 September 2022

World Health Organization

Realities!

TABLE 1 | WHO Blueprint Diseases and their principal mammalian reservoirs.

WHO Blueprint Disease (20)	Mammalian reservoir(s)
COVID-19 (recently added)	Fruit bats (speculative) (21), pangolin (speculative) (22)
Crimean-Congo Haemorrhagic Fever (CCHF)	Cattle (23), goats (24), sheep (23), camels (25), horses (26), donkeys (27)
Ebola virus disease	Fruit bats (28)
Marburg virus disease	Fruit bats (29)
Lassa fever	Multimammate mouse (*Mastomys natalensis*) (30)
MERS coronavirus disease	Bats, alpacas, camels (31)
SARS coronavirus disease	Horseshoe bats, palm civets (32)
Nipah virus disease	Flying foxes (33), pigs (33)
Rift Valley Fever	Sheep, goats, cattle (34)
Zika	Rhesus monkeys, sheep, goats, cows, horses, bats, carabaos, orangutans (35)
Disease X (future disease outbreak of unknown origin)	Unknown

Gilbride et al. 2021

- ✓ 3 billion people at risk
- ✓ Estimated 500 deaths each year

Endemic in Africa, Balkans, Middle East and Asia

- ✓ Estimated 10,000 to 15,000 Crimean-Congo Haemorrhagic Fever infections each year

Epidemiology

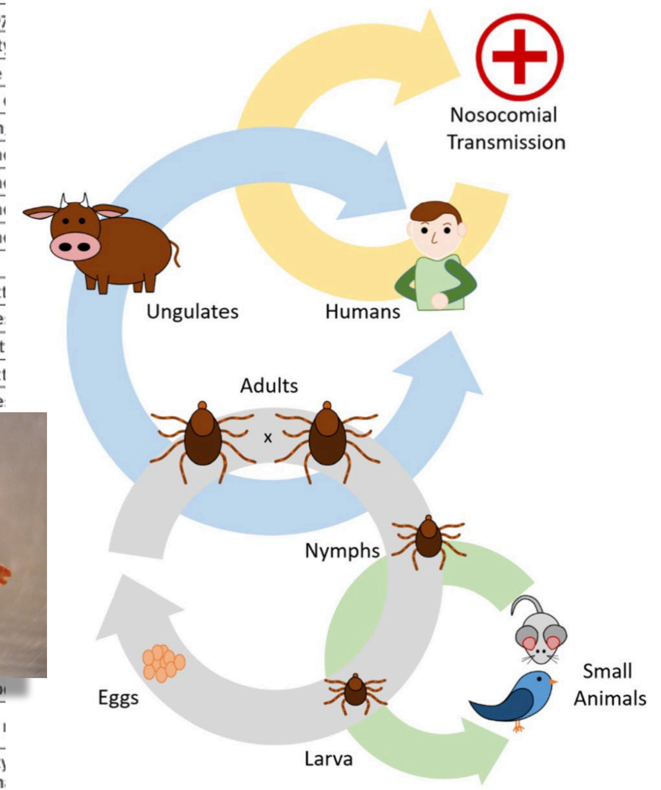
Affecting factors

- ➢ Abiotic
  - ✓ Climate
  - ✓ Humidity
  - ✓ Vegetation
- ➢ Biotic
  - ✓ Vector
    - • Ticks
  - ✓ Host
    - • Human (Accidental)
    - • Animals (natural reservoir)

Table

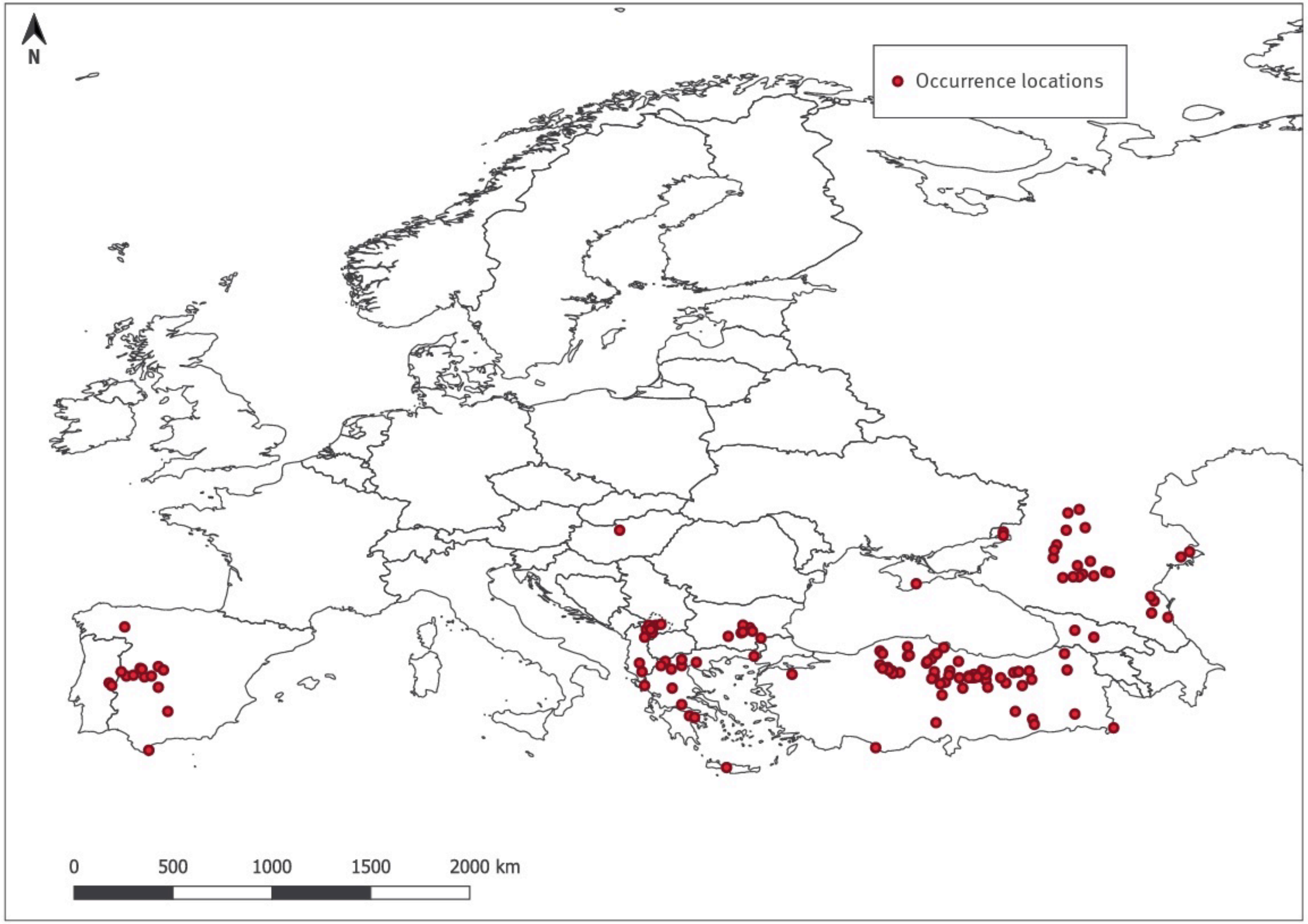
Variables collated for use in the spatial model on Crimean-Congo haemorrhagic fever occurrence in 52 countries and territories within the European Region, 2012–2022

