

Crimean-Congo Hemorrhagic Fever



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30 March 2018

Content

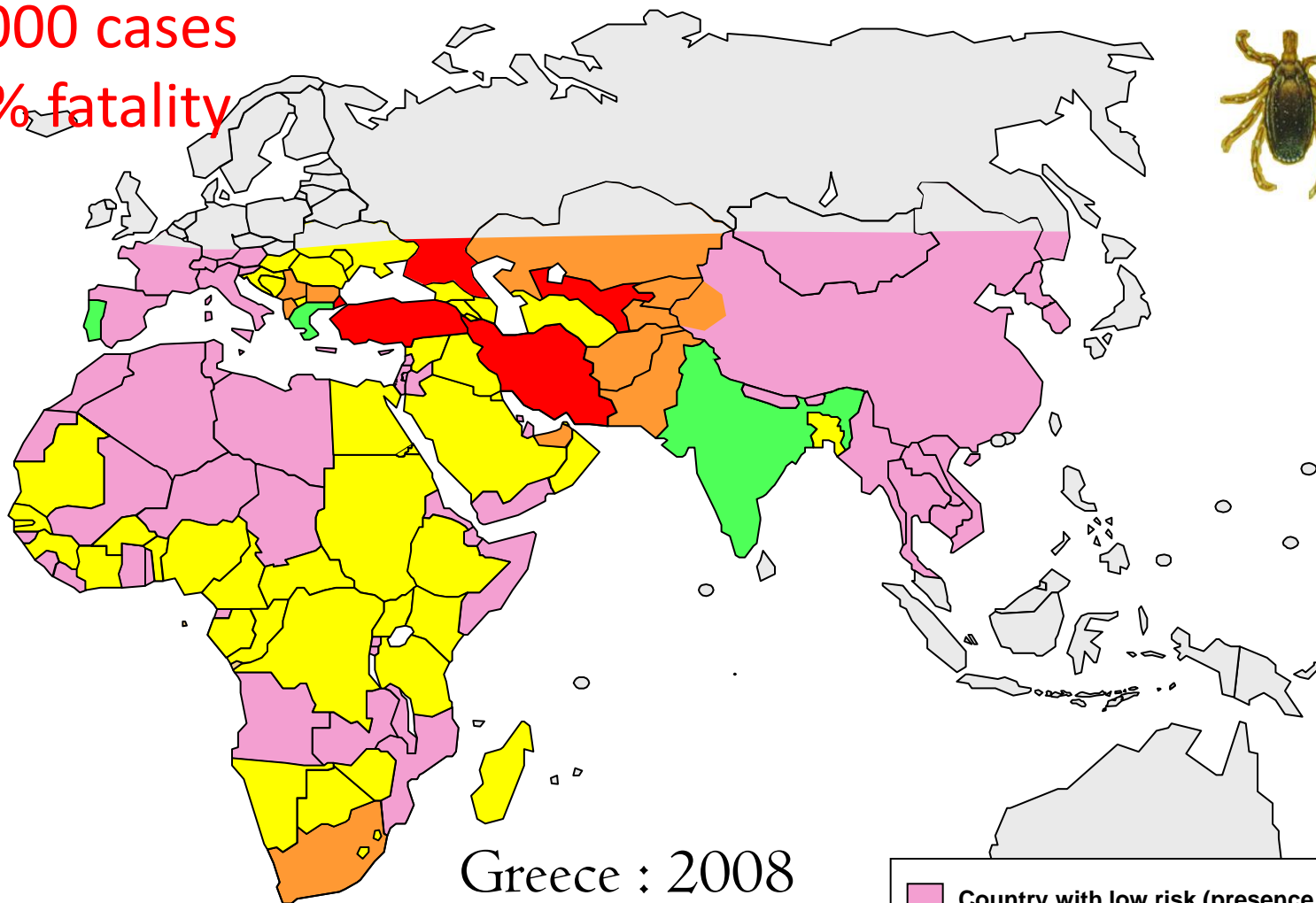
- Epidemiology
- Diagnosis
- Clinical course
- Therapy
- Post-exposure prophylaxis

Crimean-Congo Haemorrhagic Fever Geographic Distribution

50° North limit for the geographic distribution of genus *Hyalomma* ticks

>20 000 cases

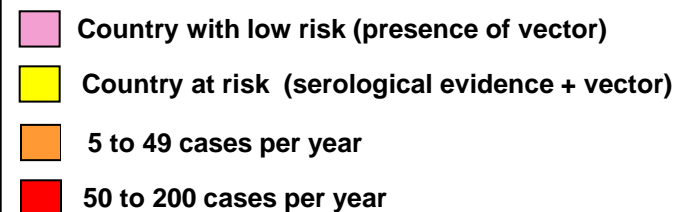
2-40% fatality



Greece : 2008

India : 2011

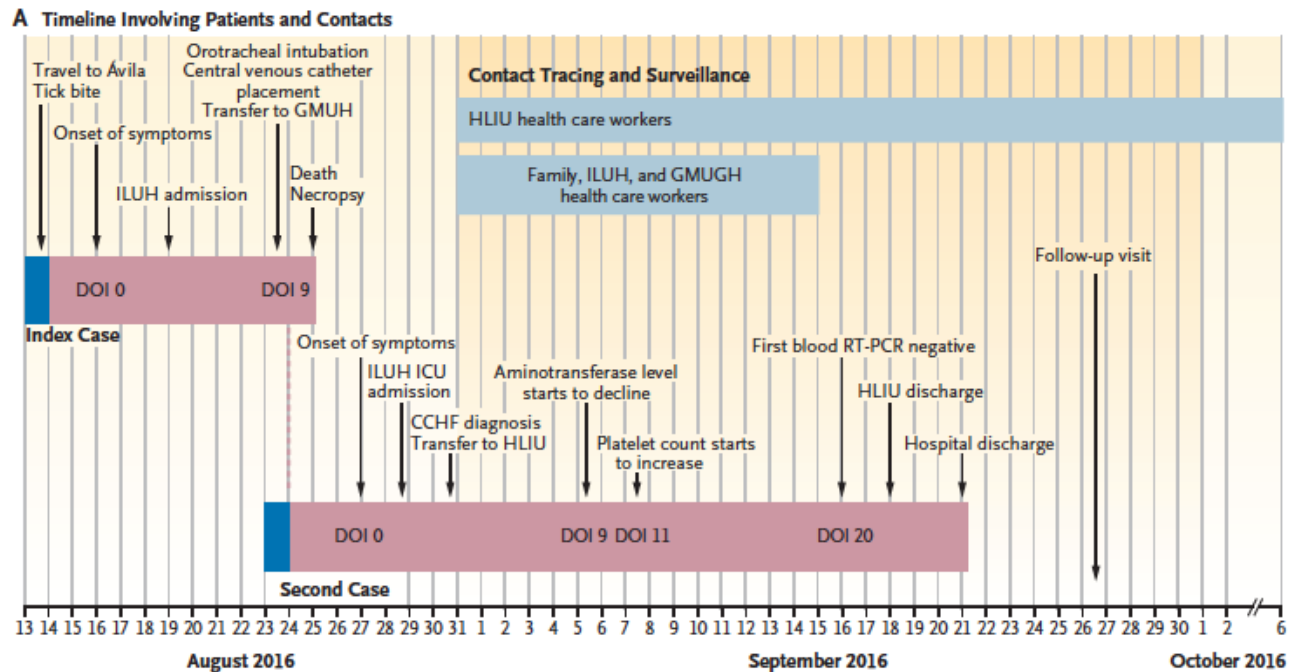
Spain : 2016



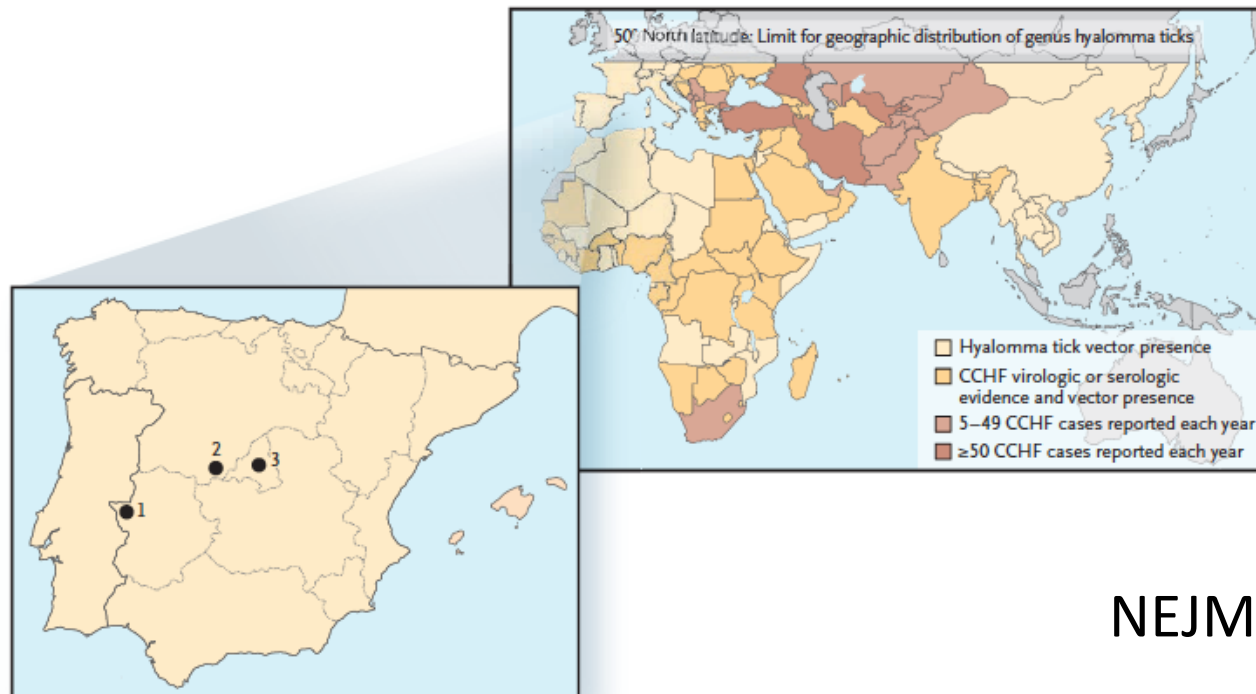
BRIEF REPORT

Autochthonous Crimean–Congo Hemorrhagic Fever in Spain

A. Negredo, F. de la Calle-Prieto, E. Palencia-Herrejón, M. Mora-Rillo, J. Astray-Mochales, M. P. Sánchez-Seco, E. Bermejo Lopez, J. Menárguez, A. Fernández-Cruz, B. Sánchez-Artola, E. Keough-Delgado, E. Ramírez de Arellano, F. Lasala, J. Milla, J.L. Fraile, M. Ordobás Gavín, A. Martínez de la Gándara, L. López Perez, D. Diaz-Diaz, M.A. López-García, P. Delgado-Jimenez, A. Martín-Quirós, E. Trigo, J.C. Figueira, J. Manzanares, E. Rodriguez-Baena, L. Garcia-Comas, O. Rodríguez-Fraga, N. García-Arenzana, M.V. Fernández-Díaz, V.M. Cornejo, P. Emmerich, J. Schmidt-Chanasit, and J.R. Arribas, for the Crimean Congo Hemorrhagic Fever@Madrid Working Group*



