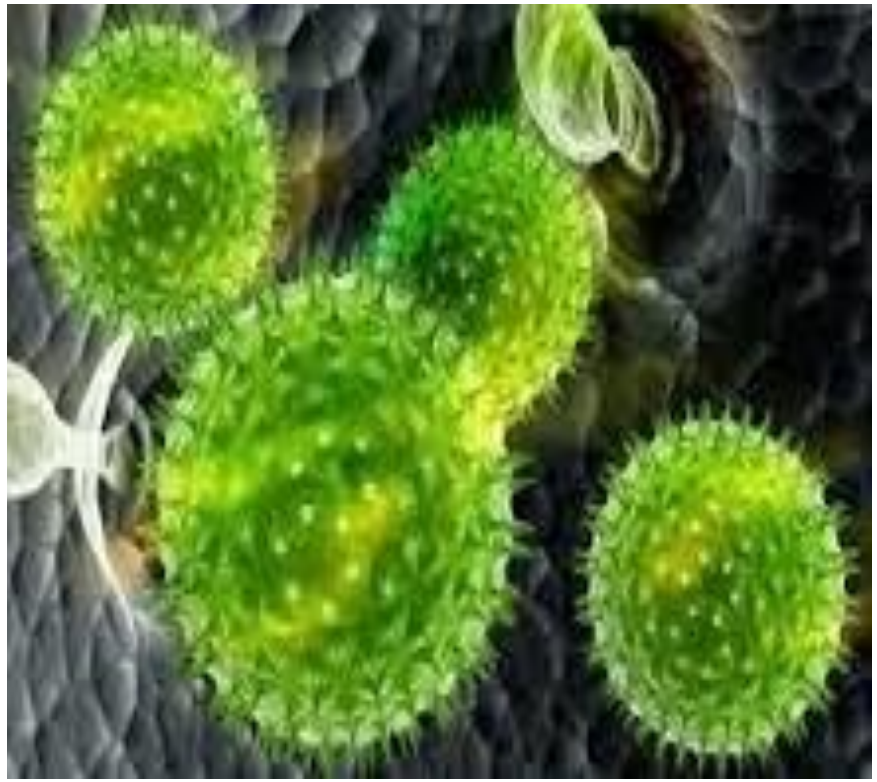


LSTM
LIVERPOOL SCHOOL
OF TROPICAL MEDICINE

Crimean-Congo Haemorrhagic Fever

14 December 2023

Tom Fletcher

Conflicts of interest

- Nil significant
- Received research grant funding from:

- Wellcome Trust (CCHF, Lassa, VHF & AGILE)
- National Institute Health Research (HPRU)
- Medical Research Council UK (AGILE & CCHF)
- UK Ministry of Defence (CCHF)
- Unitaid (AGILE CST3)
- Ridgeback pharmaceuticals (AGILE CST2)
- GSK (AGILE CST5)
- GuardRX (UMIT trial)
- The Pandemic Institute (CCHF)


LSTM
LIVERPOOL SCHOOL
OF TROPICAL MEDICINE

Daily Mail 2 Aug 2014

Just two beds: There is only one operational High Secure Infectious Diseases Unit (HSIDU) in the UK, at the Royal Free Hospital in London. It has an array of equipment to ensure the patient did not pass on the killer virus