Definition	Code	Source
Annual mean temperature	WC_bio1	WorldClim [27]
Mean diurnal range (mean of monthly (max temperature – min temperature))	WC_bio2	WorldClim [27]
Isothermality (bio2/bio7		WorldClim [27]
Temperature seasonality		WorldClim [27]
Max temperature of the		WorldClim [27]
Min temperature of the		WorldClim [27]
Temperature annual ran		WorldClim [27]
Mean temperature of th		WorldClim [27]
Mean temperature of th		WorldClim [27]
Mean temperature of th		WorldClim [27]
Mean temperature of th		WorldClim [27]
Annual precipitation		WorldClim [27]
Precipitation of the wett		WorldClim [27]
Precipitation of the drie		WorldClim [27]
Precipitation seasonalit		WorldClim [27]
Precipitation of the wett		WorldClim [27]
Precipitation of the drie		WorldClim [27]
		WorldClim [27]
		WorldClim [27]
	thwaite	ENVIREM dataset [28]
	eIndex	ENVIREM dataset [28]
	ity	ENVIREM dataset [28]
	ays0	ENVIREM dataset [28]
5°C multiplied by numb	ays5	ENVIREM dataset [28]
Count of the number of	emp10	ENVIREM dataset [28]
Compensated thermicity of the coldest month, m compensations for better comparability across the globe	dex	ENVIREM dataset [28]
SAGA GIS topographic wetness index	ER_topoWet	ENVIREM dataset [28]



Disease Occurrence in MLS Geography

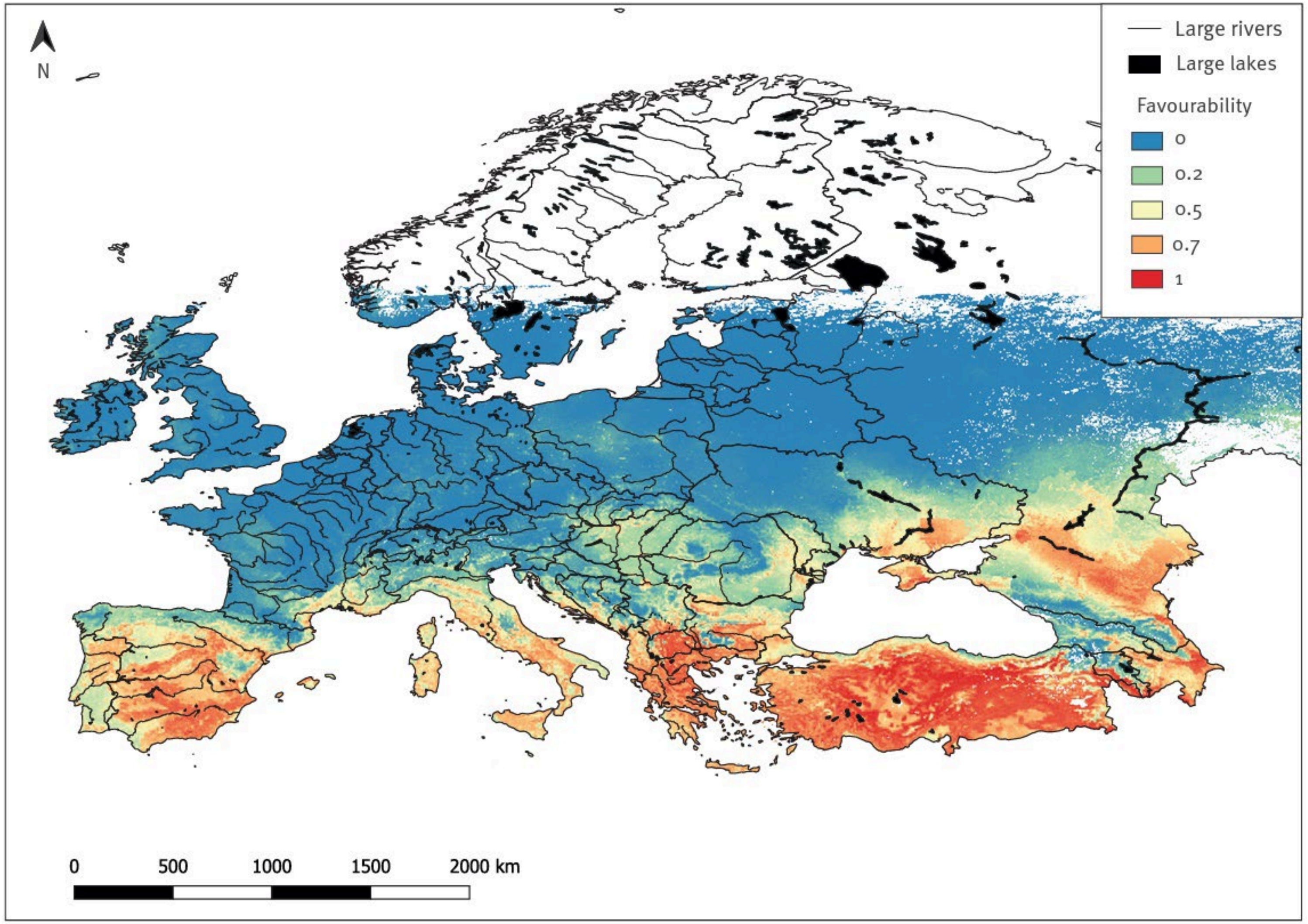
Occurrence locations of Crimean-Congo hemorrhagic fever cases in humans and Crimean-Congo hemorrhagic fever virus isolates from ticks, European Region, 2012–2022 (n = 141 before spatial thinning)