B Locations of CCHF Worldwide

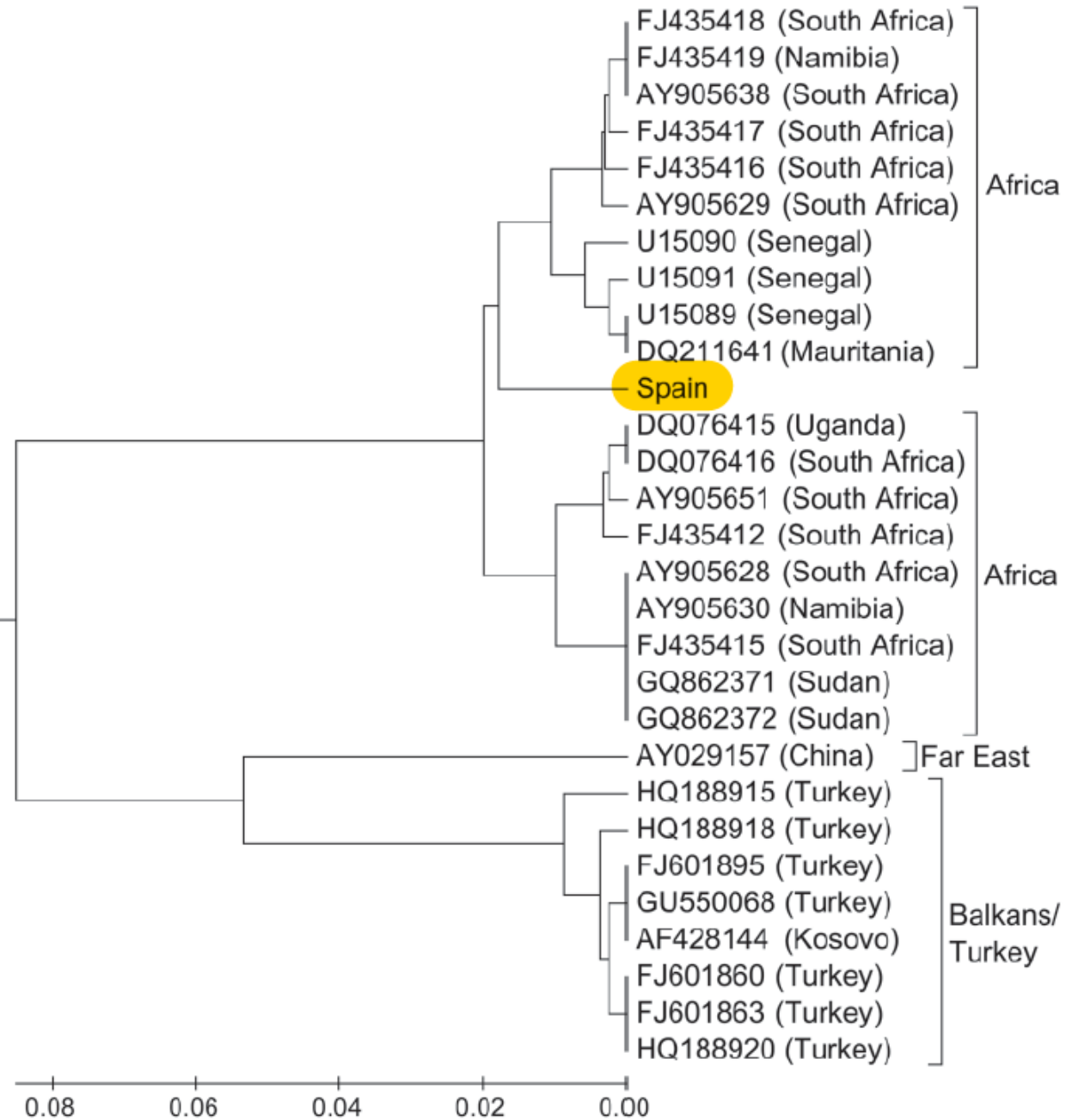


NEJM, 2017

VHF virus	Geographic Distribution	Annual Cases
Ebola	Africa	<500
Marburg	Africa	<300
Lassa	Africa	100,000-300,000
S.America	Argentine pampas	~300
Hantaan	Asia, Europe	50,000-150,000
Rift Valley	Africa	100-100,000
CCHF	Euroasia, Africa	> 2000
Yellow F	Africa, South America	5,000-200,000
Dengue	Tropics, worldwide	DF: 100 million, DHF: 100,000-200,000
Omsk	Siberia	100-200
Kyasanur	Karnataka state, India	400-500
Alkhumra	Saudi Arabia	<50

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

This finding suggests circulation of CCHFV in southwestern Europe. The close affinity of the virus from Spain with strains in western Africa and the similarity with isolates from Europe suggest the introduction of virus from nearby countries in Africa. Migratory movements of ticks could explain the presence of the virus in southwestern Europe because ticks are common hosts of *Ixodes marginatus*, which was introduced into Europe by annual migratory flights along the western coast of Africa (10). Because



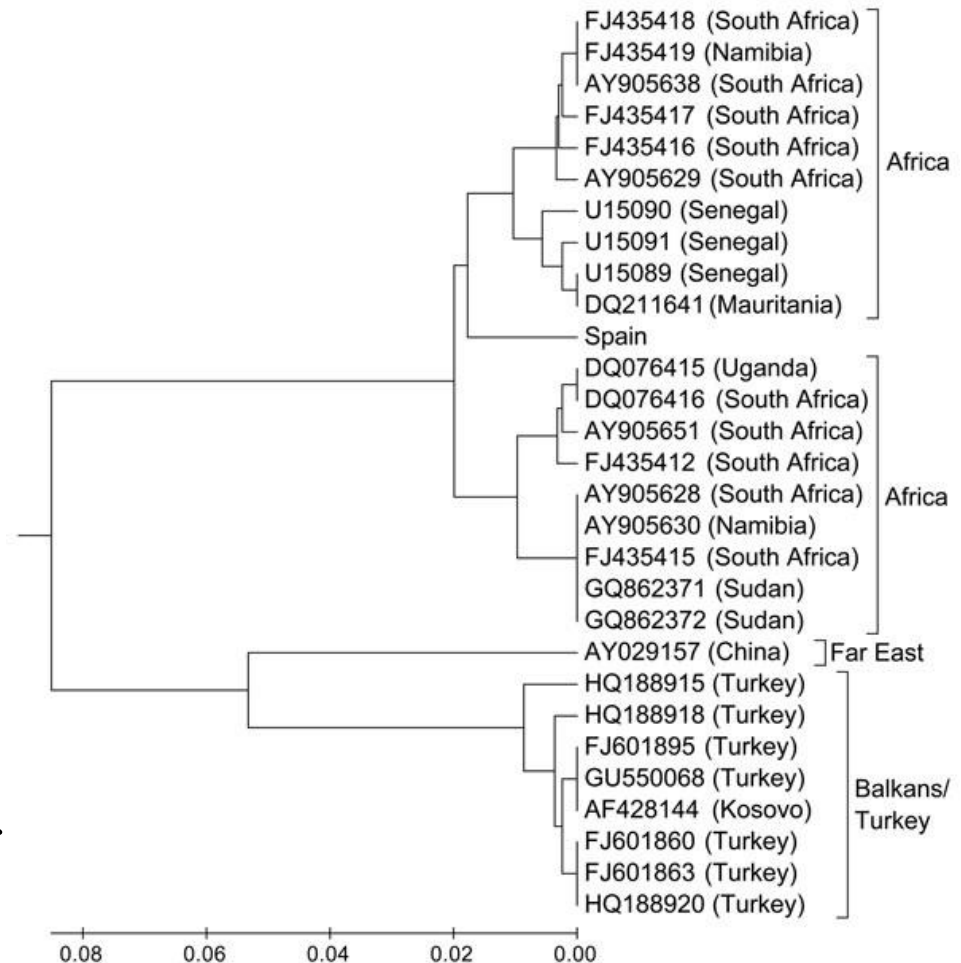
Circulation of CCHFV in Southwestern Europe

The close affinity of the strain from Spain with strains circulating in western Africa.

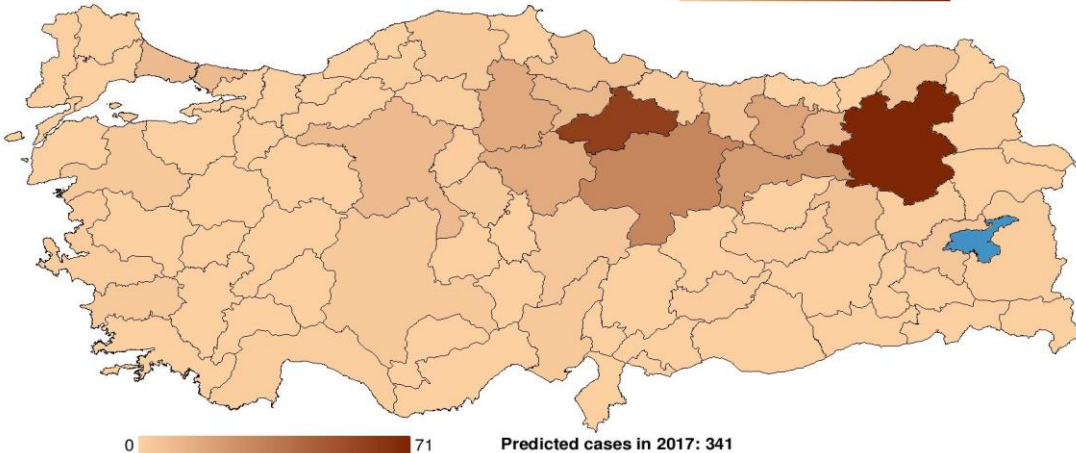
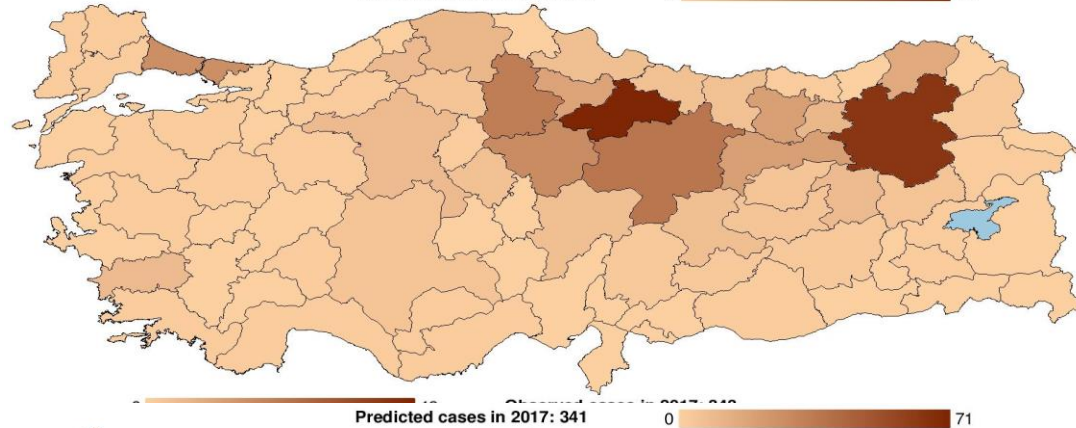
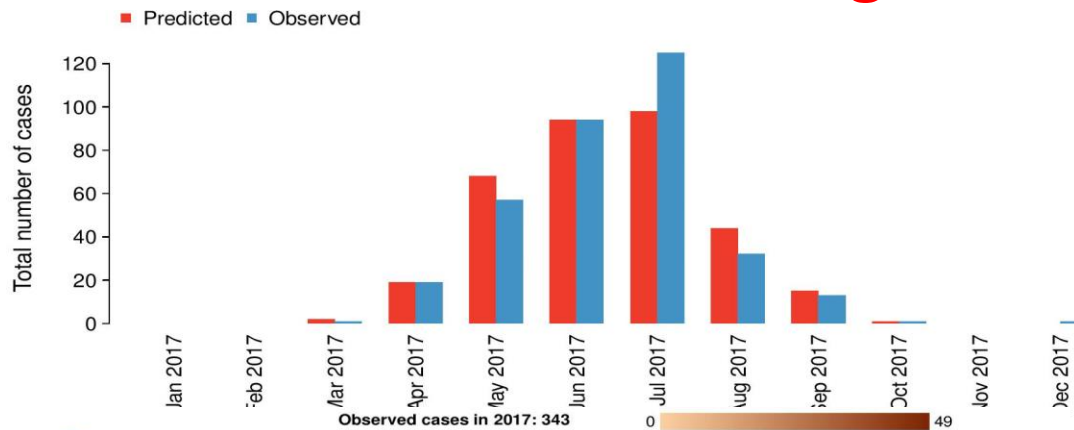
The lack of similarity with isolates from eastern Europe

Migratory movements of birds

Less likely; trade movements of domestic from eastern Europe.