World Health Organization

Definition

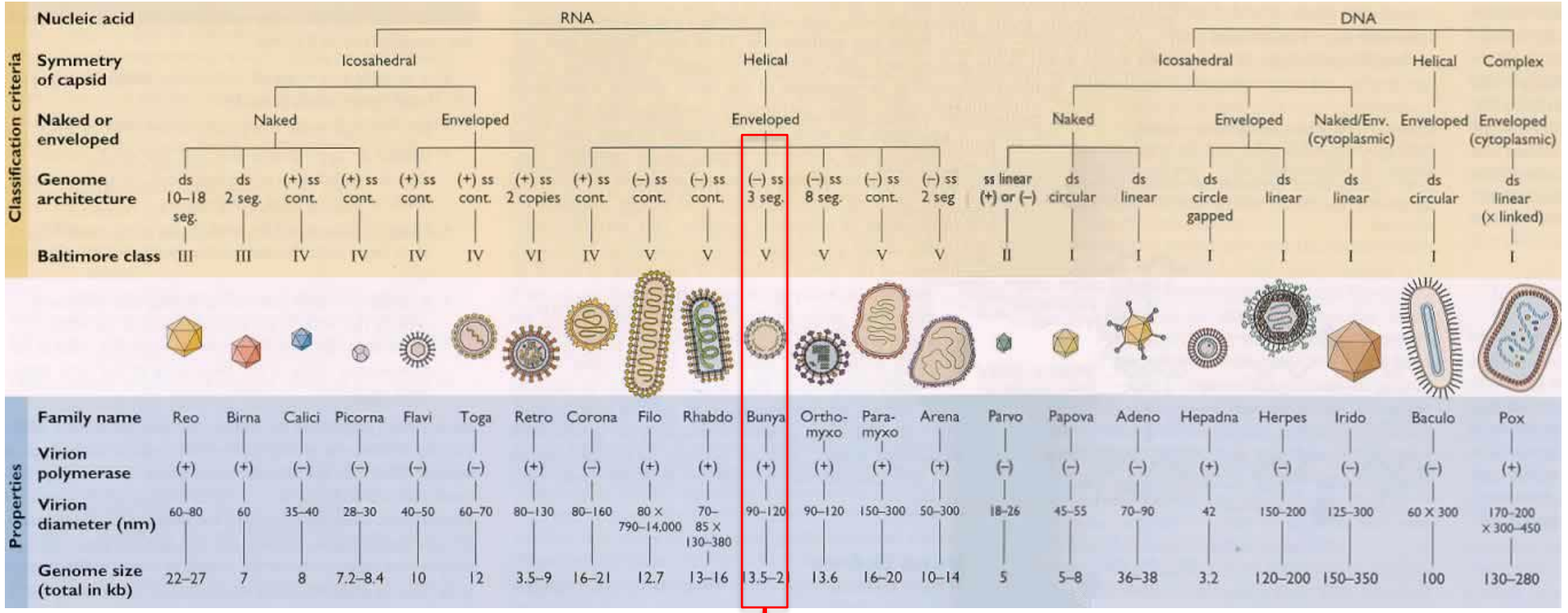
Viral haemorrhagic fever is a syndrome

By definition:

- Acute viral infection
- Fever
- Bleeding disorder

Caused by a diverse group of unrelated RNA viruses with varying pathophysiology and clinical expression

Classification by virus



e.g. Hantavirus (haemorrhagic fever with renal syndrome)
Crimean-Congo haemorrhagic fever
Rift Valley Fever

High Consequence Infectious Disease (HCID)