Fanelli et al, 2023

Epidemiological Intelligence from Open Sources (EIOS)

Favorability predictions for Crimean-Congo Hemorrhagic Fever occurrence, European Region below ~60°North latitude, 2012–2022



Fanelli et al, 2023

Russian Speaking Countries

Review of the incidence of Crimean-Congo hemorrhagic fever for 16 years in 2005-2020 based on ProMED-RUS reports

N. Pshenichnaya, V. Melnik, L. Ermakova and B. Aslanov

International Journal of Infectious Diseases, 2022-03-01, Volume 116, Pages S127-S127, Copyright © 2021

- The aim of the study was to assess the epidemiology of CCHF in the territory of the FSU (in 6 territories) over the past 16 years based on data from ProMED-RUS.
- reviewed 289 ProMED-RUS reports on CCHF published in the period from 2005 to 2020 inclusive.
- According to ProMED-RUS, during 2005-2020, cases of CCHF were registered in Russia (Rostov, Stavropol, Volgograd, Astrakhan regions, the Republics of Kalmykia, Kabardino-Balkaria, Dagestan, Ingushetia), Kazakhstan, Georgia, Kyrgyzstan, Uzbekistan, and Tajikistan.
- In Russia, during this period 1,919 cases of the disease were registered, including 43 deaths (CFR 2.8%).

Russian Speaking Countries

- The first cases of CCHF in Georgia was in 2009. In 2010-2012, sporadic cases of the disease were registered in this country, and since 2013, more than 10 cases of CCHF are diagnosed annually. In 2020, only 9 cases of CCHF were registered in Georgia, and 1 ended fatally (CFR- 30%).

- The cases of CCHF in the South of Kazakhstan (Zhambyl, Kyzylorda, and Turkestan regions) since 2008. The largest number of cases (26) registered in 2009. Later, from 6 to 20 cases of the disease with a CFR of 20- 30% are registered annually.

- The ProMED-RUS service first reported 5 cases of CCHF in Tajikistan in 2009, 3 of them were fatal (CFR 60%). Afterward, there was no information about cases of CCHF.

- In 2019, ProMED-mail first reported a case of CCHF infection in Kyrgyzstan, imported to Kazakhstan. In 2020, no cases of CCHF were registered in this country

- first reported 13 cases of CCHF in Uzbekistan in 2013-2015, 10 of them were a fatal, and 2 - in 2017.

https://doi.org/10.1016/j.ijid.2021.12.301

Russia

- Samples collected between 2007 and 2017
- 500 serum and 103 tick pools
- Segment-based partial and genome length phylogenetic analysis
- Lineage Europe 1 (596 samples)
  - Va, Vb, Vc and Vd
- Lineage Europe 3 (6 samples)
- Lineage Africa 3 (1 sample)