Model for Crimean-Congo Hemorrhagic Fever

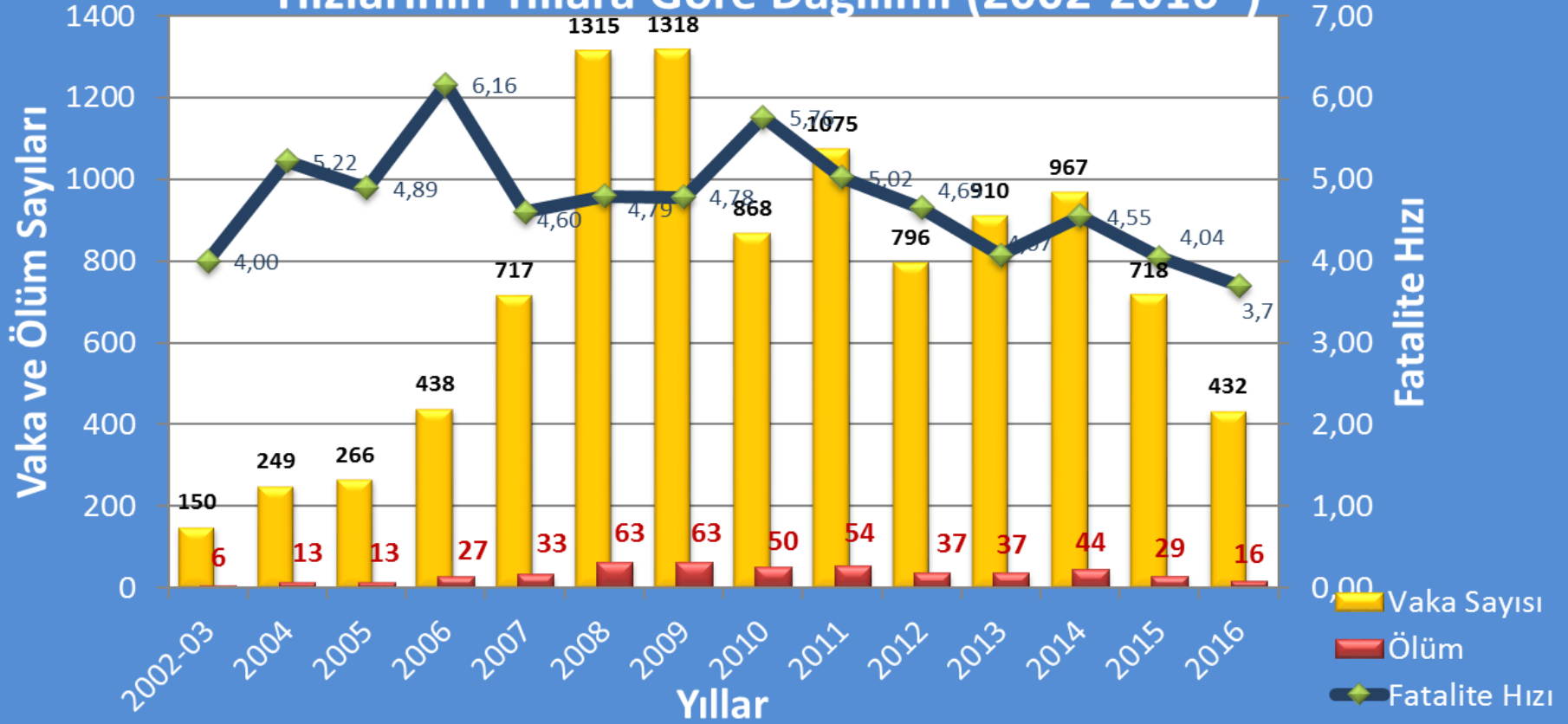


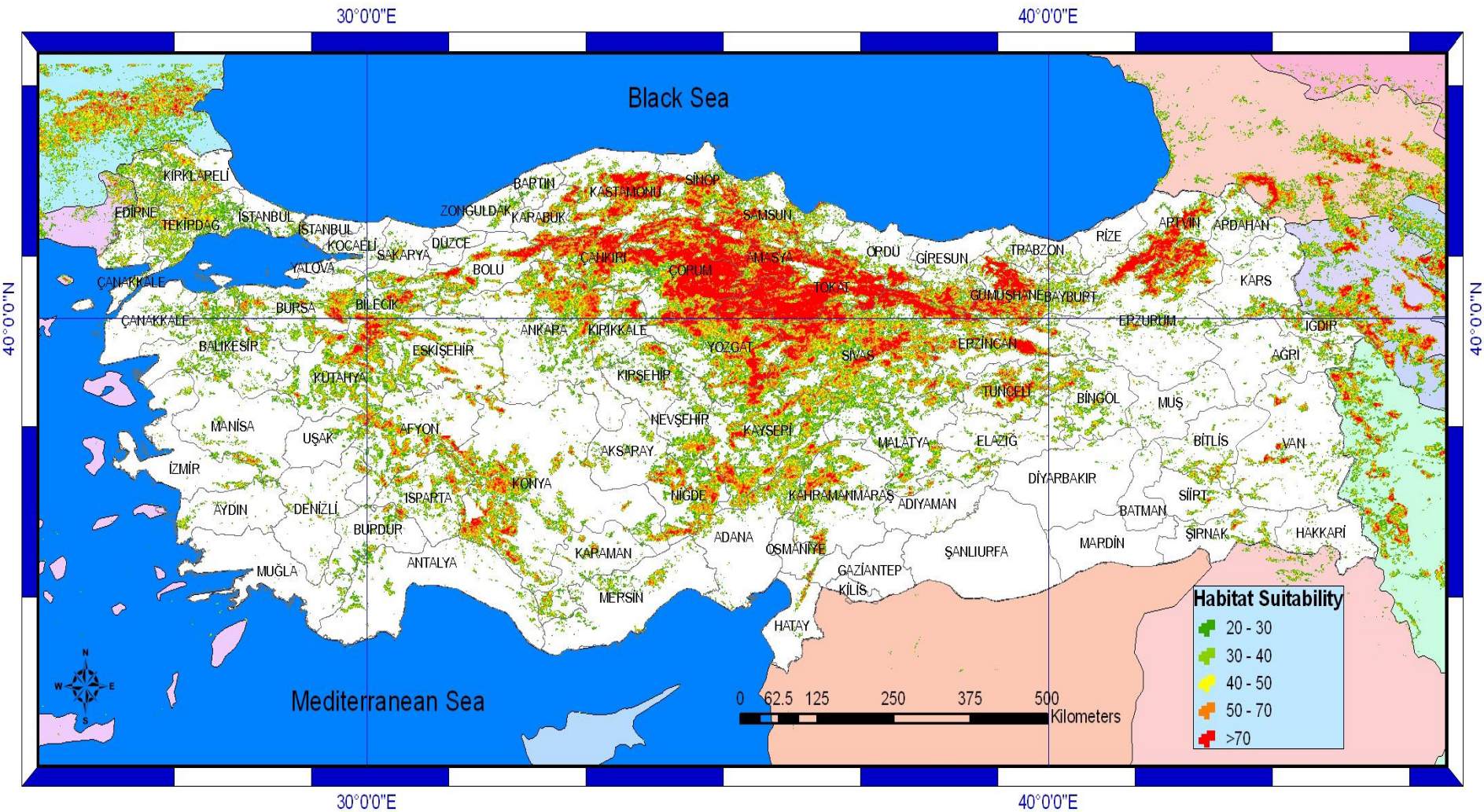
Spatial
Latitude
Longitude
Number of
settlements

Temporal
Evapotranspiration
season

Structured Gaussian
Process

Kırım Kongo Kanamalı Ateşi Vaka, Ölüm Sayıları ve Fatalite Hızlarının Yıllara Göre Dağılımı (2002-2016*)





H. marginatum spp. (MaxEnt algorithm)

Epidemiologic characteristics

Rural area: 70% of the cases

Male/female ratio: 1.13/1

Tick bite history among patients: 69%

May, June, July: 84% of the cases



A



B



C

Strong evidence for the presence of the tick *Hyalomma marginatum* Koch, 1844 in southern continental France



Tick sampling campaigns conducted on horses and birds from 2007 to 2016,

Introduction of *H. marginatum*, as well as *H. rufipes*, into France probably through trans-Mediterranean bird migrations.

Laboratory and Epidemiology Communications

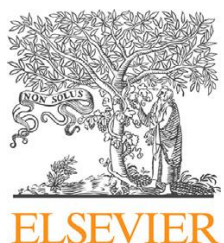
Potential Sexual Transmission of Crimean-Congo Hemorrhagic Fever Infection

Onder Ergonul^{1*} and Ismet Battal²

¹*Infectious Diseases Department, School of Medicine, Koc University, Istanbul; and*

²*Viral Hemorrhagic Fever Unit, Zoonotic Diseases Department, Public Health Institute, Ankara, Turkey*

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



Case Report

Possible sexual transmission of Crimean-Congo hemorrhagic fever

Natalia Yurievna Pshenichnaya^{a,*}, Irina Stanislavovna Sydenko^b,
Elena Pavlovna Klinovaya^b, Elena Borisovna Romanova^a, Alexey Sergeevich Zhuravlev^c

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

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^c First Moscow Medical University "I.M. Sechenov", Moscow, Russia



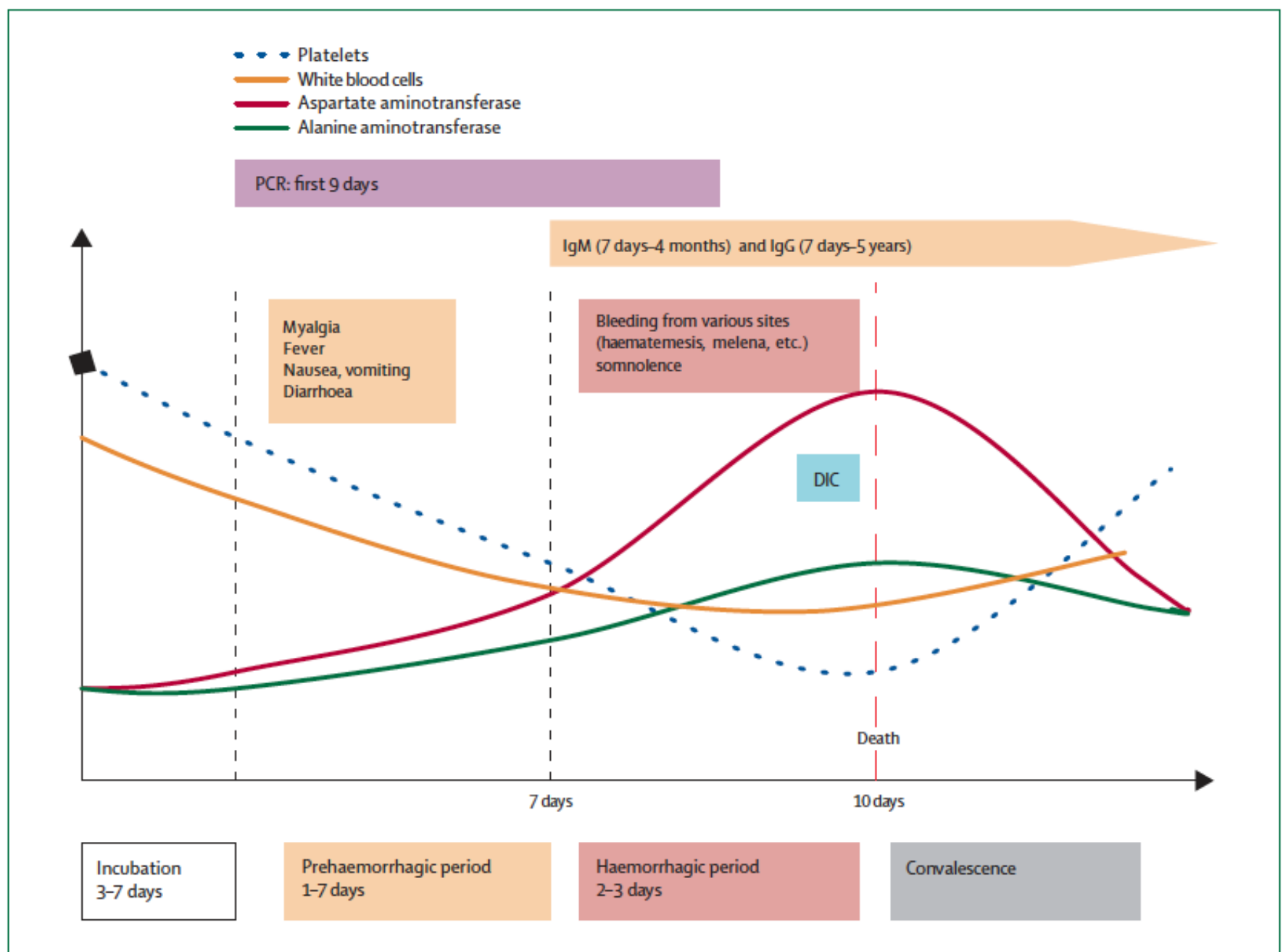


Figure 3: Clinical and laboratory course of CCHF
DIC=disseminated intravascular coagulation.