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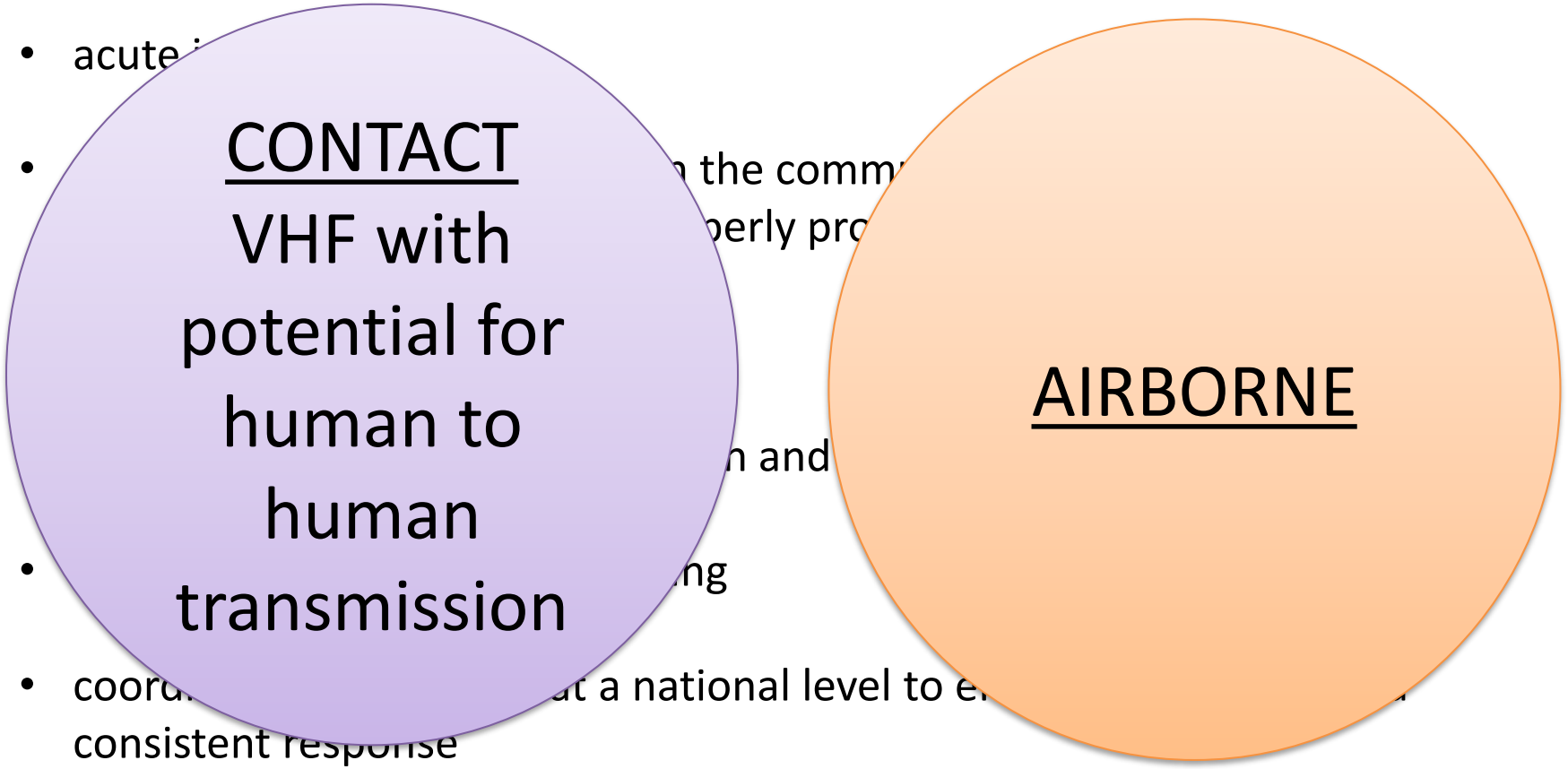
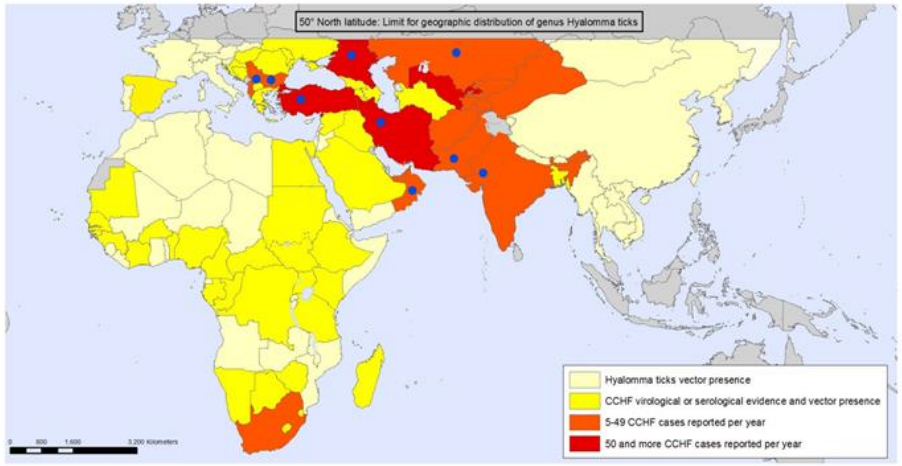
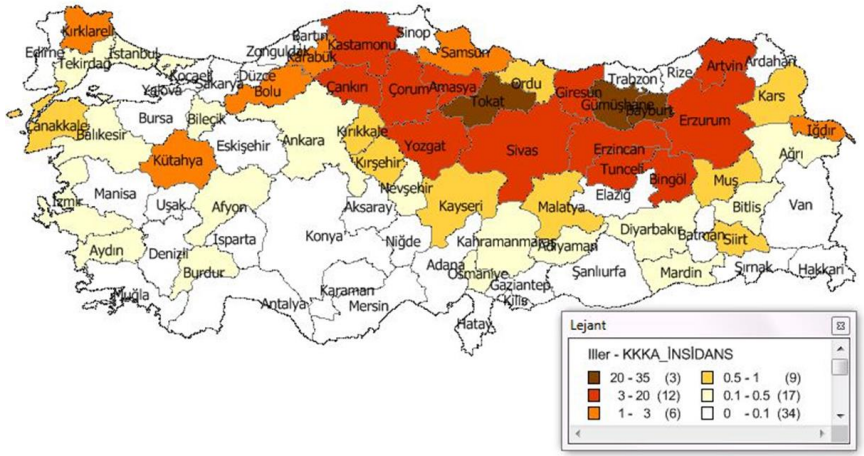


Crimean-Congo haemorrhagic fever

- Tick-borne zoonosis
- Nairovirus group in the family of Bunyavirale
- First documented in Crimea (1944), observed in Congo (1956)
- Characterized by fever, thrombocytopenia and haemorrhage
- Treatment is mainly supportive +/- ribavirin / Favipiravir
- Designated a priority pathogen for R&D by WHO