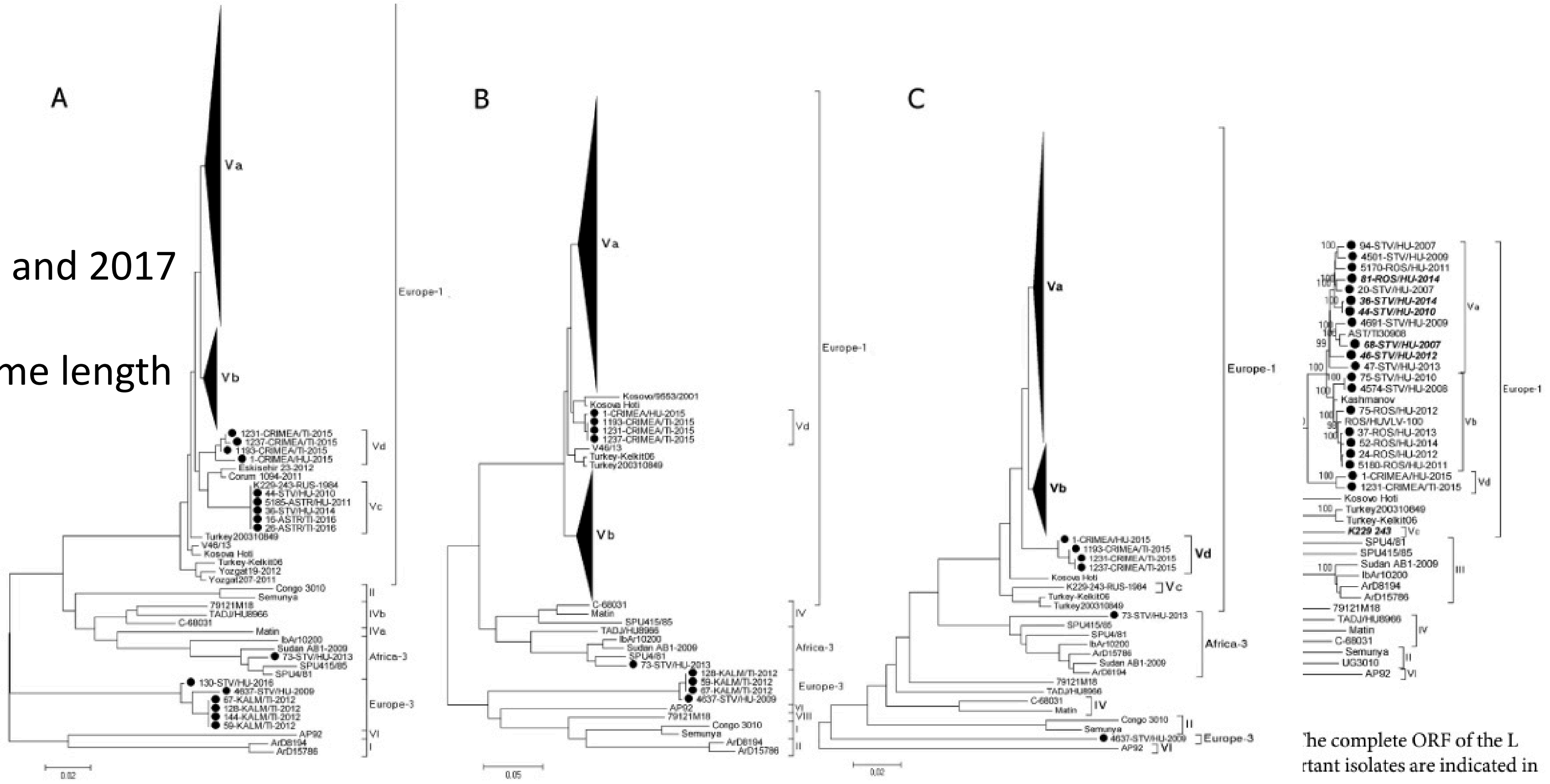


Fig 1. Neighbor-joining phylogenetic trees based on: A: A 538 bp fragment of the S segment; B: A 435 bp fragment of the M segment; C: A 437 bp fragment of L segment; sequences from the present study are marked.

https://doi.org/10.1371/journal.pone.0266177.g001

Occurrence of Europe 1 Variants -- Disease Severity vs Variants

Table 2. Compari

Genetic li	cases (abs.)
Europe-1	8
Va-Va-Va genetic	2
Vb-Vb-Vb geneti	0
Vd-Vd-Vd geneti	
Va-Vb-Va genetic	3
Other reassortme	2
Europe-3	
Africa-3	

https://doi.org/10.13

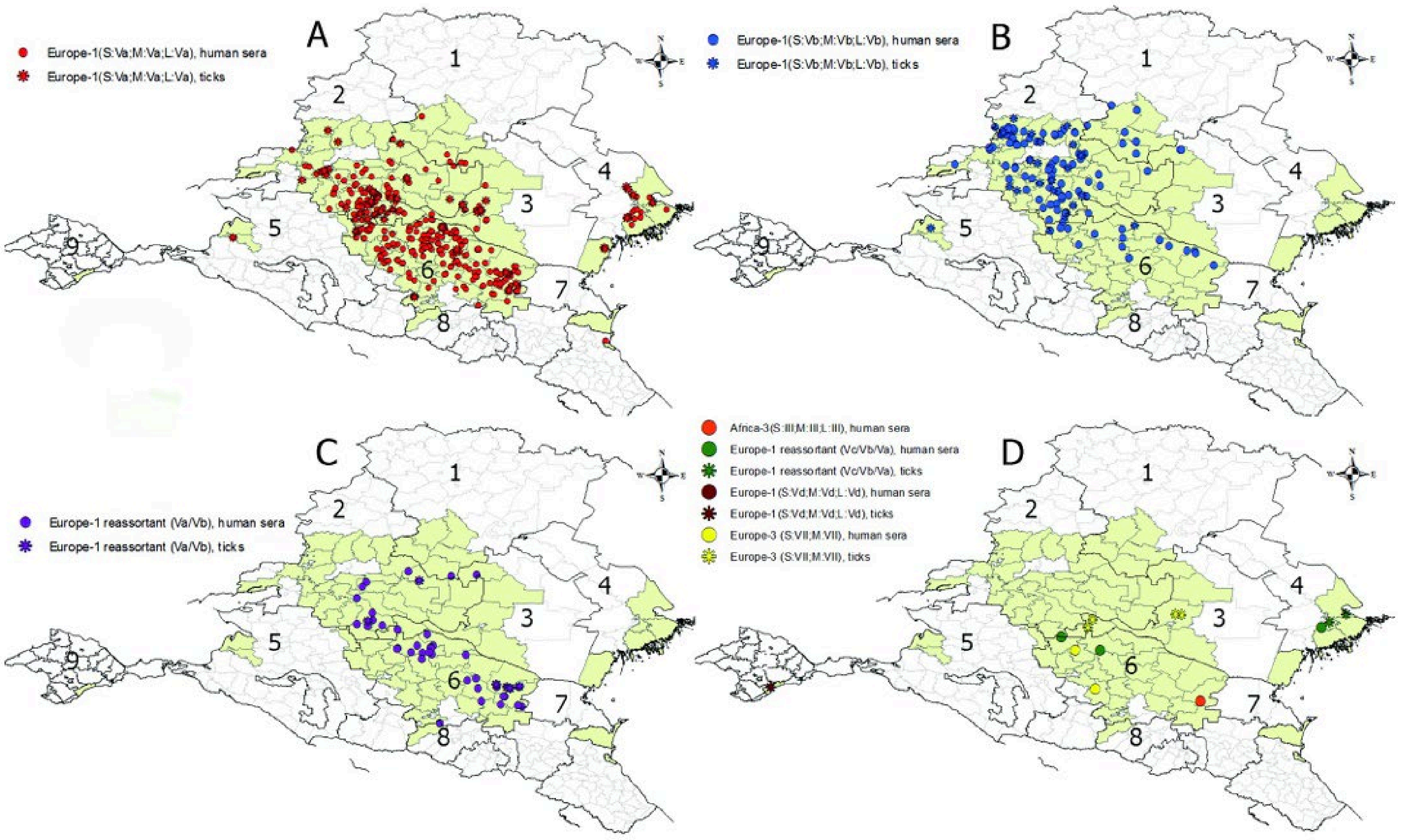


Fig 3. Geographic distribution of genetic variants of CCHFV in Russia. A: Europe 1, subtype Va, B: Europe 1, subtype Vb, C: Europe 1, reassortant variants between subtypes Va and Vb, D: Europe 1, subtype Vd, Europe 1, reassortant variants between subtypes Va, Vb and Vc, Africa 3, Europe 3. 1: Volgograd region, 2: Rostov region, 3: Republic of Kalmykia; 4: Astrakhan region, 5: Kransnodar territory, 6: Stavropol territory, 7: Republic of Dagestan, 8- Kabardino-Balkaria Republic; 9- Republic of Crimea. The districts where CCHF patient sera and ticks were collected are indicated in green. Esri reserves the right to grant permission for any other use of the Image.