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 Nurdar Önder Ergönül²

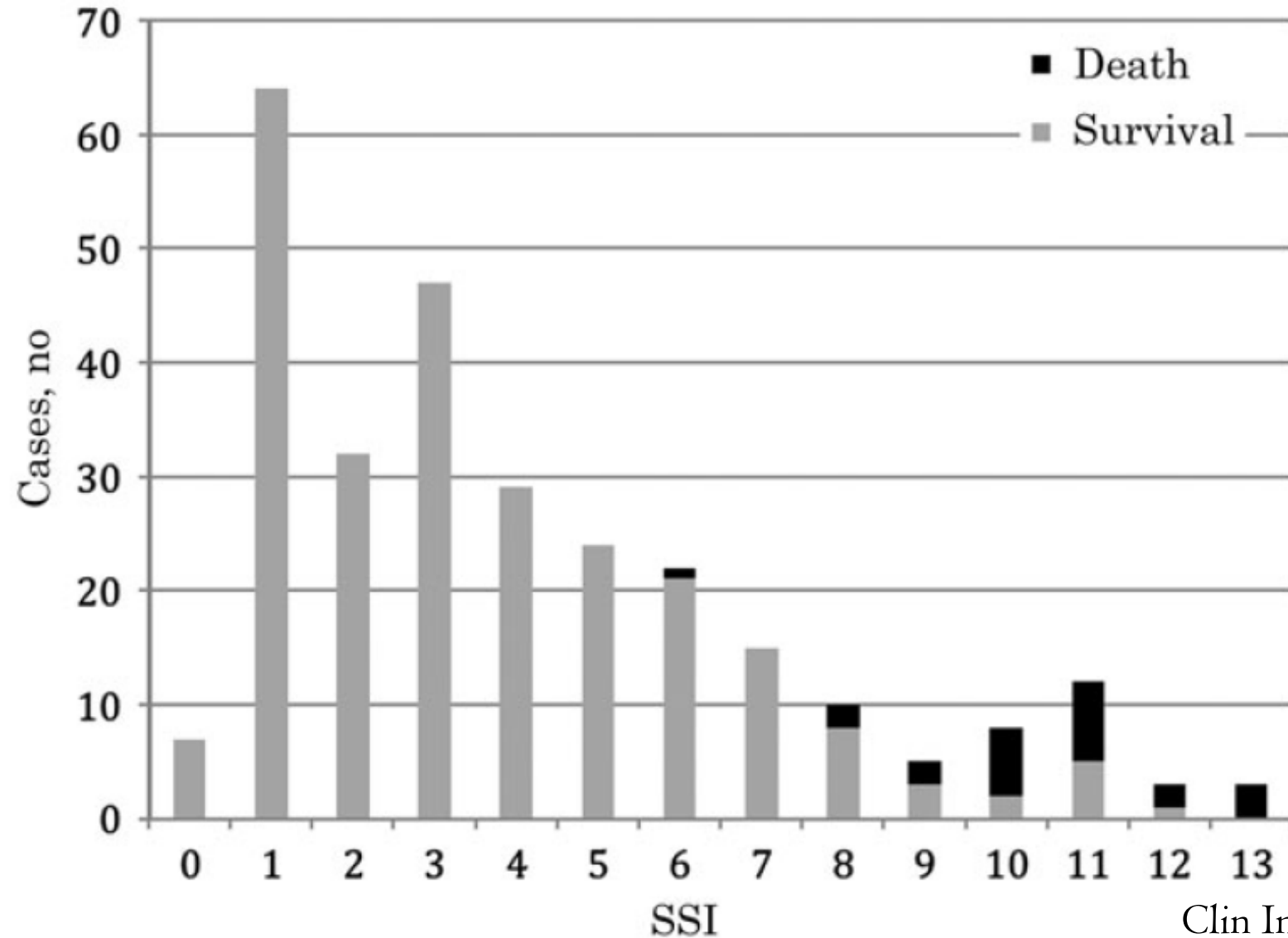
¹Clinical Microbiology and Infectious Diseases Clinic, Ankara Numune Education and Research Hospital, Ankara, Turkey
²Microbiology, Koç University, School of Medicine, Istanbul, Turkey

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

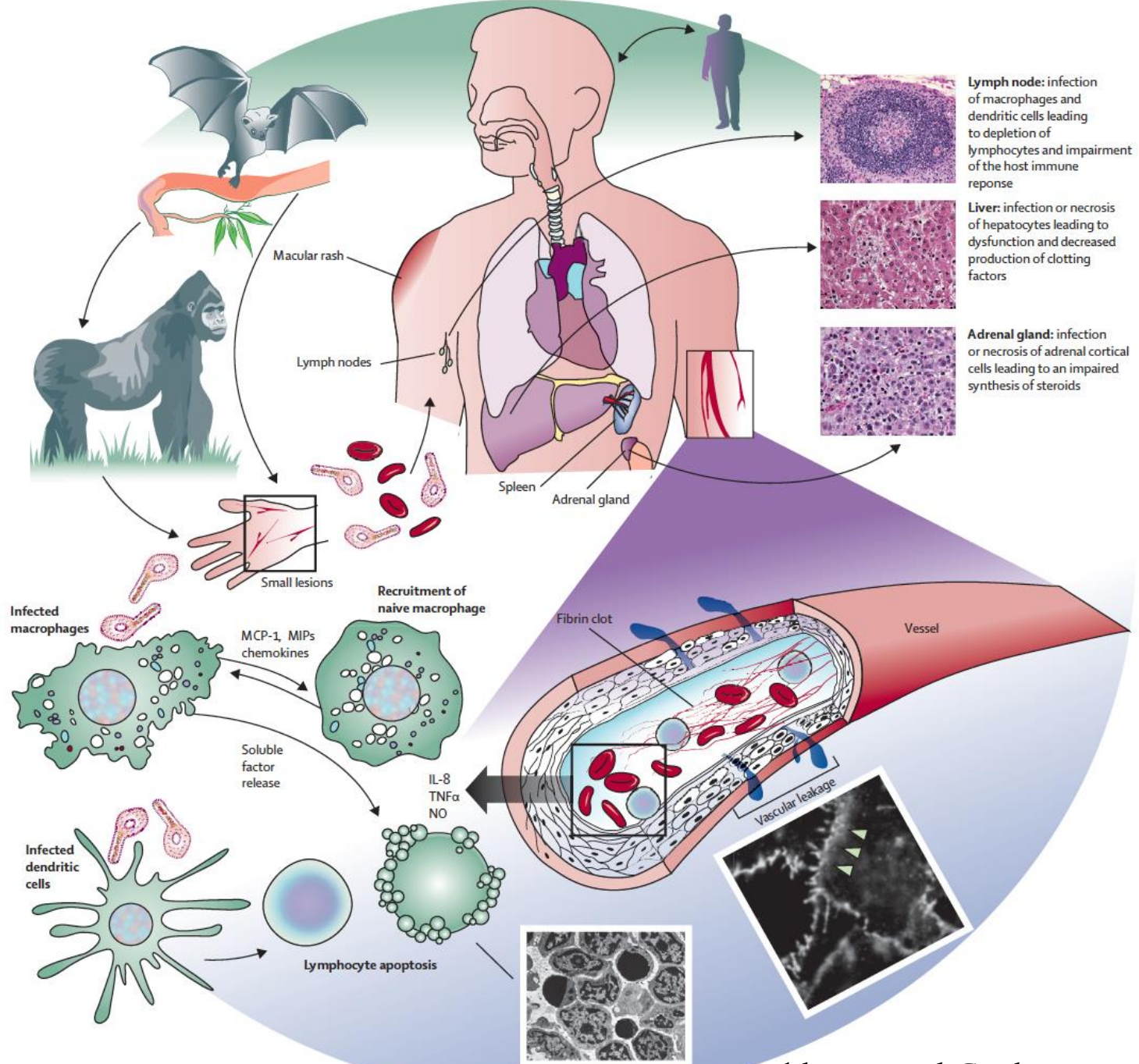
Severity Scoring Index for Crimean-Congo Hemorrhagic Fever and the Impact of Ribavirin and Corticosteroids on Fatality

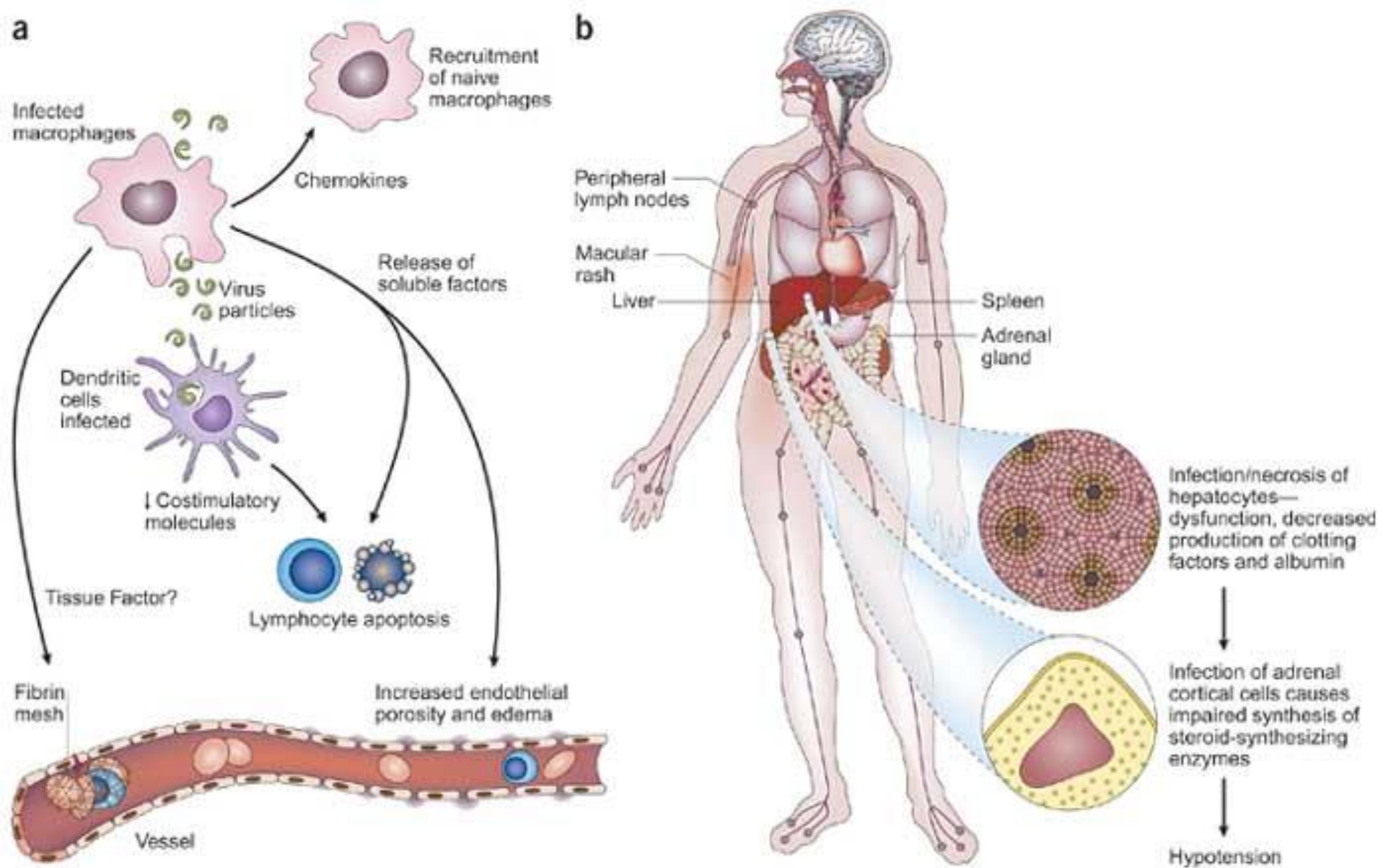
Başak Dokuzoguz,¹ Aysel Kocagül Celikbas,¹ Şebnem Eren Gök,¹ Nurcan Baykam,¹ Mustafa Necati Eroglu,¹ and Önder Emrullah²



Host Dynamics

From Epidemiology to Immunology





Geisbert TW, *Nature Med* 2004

Why The Case Fatality Rate Differs?

1. Different strains

Burt FJ, et al. Epidemiol Infect 2009

2. Co-existent infection

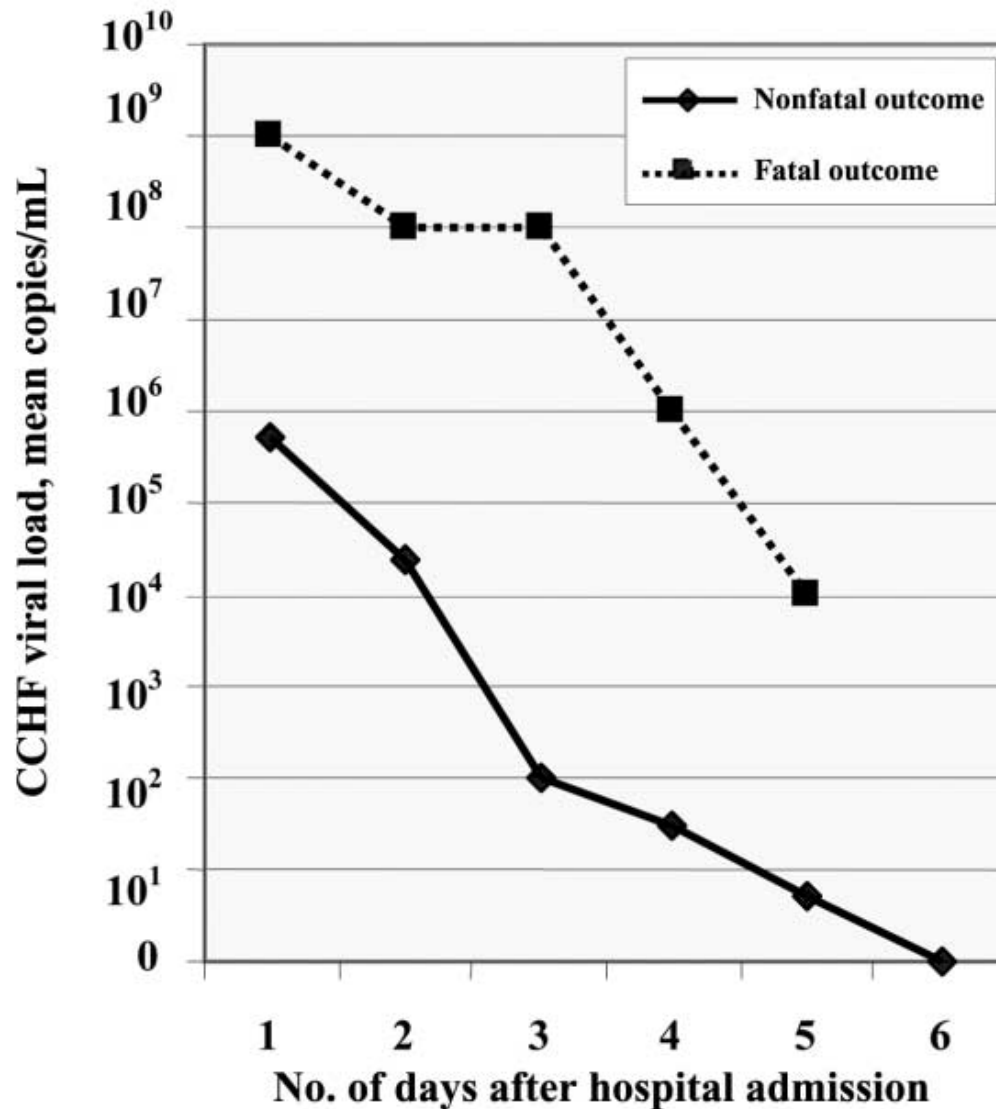
very rare; Malaria, Iran, 2012; Leishmania, Turkey, 2011

3. Health care facility

- Access
- Quality

4. The sensitivity threshold for the symptoms: inclusion of the milder cases inflates the denominator

Viral Load is Higher Among Fatal Cases



Cevik, et al. Clin Infect Dis 2007
Duh, et al. Emerg Infect Dis 2007

Antibody production is weaker among fatal cases

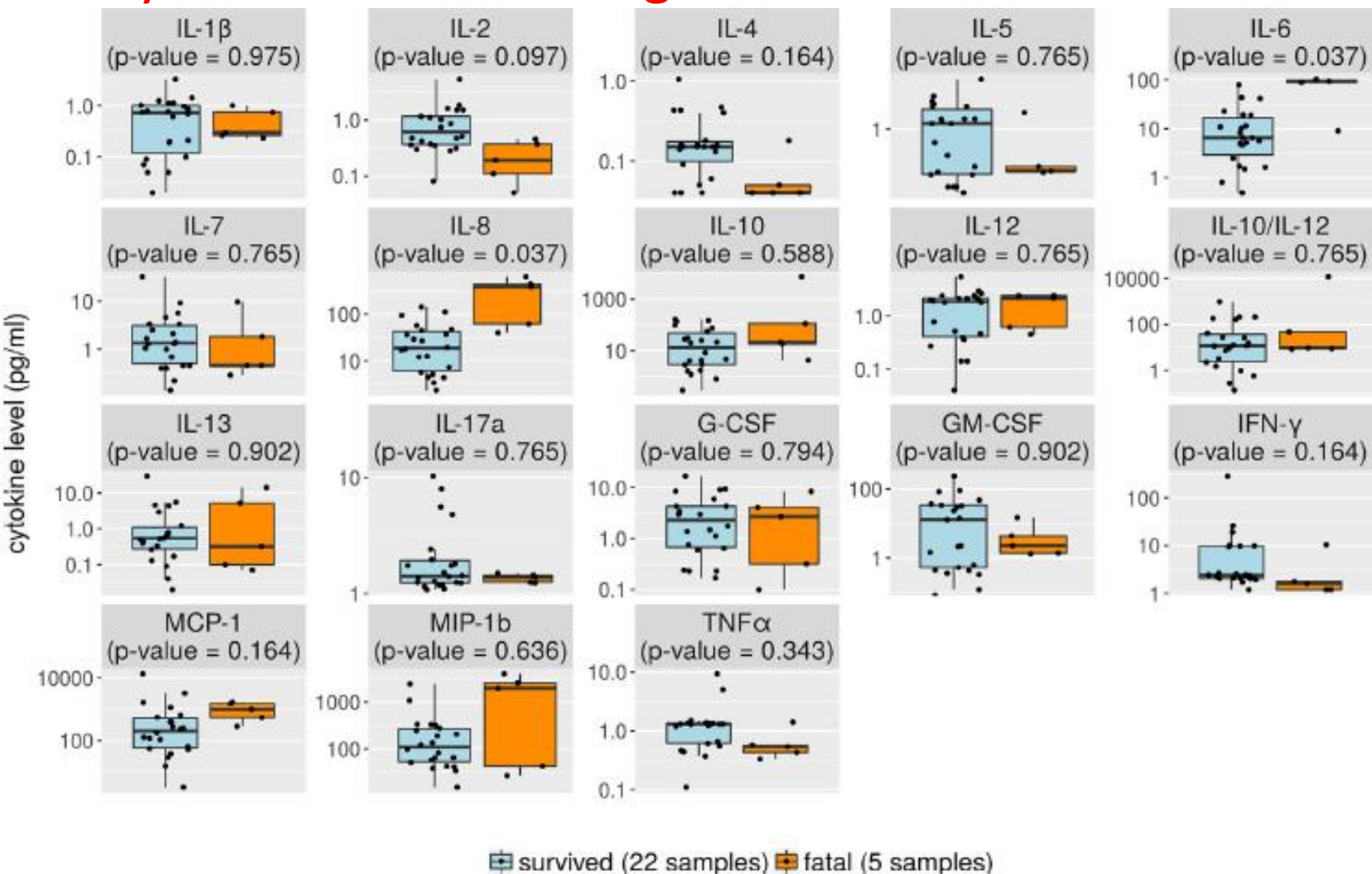
	Patients survived n=50	Fatal cases n=4
IgM positives	37/40 (93)	1/4 (25)
IgG positivity	27/40 (68)	0/4 (0)
PCR positivity	19/40 (48)	3/4 (50)

Ergonul, et al. CMI 2006

CCHFV delays activation of the innate immune response.

Andersson I, J Med Virol 2008

Cytokine Levels among Survived and Fatal Cases

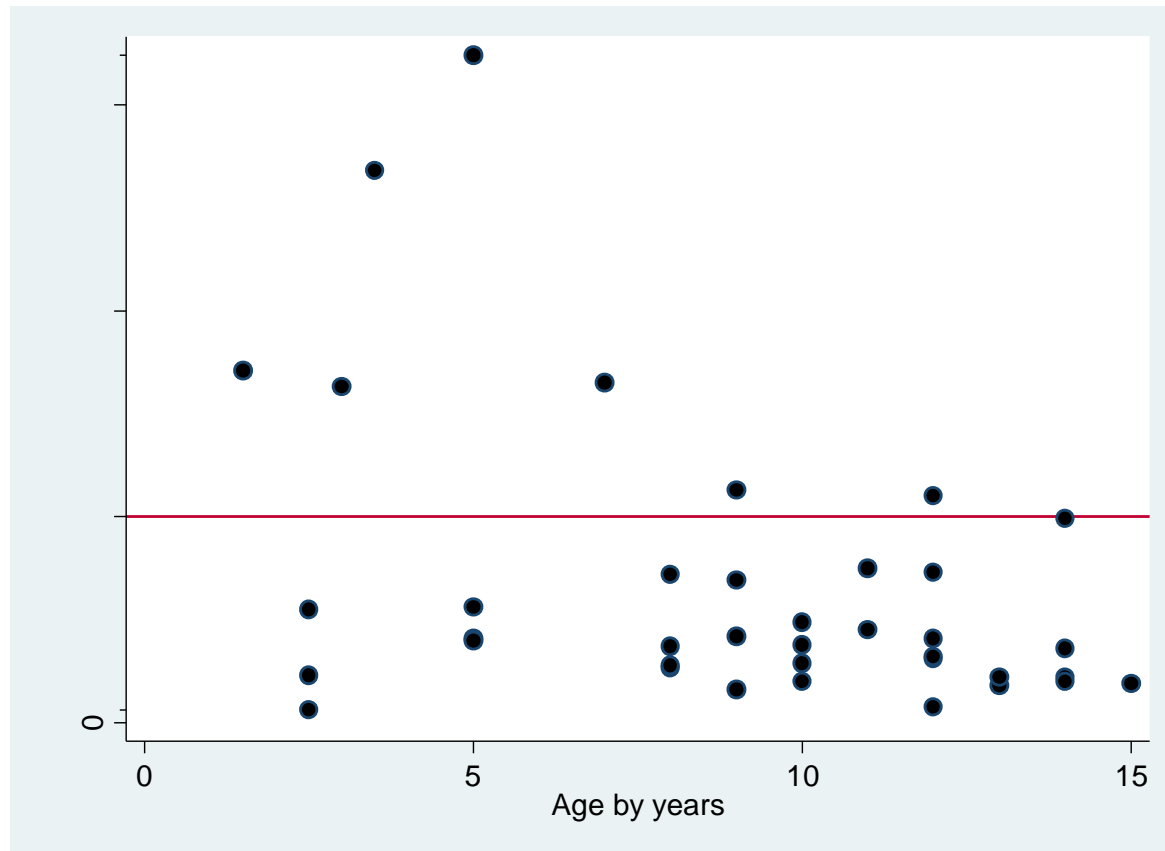


Fatality Among Hospitalized Children

33 children in Iran: 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)



Universal precautions

Hospitalization

Isolation

Avoid from the trauma that could cause bleeding

Watch for bleeding

Protect oral cavity

- Remove crusts from the oral cavity,

- Brush teeth carefully,

- Keep mouth and lips clean

WHO, CDC

Hematologic support

Fluid and electrolyte balance should be sustained

If necessary;

Blood,

Trombocyte suspension,

Fresh frozen plasma

Ribavirin: A Broad Spectrum Antiviral

Only Drug for VHFs

Arenaviridae
Lassa Fever
South America HF
Bunyaviridae
Hanta
Rift Valley
CCHF

Inspirations from EBV and other HFs

favipiravir

brinsidofovir

ZMapp

TKM-Ebola

“antisense” oligonükleotidler (PMOs)

BCX4430

Efficacy of T-705 (Favipiravir) in the Treatment of Infections with Lethal Severe Fever with Thrombocytopenia Syndrome Virus

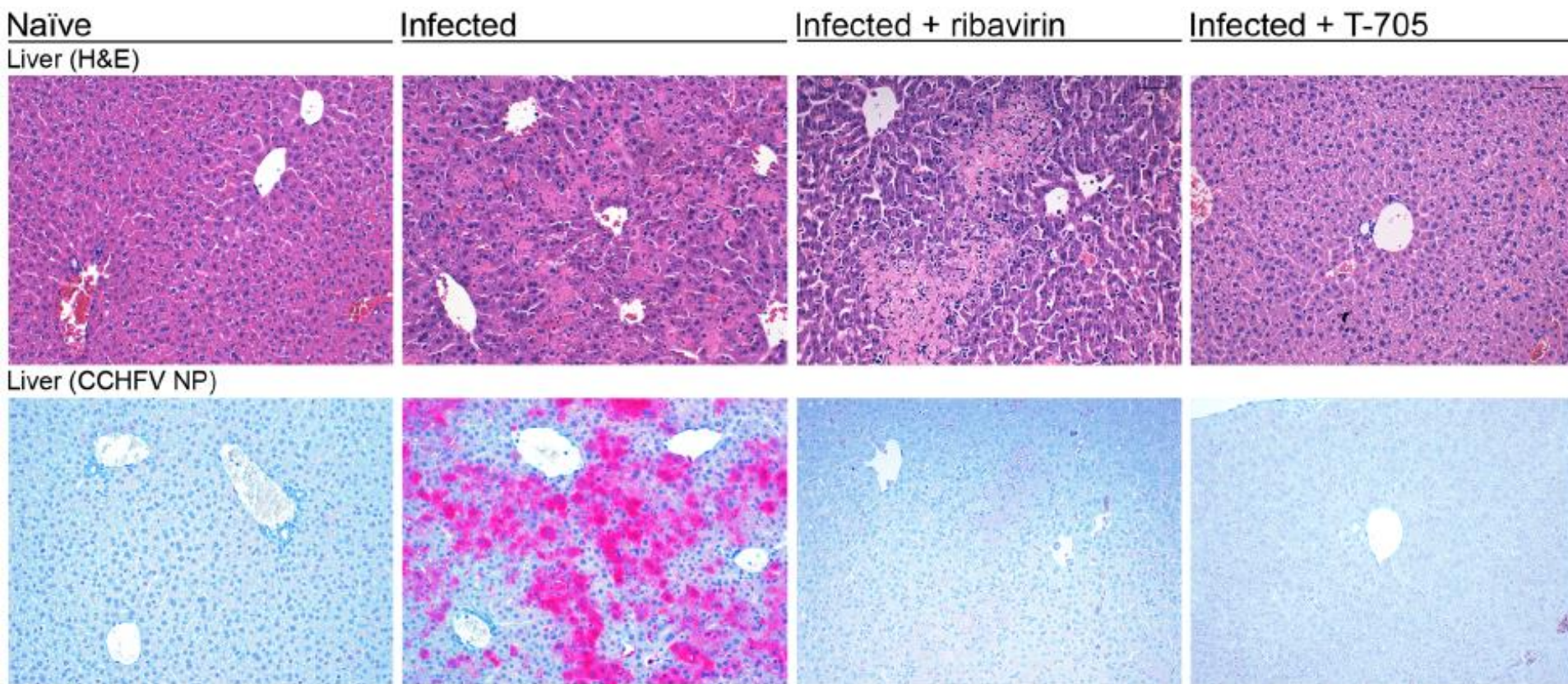
Hideki Tani,^a Aiko Fukuma,^a Shuetsu Fukushima,^a Satoshi Taniguchi,^a
Tomoki Yoshikawa,^a Naoko Iwata-Yoshikawa,^b Yuko Sato,^b Tadaki Suzuki,^b
Noriyo Nagata,^b Hideki Hasegawa,^b Yasuhiro Kawai,^c Akihiko Uda,^d
Shigeru Morikawa,^d Masayuki Shimojima,^a Haruo Watanabe,^e Masayuki Saijo^a