https://doi.org/10.1371/journal.pone.0266177.g003

Turkiye-1

➢ Anatolia

- Adult ticks were collected from the animals (cows, sheep, dogs, and cats) 5 distinct regions. A total of 901 ticks (in 158 pools)
- Rhipicephalus sanguineus complex was the most abundant species (44.1%), followed by Rhipicephalus bursa (38.3%), Haemaphysalis parva (7.2%), and others.
- Crimean– Congo hemorrhagic fever virus (CCHFV) lineage Europe 2 sequences were detected in R. bursa in five (3.2%) of the pools

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Several Tick-Borne Pathogenic Viruses in Circulation in Anatolia, Turkey

Ender Dinçer,[1] Mehmet Özkan Timurkan,[2] Bekir Oğuz,[3] İsmail Şahindokuyucu,[4] Adem Şahan,[5] Mustafa Ekinci,[6] Ceylan Polat,[7] and Koray Ergünay[7]

Ticks and Tick-borne Diseases 12 (2021) 101622

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

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

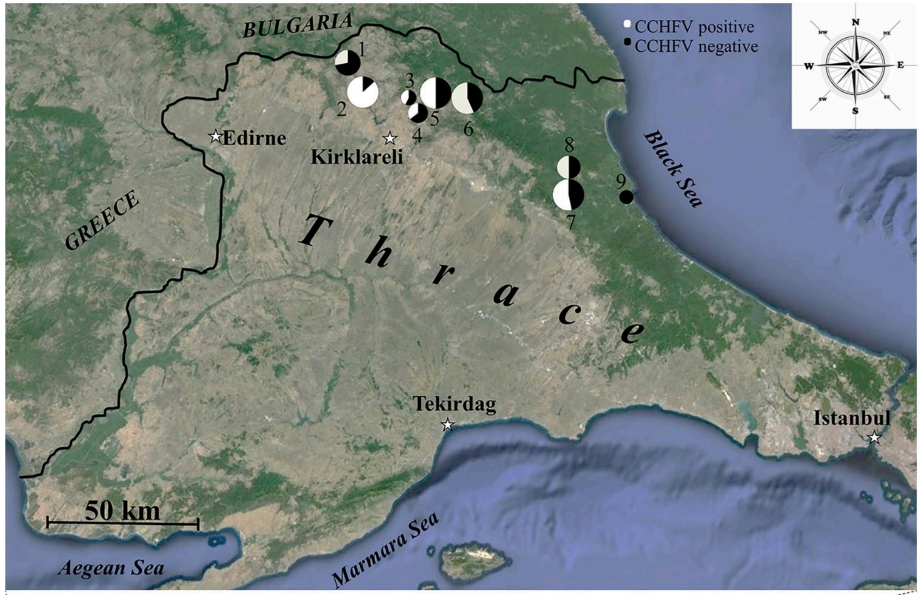
ELSEVIER

Original article

High prevalence and different genotypes of Crimean-Congo hemorrhagic fever virus genome in questing unfed adult *Hyalomma marginatum* in Thrace, Turkey

Gurkan Akyildiz[a], Dennis Bente[b], Aysen Gargili Keles[c], Zati Vatansever[d], Sirri Kar[a,b,*]

- Thrace
- Hyalomma marginatum
- 9 villages 24 sites and 200 ticks were collected.
- 51% was CCHFV positive and belonged to Clade VI.



Viremia in Human and Infected Ticks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Antiviral Research

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

Invited Review

Vector-borne viruses in Turkey: A systematic review and bibliography

Koray Ergünay[a,*], Ceylan Polat[a], Aykut Özkul[b]

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[b] Ankara University, Faculty of Veterinary Medicine, Department of Virology, Ankara, 06110, Turkey

Virus detection in humans

Virus detection in ticks

Greece

- A CCHFV strain (AP92) was isolated from Rhipichepahlus bursa ticks collected from goats in Northern Greece, in 1975. Antibodies to CCHFV were found in 6.25% of residents where strain AP92 was isolated; however, positive cases did not have any symptoms of CCHF.

Maltezou, et al. 2009

- According to a survey conducted in Greece between 1981 and 1988, the seroprevalence of CCHFV was 1% among the population surveyed, and approximately 3% were positive for CCHFV-reactive IgG in a 2008–2009 study.

Antoniadis, et al. 1990

- The first serious case of CCHF in Greece was registered in 2008 when a woman died in Komotini, a town in northeastern Greece. Molecular analysis revealed that the causative strain (Rodopi) was genetically distinct from strain AP92.

Papa, et al. 2011

Greece - Seroprevalence

Table 1. Principal results of CCHF studies in western Europe.

Author	Publication year	Study years	Country	Objective (related to CCHF seroprevalence in humans)	N	Risk factors	Seroprevalence of IgG: Value (%)
Antoniadis *et al.* [26]	1982	1980–1981	Greece (rural area, Northern Greece)	To determine the prevalence of CCHFV antibodies in a rural population of Northern Greece	65	Farming Living in Northern Greece (CCHF isolated in this zone from Rhipicephalus bursa since 1978)	4 (6.2)
Filipe *et al.* [27]	1985	1980	Portugal	To establish the seroprevalence of CCHFV virus in Southern Portugal	190	Living in certain areas of Southern Portugal	2 (1.1)
Palomar *et al.* [28]	2017	2010–2014	Spain	To evaluate the presence of antibodies against the virus in individuals exposed to tick bites	228	No risk factors found	0 (0.0)
Papa *et al.* [29]	2014	2012	Greece	To make a small-scale serologic survey in humans and animals in the area where CCHFV-positive tick had been detected	100	Ageing	6 (6.0)
Papa *et al.* [30]	2013	2010–2012	Greece (Western, border to Albania and Ionian Sea Coast)	To check in more detail the CCHFV situation in Thesprotia prefecture (western region, border with Albania) and find out any risk factors associated with seropositivity	166	Ruminants husbandry Slaughtering Ageing	24 (14.4)
Papa *et al.* [31]	2011	2008–2009	Greece (Eastern, border to Bulgaria)	To determine the prevalence of CCHFV antibodies in the human population of Northeastern Greece	1178	Female sex Ageing Ruminants husbandry Slaughtering Tick exposure	37 (3.1)
Sargianou *et al.* [32]	2013	2012	Greece (Coast of the Gulf of Corinth)	To estimate the seroprevalence of CCHFV in humans in Achaia Prefecture, Greece, and to assess risk factors in seropositivity	207	Agropastoral occupation Ruminants (especially with sheep) Living at an altitude of ≥400m	7 (3.4)
Sidira *et al.* [33]	2013	2010–2011	Greece (Northern coast of the Aegean Sea)	To estimate the CCHFV seroprevalence among humans residing in the prefecture of Imathia, and the neighbouring prefecture of Pella, and to investigate demographics and probable risk factors associated with the seropositivity	277	Tick exposure Residence in a hilly territory Ageing Agropastoral occupation	6 (2.2)
Sidira *et al.* [6]	2012	2009–2010	Greece	To estimate endemic areas CCHF in Greece	1611	Slaughtering Agropastoral occupation Ruminants husbandry	68 (4.2)