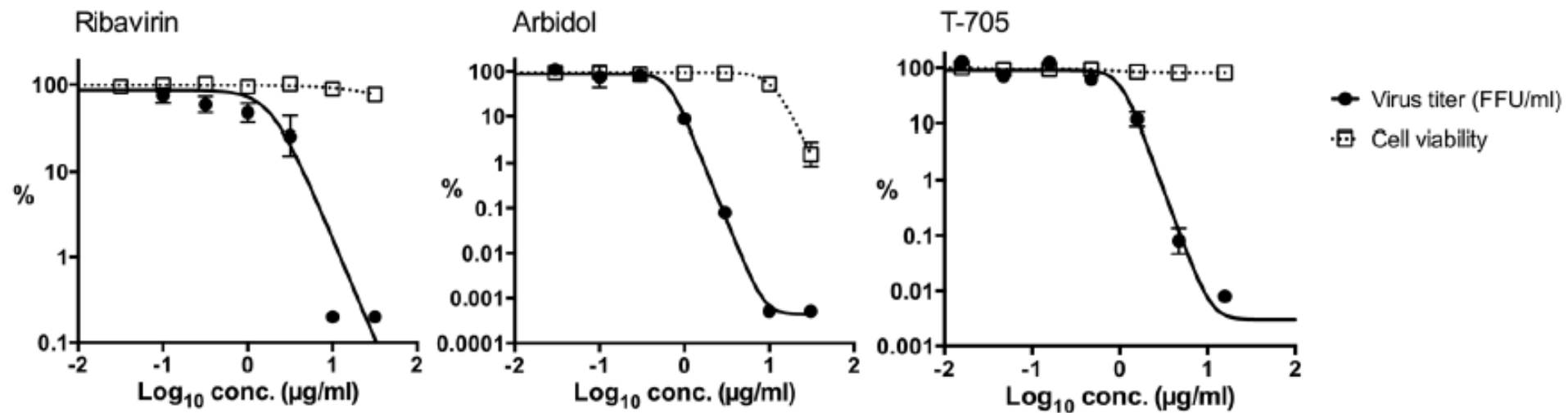
Department of Virology I,^a Department of Pathology,^b Division of Experimental Animal Research,^c and
Department of Veterinary Science,^d National Institute of Infectious Diseases, Tokyo, Japan; National Institute of
Infectious Diseases, Tokyo, Japan^e

vitro and *in vivo*. A time-of-drug-addition study revealed that therapeutic T-705 treatment of SFTSV infection in IFNAR^{-/-} mice was effective. These results suggest that T-705 is a promising candidate for the treatment of SFTS.

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 Neumann³, Christian Bernreuther⁴, Maria Lehmann^{1,2}, Susanne Krasemann³, Stephanie Wurr^{1,2}, Petra Emmerich^{1,2}, Xavier de Lamballerie⁵, Stephan Ölschläger^{1†}, Stephan Günther^{1,2†*}





	Ribavirin (n=2)	Arbidol (n=3)	T-705 (n=2)
IC ₅₀	2.8 μg/ml (1.9–3.7)	0.6 μg/ml (0.08–1.2)	1.1 μg/ml (1.0–1.1)
IC ₉₀	4.7 μg/ml (4.6–4.8)	1.2 μg/ml (0.2–2.4)	1.6 μg/ml (1.5–1.7)
IC ₉₉	9.5 μg/ml (5.8–13.2)	2.0 μg/ml (0.5–3.8)	2.5 μg/ml (2.0–2.9)

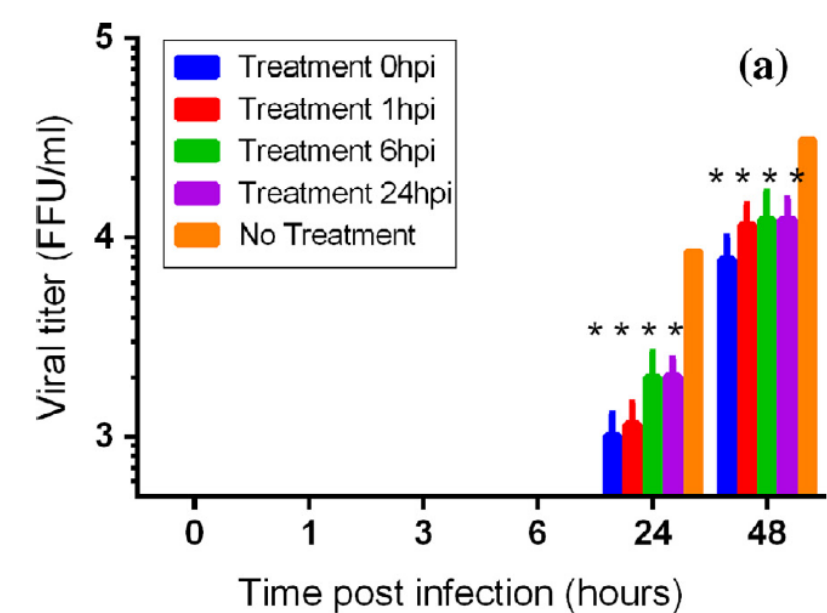
Evaluation of Crimean-Congo hemorrhagic fever virus *in vitro* inhibition by chloroquine and chlorpromazine, two FDA approved molecules

O. Ferraris^a, M. Moroso^b, O. Pernet^{c,1}, S. Emonet^a, A. Ferrier Rembert^a, G. Paranhos-Baccalà^b, C.N. Peyrefitte^{a,b,*}

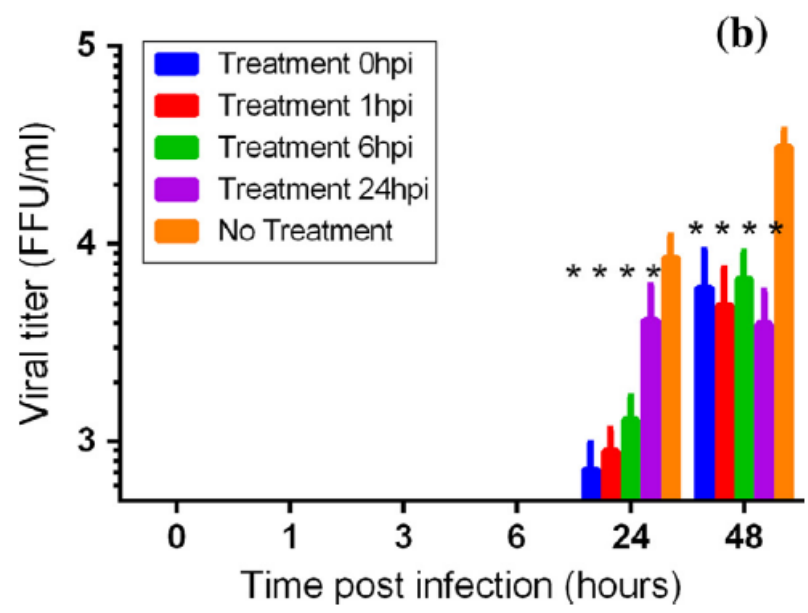
^a Institut de Recherche Biomédicale des Armées, Unité de Virologie, Lyon, France

^b Fondation Mérieux, Laboratoire des Pathogènes Émergents, Lyon, France

^c Unité de Virologie Humaine – INSERM U758, Lyon, France



Chloroquine



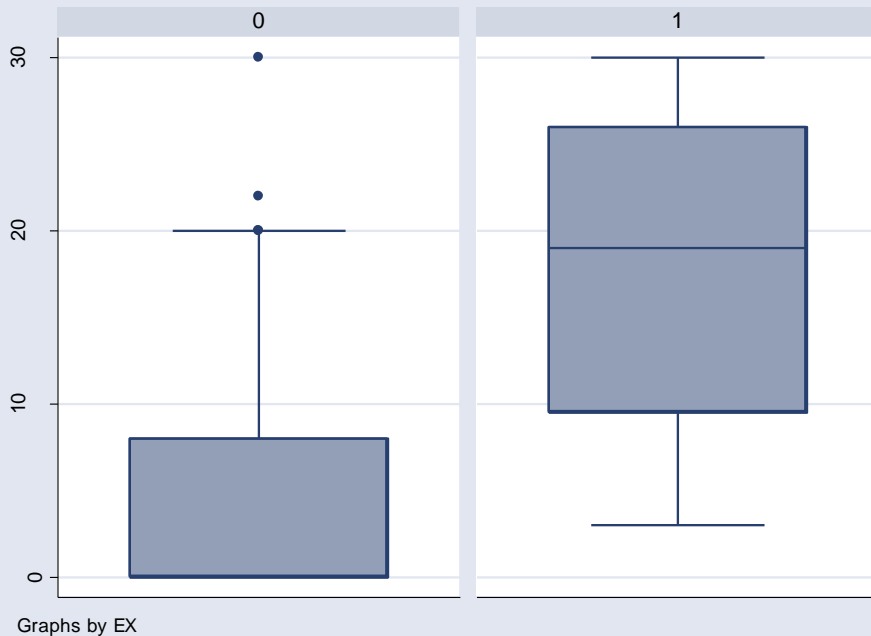
Chlorpromazine

Confounding by indication

Fresh frozen plasma

Survived cases

fatal cases

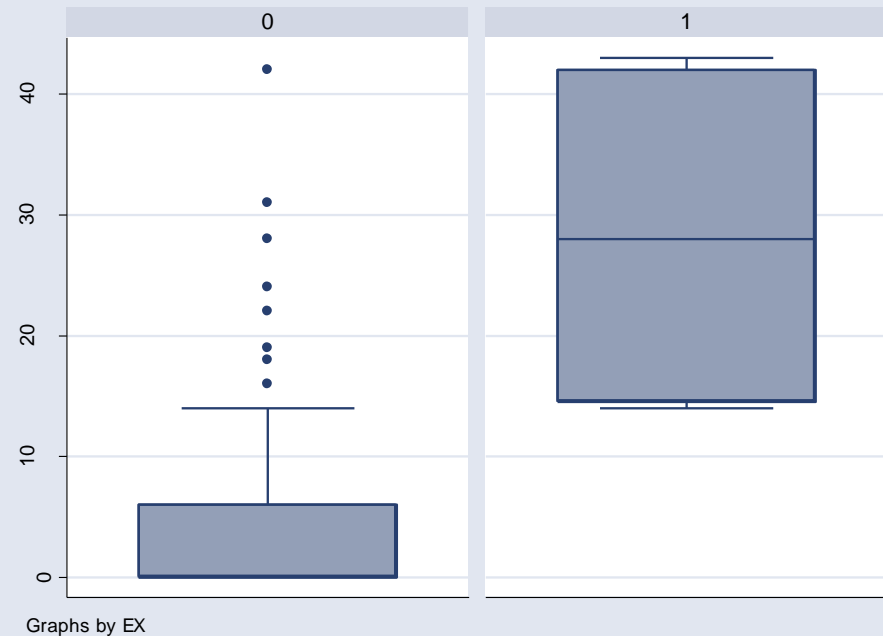


$p=0.002$

Thrombocyte suspension

Survived cases

fatal cases



$p=0.001$

Ergonul, et al. *CMI* 2006

Characteristics of Patients with Crimean-Congo Hemorrhagic Fever in a Recent Outbreak in Turkey and Impact of Oral Ribavirin Therapy

Önder Ergönül, Aysel Çelikbaş, Başak Dokuzoğuz, Şebnem Eren, Nurcan Baykam, and Harika Esener

Infectious Diseases and Clinical Microbiology Department, Ankara Numune Education and Research Hospital, Ankara, Turkey

patients infected with CCHF virus is suggested, which will be helpful for future outbreaks.

Patients and methods. Ankara Numune Education and Research Hospital (Ankara, Turkey) is one of the largest referral-based tertiary care community hospitals in Turkey. Patients with acute febrile syndrome characterized by malaise, bleeding, leukopenia, and thrombocytopenia were admitted to our clinic during the spring and summer of 2002 and 2003. Patients who had IgM antibodies or PCR results positive for CCHF virus in blood or tissue specimens were included to the study. Written informed consent was obtained from patients

Clin Infect Dis 2004

Table 3. Univariate and Adjusted Analysis for Prediction of Death

Factor	Univariate Analysis		Adjusted Analysis	
	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.