https://doi.org/10.1371/journal.pntd.0008094.t001

MediLabSecure

Albania

- An outbreak of eight cases of CCHF occurred in Albania during the spring and summer of 2001, with the infection of seven cases confirmed by laboratory tests.
- A nosocomial infection was discovered, as well as a familial cluster of cases. Genetic analysis revealed that the causative virus clustered together with other European CCHFV cases

Papa, et al. 2002

BALKANS – Bosnia-Herzegovina


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Ticks and Tick-borne Diseases

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

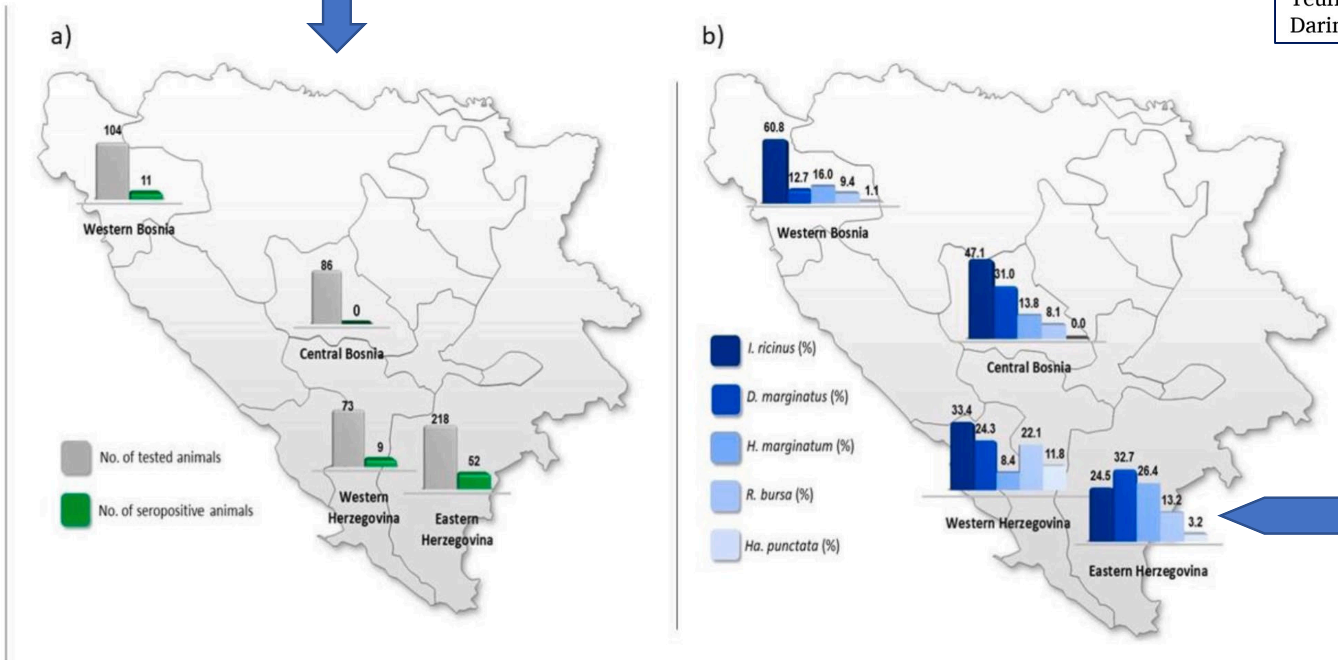
ELSEVIER

Original article

Serologic and molecular evidence for circulation of Crimean-Congo hemorrhagic fever virus in ticks and cattle in Bosnia and Herzegovina

Teufik Goletic *, Lejla Satrovic, Adis Softic, Jasmin Omeragic, Sejla Goletic, Darinka Klaric Soldo, Amira Koro Spahic, Almedina Zuko, Edin Satrovic, Amer Alic

Approximately 1/10 of cattle in the region of western Bosnia, western and eastern Herzegovina showed CCHFV seroconversion.



One pool of H. marginatum ticks collected from cattle in the region of eastern Herzegovina was positive for CCHFV gRNA (3/760 - 0.39%).

Bulgaria

- Between 1953 and 1974, numerous CCHF cases were detected in Bulgaria, and the death ratio was around 17%. During this time, 20 nosocomial infections were reported.
- The first inactivated virus vaccine (mouse brain) was developed!
- Between 1975 and 1996, the number of reported CCHF cases decreased, with a death ratio also decreasing to 11.4%. The CCHFV strains from Bulgaria were found to cluster with other Balkan strains from Kosovo and Albania (Papa et al, 2002).

Kosovo

- The first cases of CCHF were reported in 1989. In 1995, 2001, and 2004, there were three major outbreaks with a total of 186 serologically confirmed cases.

  Ahmeti et al, 2006

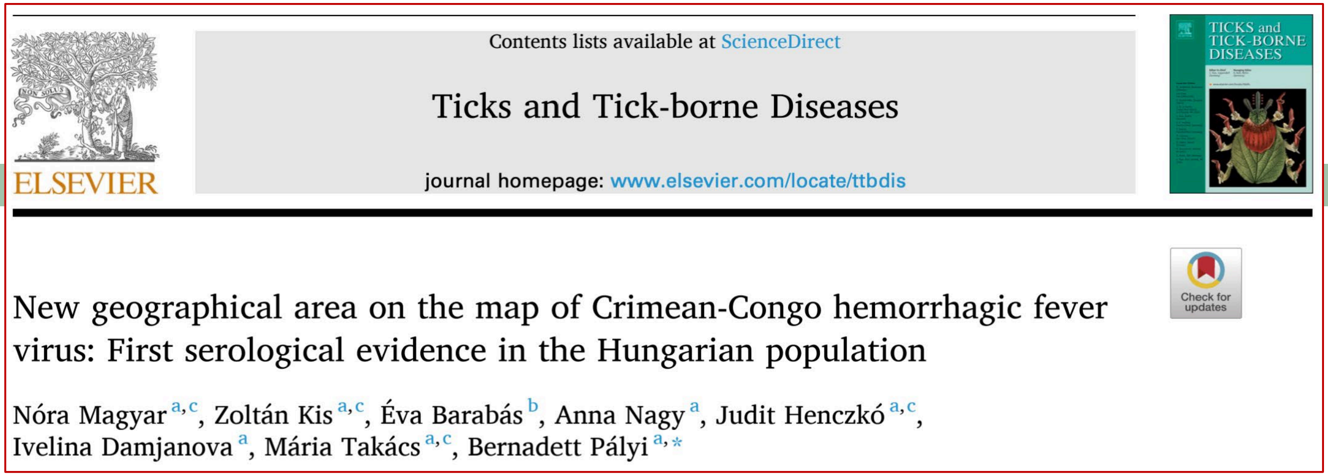
- The central and southwestern parts of Kosovo are hyper-endemic for CCHF.

  Humolli et al, 2010

- A phylogenetic study suggested that CCHFV was recently introduced to Kosovo (within the last 50 years), sharing a common ancestor with strains from Turkey.

  Emmerich et al, 2018

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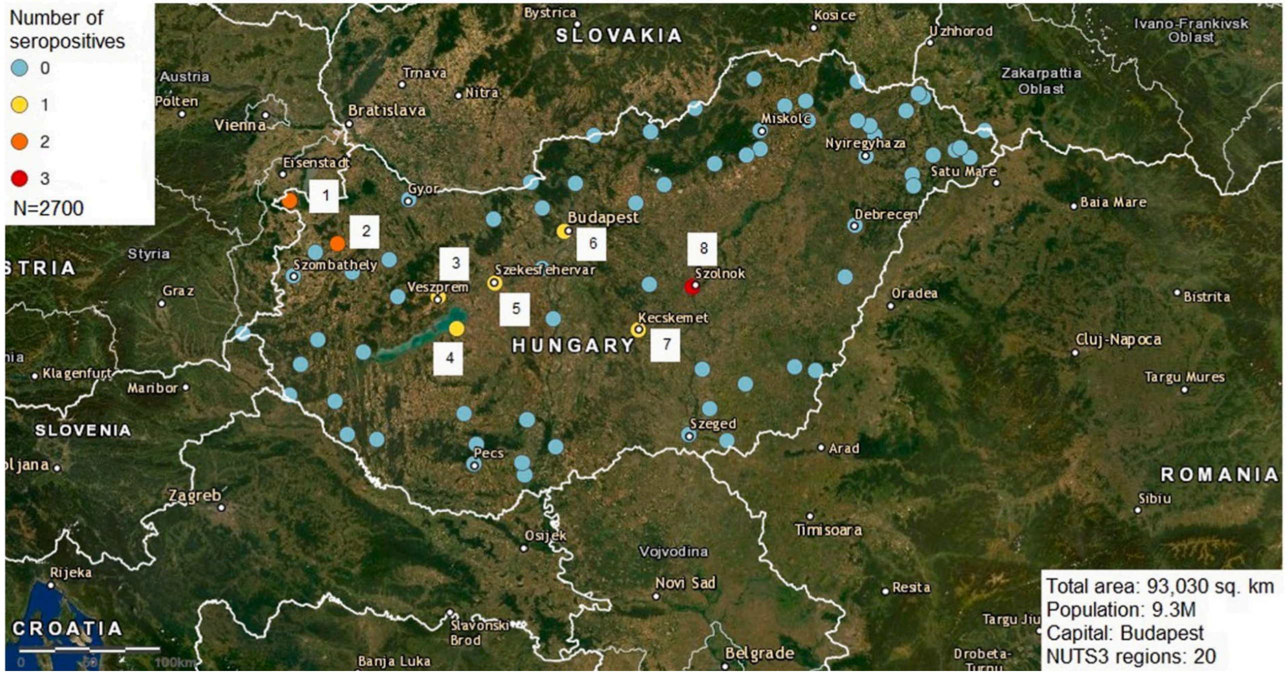
journal homepage: www.elsevier.com/locate/ttbdis

ELSEVIER

New geographical area on the map of Crimean-Congo hemorrhagic fever virus: First serological evidence in the Hungarian population

Nóra Magyar[a,c], Zoltán Kis[a,c], Éva Barabás[b], Anna Nagy[a], Judit Henczkó[a,c], Ivelina Damjanova[a], Mária Takács[a,c], Bernadett Pályi[a,*]



- A total of 2700 serum samples obtained from healthy volunteer blood donors were screened using an in-house immunofluorescence assay and a commercially available ELISA kit.
- They found ten (0.37 %) seropositive donors.