Clin Infect Dis 2013

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 Ergönül²

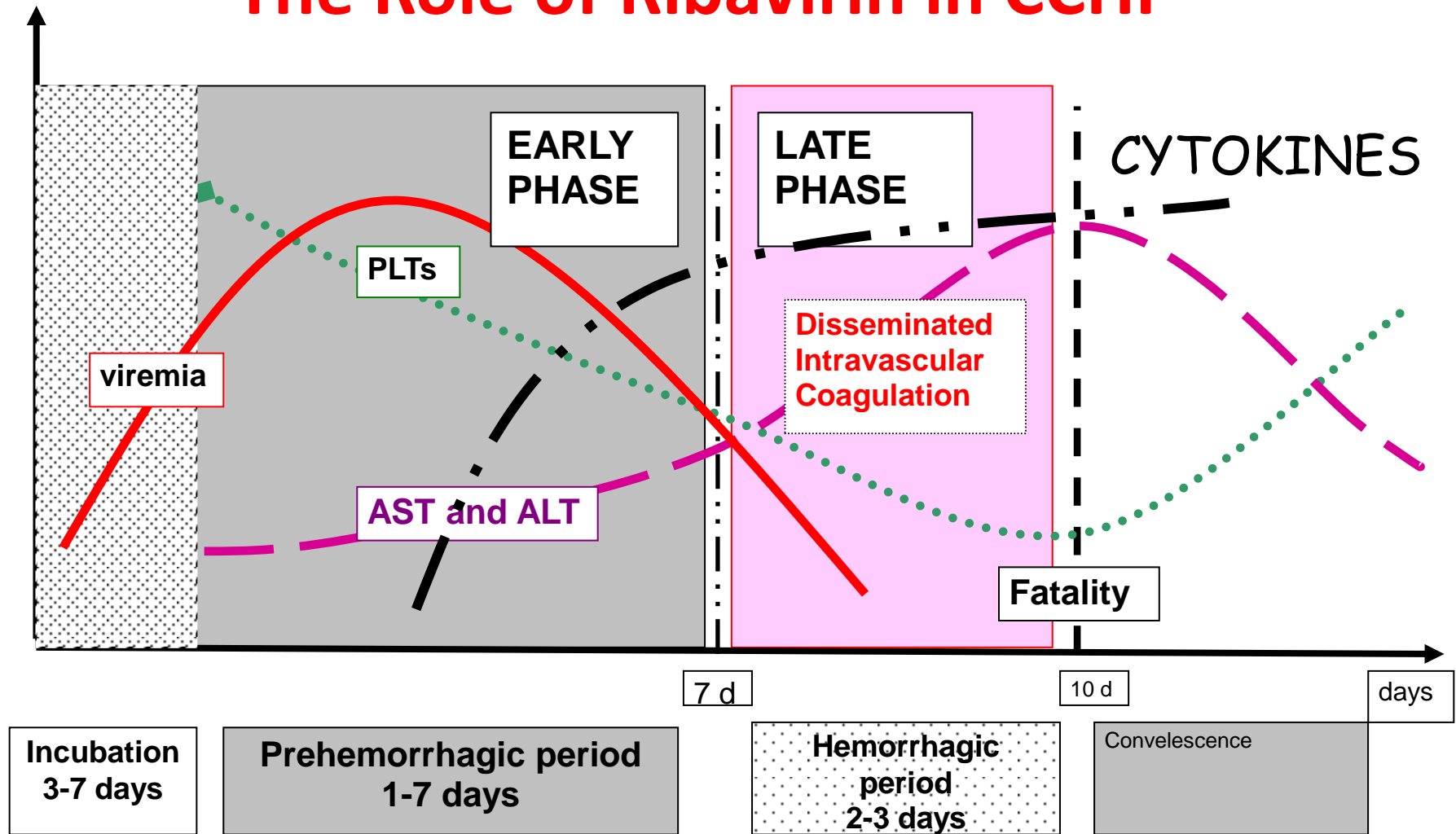
¹Clinical Microbiology and Infectious Diseases Clinic, Ankara Numune Education and Research Hospital, Ankara, and ²Infectious Diseases and Clinical Microbiology, Koç University, School of Medicine, Istanbul, Turkey

Table 2. Effects of RBV and Additional Therapy on CFRs Among Patients With Crimean-Congo Hemorrhagic Fever, Stratified by SSI

SSI, Disease Severity	CFR, % (Proportion of Patients), by RBV Status			CFR, % (Proportion of Patients), by CS Status		
	RBV	No RBV	<i>P</i> Value	CS	No CS	<i>P</i> Value
0–2, mild	0 (0/77)	0 (0/26)		0	0 (0/103)	
3–9, moderate	1.49 (2/134)	17 (3/18)	.001	4 (1/28)	1 (1/106)	.308
10–13, severe	67 (16/24)	100 (2/2)	.326	50 (8/16)	100 (8/8)	.014

Abbreviations: CFR, case-fatality rate; CS, corticosteroid; RBV, Ribavirin; SSI, severity scoring index.

The Role of Ribavirin in CCHF



Ribavirin could be more effective in early phase

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

B Arda,¹ A Aciduman,¹ J C Johnston^{2,3}

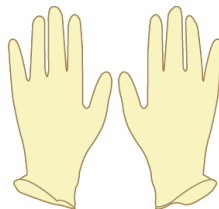
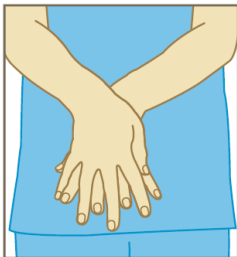
CONCLUSION

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.

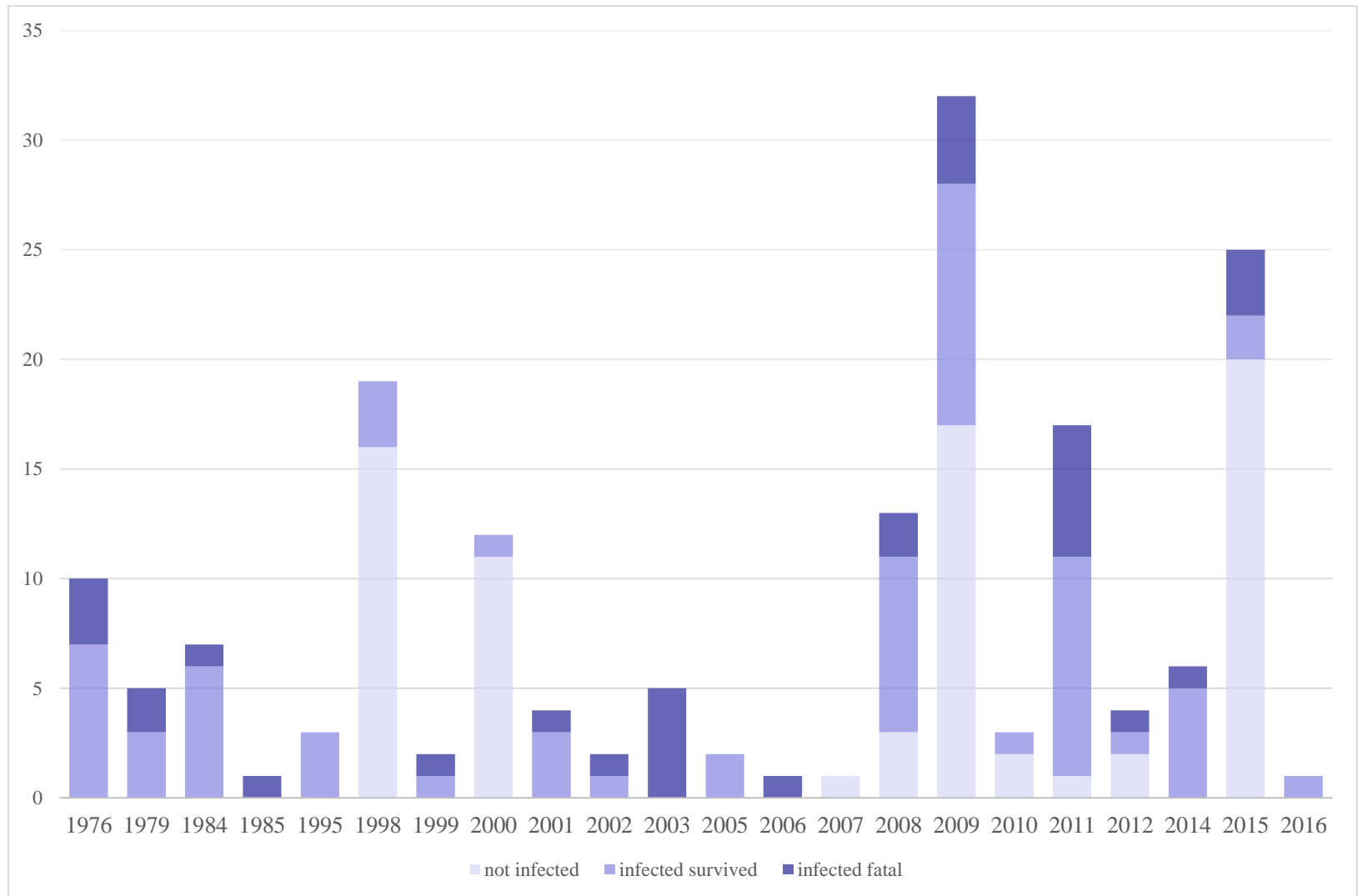
VHF	Human to human transmission
Ebola	High
Marburg	High
Lassa	Moderate
S.America	Low
Hantaan	No
RV	No
CCHF	High
Yellow fever	No
Dengue	No
Omsk	Not reported
Kyasanur	Not reported
Alkhumra	Not reported

Hand hygiene and use of PPE based on risk assessment

- Always before and after patient contact, and after contact with contaminated environmental surfaces or equipment
- If direct contact with patient's blood and body fluids, secretions, excretions, mucous membranes or non-intact skin
- If there is a risk of spills onto the health-care worker's face