Pan-Europe Seroprevalance

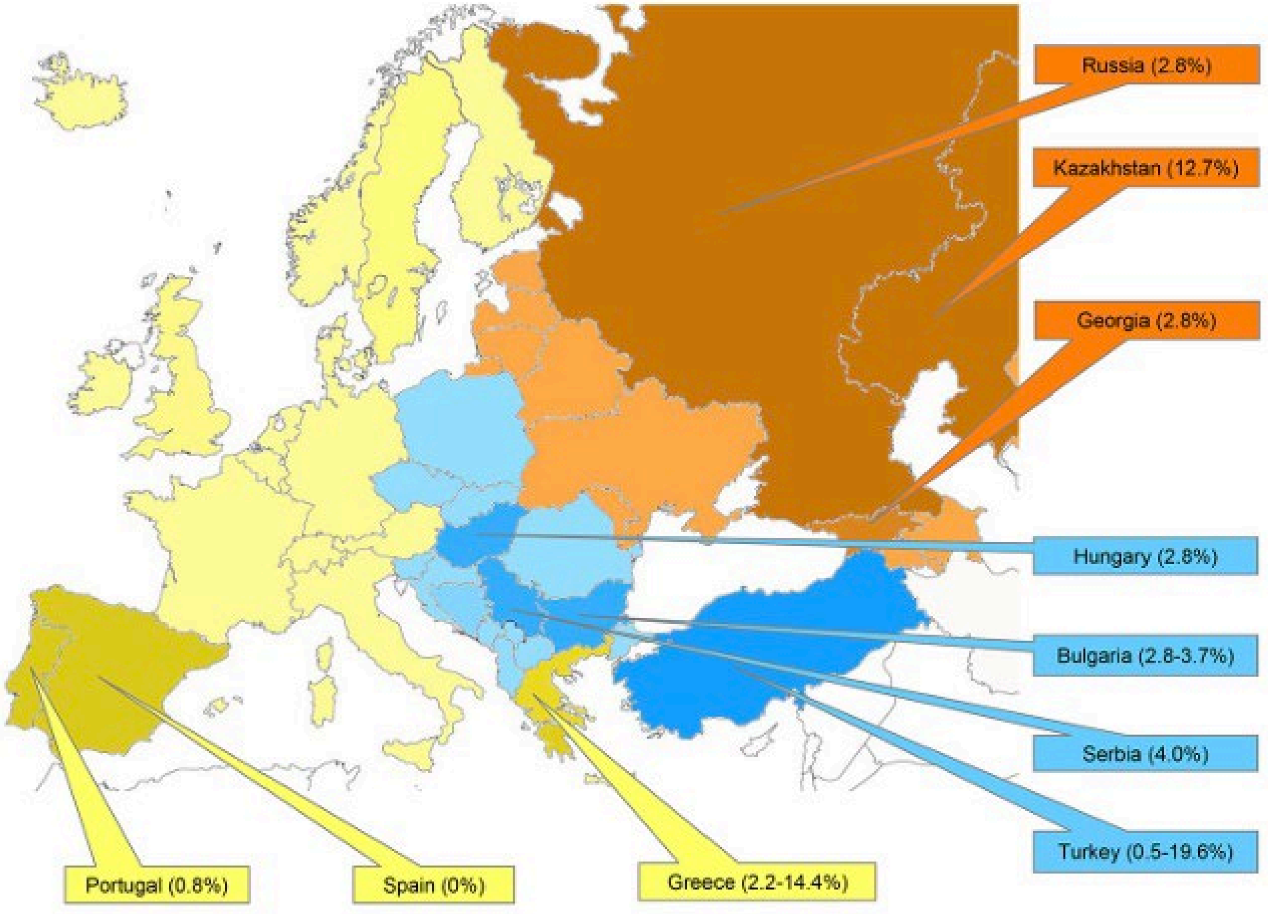


Fig 2. Seroprevalence of CCHFV in Western Europe (yellow), Center Europe (blue) and Eastern Europe (orange).

https://doi.org/10.1371/journal.pntd.0008094.g002

TICKS & The Virus

Table 1. A list of tick species that have been confirmed CCHFV-positive in different regions.

Family	Genus	Species	Geographical Distribution
Ixodidae	*Hyalomma*	*Hy. marginatum*	Middle East, Northern Africa, Southern Europe
		Hy. dromedarii	Middle East, Northern Africa
		Hy. rufipes	Middle East, Africa
		Hy. turanicum	Asia, Africa
		Hy. nitidum	Central Africa
		Hy. anatolicum	Asia
		Hy. asiaticum	Asia
		Hy. detritum	Middle East, Africa
		Hy. excavatum	Africa, Middle East
		Hy. truncatum	Africa
		Hy. schulzei	Arabia peninsula
		Hy. impeltatum	Northern Africa, Arabian Peninsula
		Hy. lusitanicum	Africa, Spain
		Hy. isaaci	Africa
		Hy. impressum	Africa, Pakistan
	Rhipicephalus	*Rh. sanguineus*	Asia
		Rh. bursa	Southeastern Europe, Middle East
		Rh. annulatus	Middle East, Central parts of Africa
		Rh. turanicus	Southern Europe, Asia
		Rh. rossicus	Caucasia, southern Russia
		Rh. evertsi	Sub-Saharan Africa
		Rh. decoloratus	Uganda
		Rh. appendiculatus	Iran
		Rh. microplus	Africa, Pakistan
		Rh. guilhoni	Senegal
	Haemaphysalis	*Ha. punctata*	Some parts of Asia, South-East of Europe
		Ha. inermis	Iran
		Ha. concinna	Turkey
		Ha. sulcata	Iran
		Ha. parva	Turkey, North Caucasus
	Dermacentor	*De. marginatus*	Southern Europe, Middle East, Mediterranean
		De. niveus	Tajikistan
	Ixodes	*Ix. ricinus*	Europe, Mediterranean, Northern Africa
	Amblyomma	*Am. variegatum*	Sub-Saharan Africa
Argasidae	*Ornithodoros*	*Or. lahorensis*	Iran

What do we need? Obstacles!

- One Health Approach (Gilbride et al. 2021)

TABLE 3 | The different control measures that may facilitate a CCHF One Health approach and the current status or challenges for their implementation.

Control measure strategy	Current status
Immunisation of humans	• Limited licensure of one inactivated vaccine in Eastern Europe • Multiple vaccine candidates show promise in pre-clinical studies • No published assessment of candidates in human trials
Immunisation of animals	• Multiple vaccine candidates show promise in pre-clinical studies • Lack of disease burden means a lack of economic incentive to vaccinate
Tick control	• Acaricidal agents known to be effective at reducing vector-borne disease rates • Environmental implications and logistical issues of widespread usage
Diagnostic, education, and surveillance	• PCR available but often limited in capacity or inaccessible • Sero-surveillance rates increasing (44)

Queries

- Lack of systematic epidemiological data from all endemic countries.
- Difficult to calculate attack rates in most of the endemic countries.
- NO knowledge about the Re-infection.
- Is the tick control effective? Is it enough?
- Risky tick viruses (for possible recombinations) , such as Jingmen tick virus, Tacheng tick virus

Thank you

Contact: ozkul@ankara.edu.tr