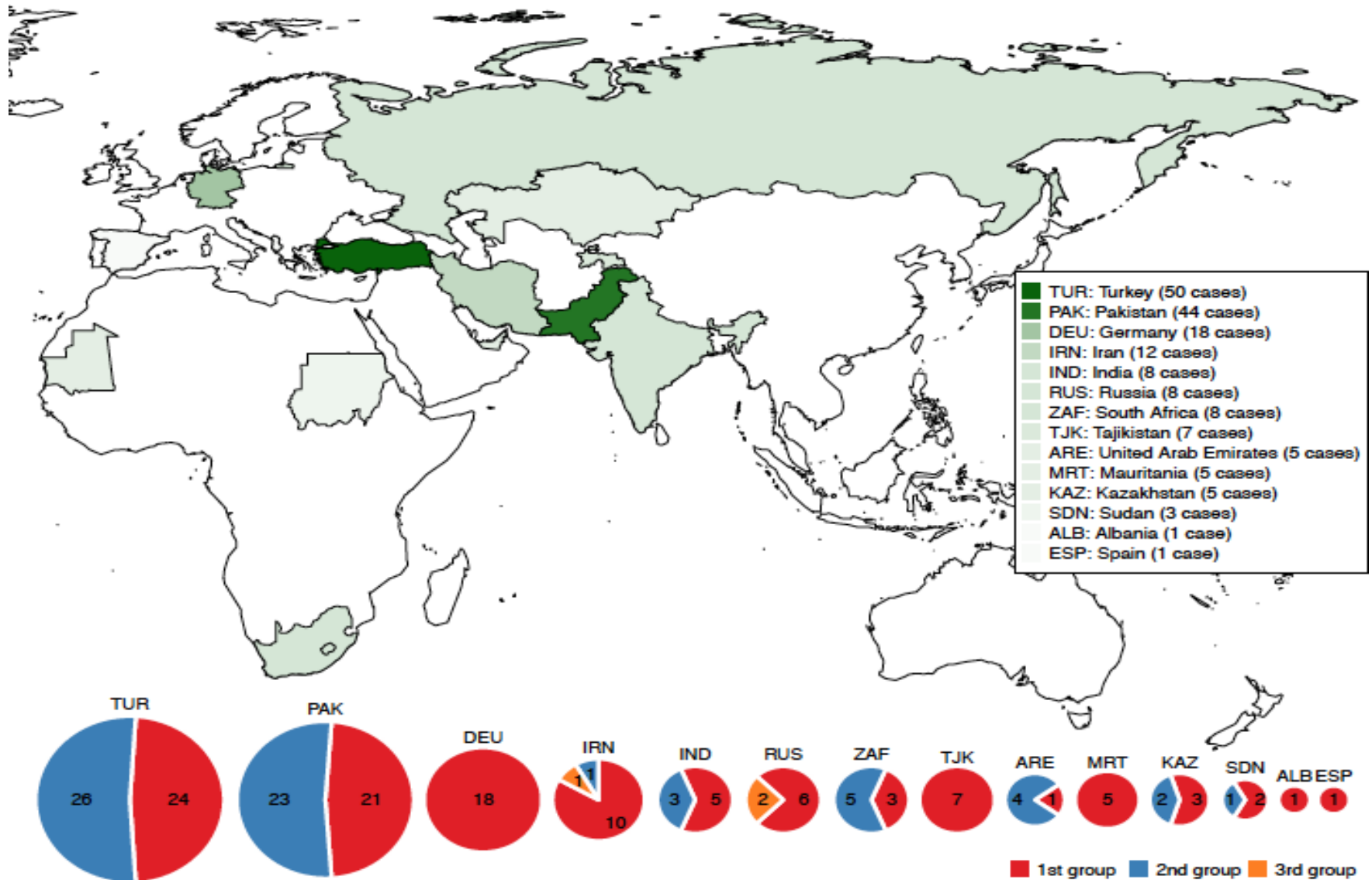


Crimean-Congo Hemorrhagic Fever among Health Care Workers



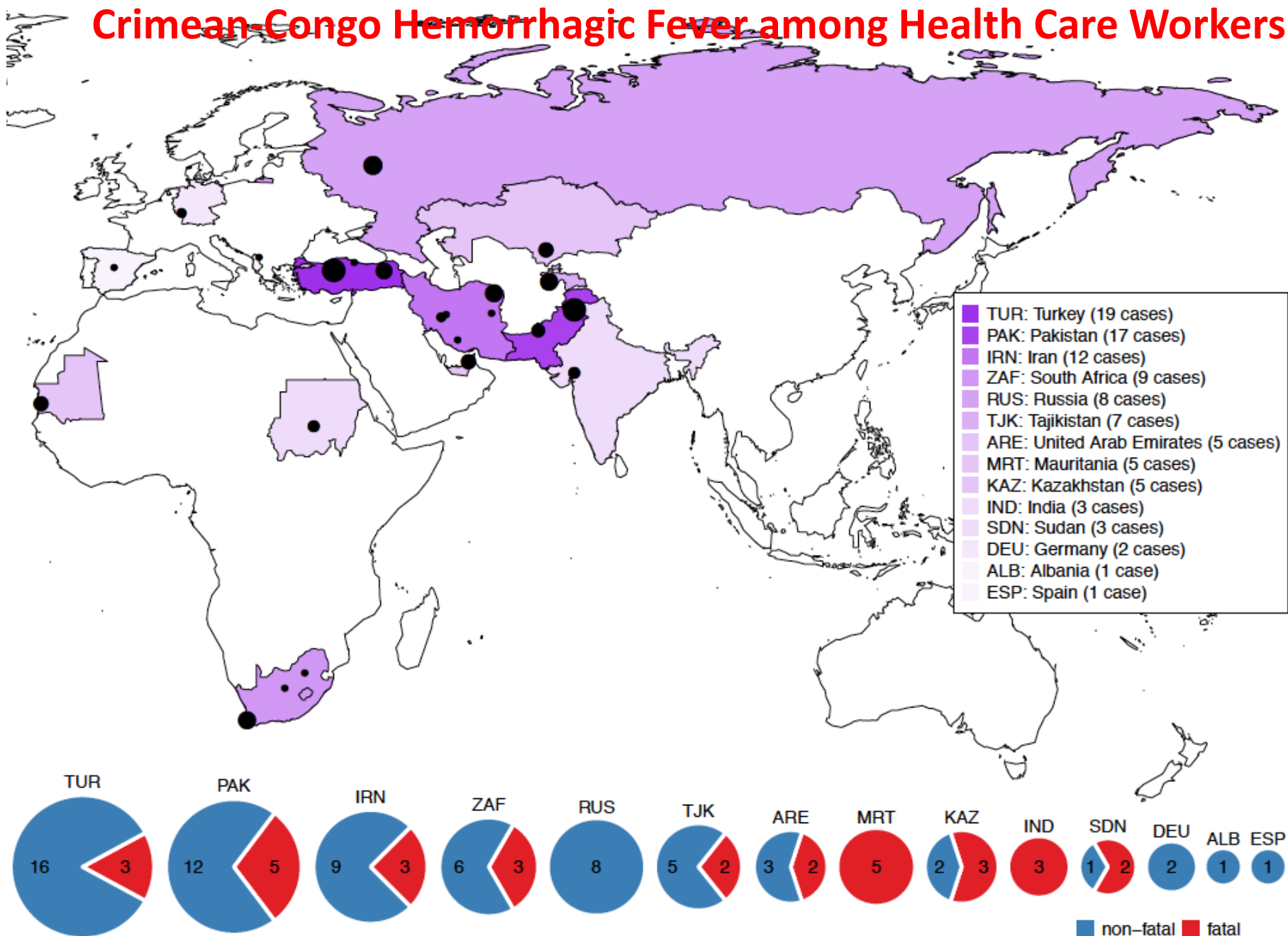
submitted

Crimean-Congo Hemorrhagic Fever among Health Care Workers

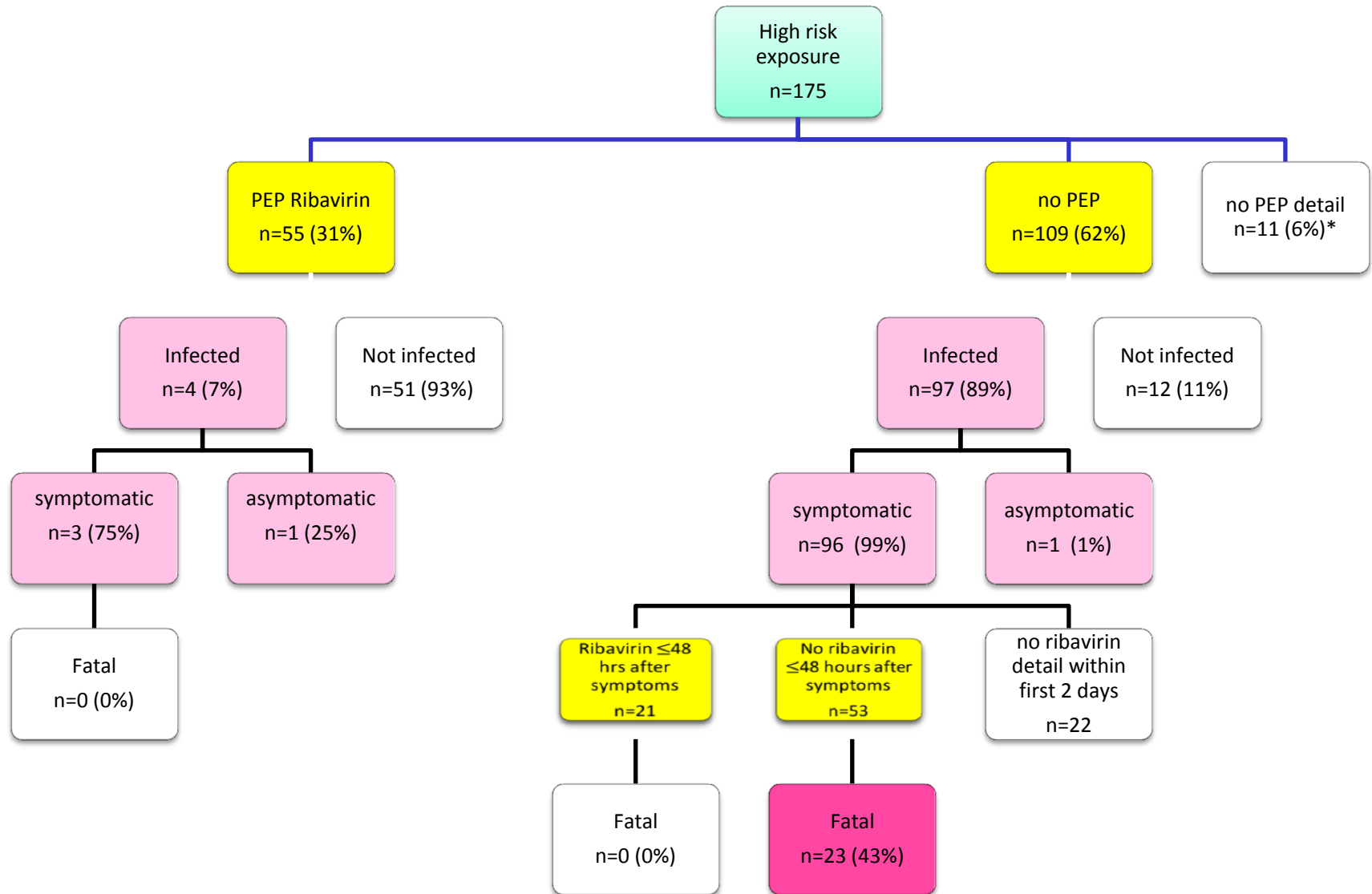


● 12 cases ● 8 cases ● 7 cases ● 6 cases ● 5 cases ● 3 cases ● 2 cases ● 1 case

Crimean-Congo Hemorrhagic Fever among Health Care Workers



Crimean-Congo Hemorrhagic Fever among Health Care Workers



Ribavirin use among Health Care Workers

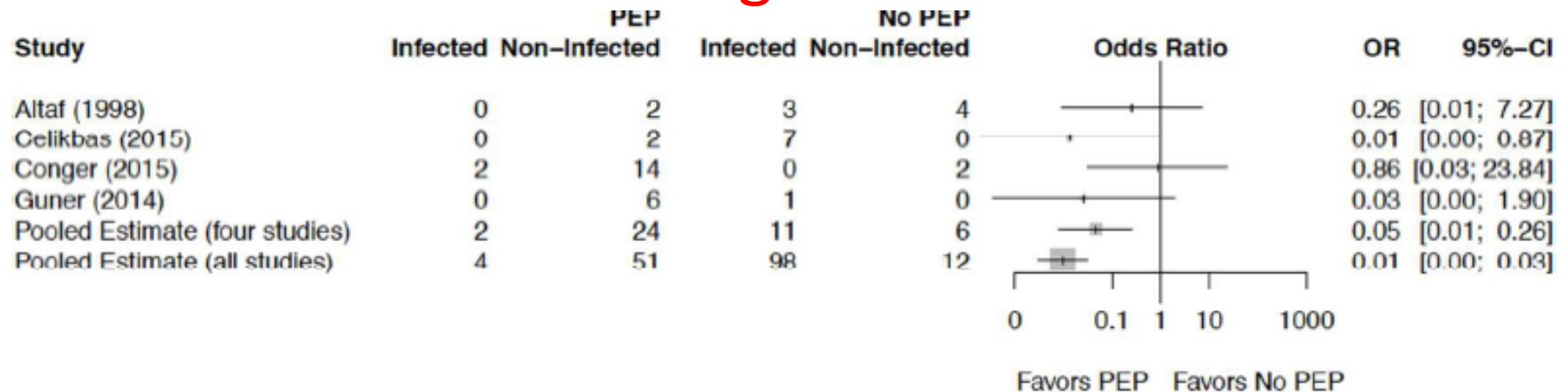


Figure 2 (A). Two step meta-analysis for effectiveness of PEP against CCHF infection.

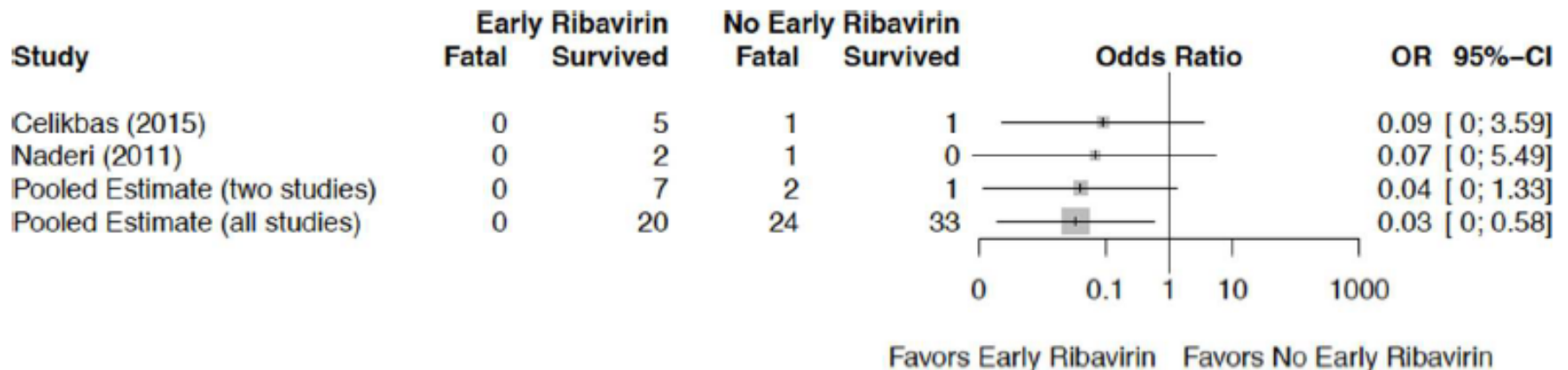


Figure 2 (B). Two step meta-analysis for effectiveness of early ribavirin use for survival in CCHF infection.

Future Research is needed

Diagnosis	Standard case definitions
	Rapid and cheap diagnostic test
Transmission dynamics	Ro Detection in nature
Risk Prediction	Risk maps, Models
Treatment	Evaluation of studies New antivirals: favipiravir
Prevention	Vaccine studies
Vector control	Little known about repellents
Education	More effective methods

Thank you

Nurcan Baykam

Füsün Can

Aysel Çelikbaş

Başak Dokuzoğuz

Şebnem Eren

Ayşen Gargılı

Mehmet Gönen

Şiran Keske

Kenan Midilli

Zati Vatansever