Akinci E, Bodur H, Leblebicioglu H. Vector Borne Zoonotic Dis 2013;13(7):429-37
Leblebicioglu H. Int J Antimicrob Agents 2010;36 Suppl 1:S43-6
Bodur H et al. Emerg Infect Dis 2012;18(4):640-2

WHO's R&D Blueprint 2018

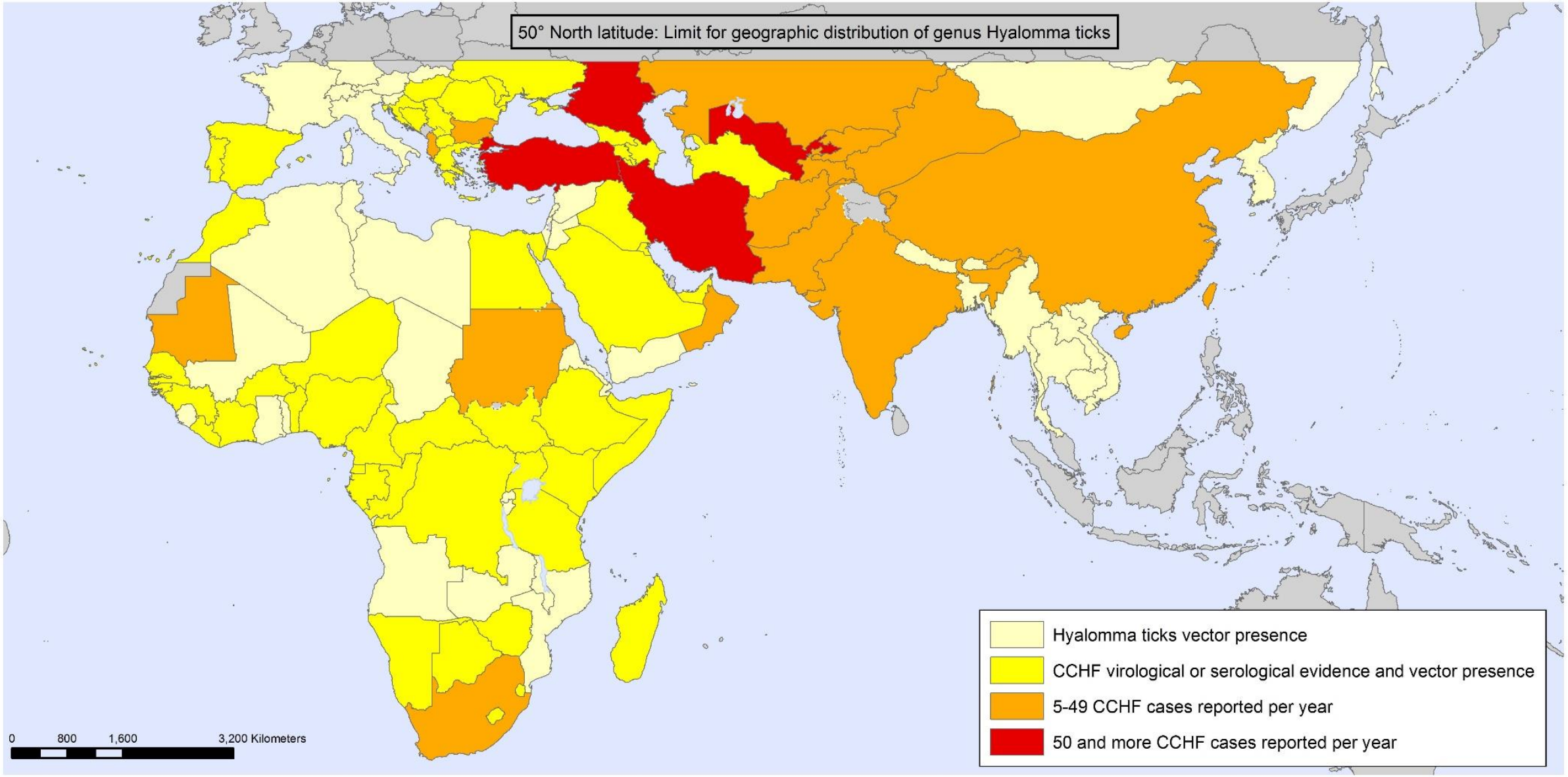
Action to prevent epidemics

Priority Pathogens

- COVID-19 (updated)
- Crimean-Congo Haemorrhagic Fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- "Disease X"*

** Disease X represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease. The R&D Blueprint explicitly seeks to enable early cross-cutting R&D preparedness that is also relevant for an unknown "Disease X".*

Geographic distribution of Crimean-Congo Haemorrhagic Fever



Sudan – UK Public Health Rapid Support Team

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Detection of Crimean-Congo Haemorrhagic Fever cases in a severe undifferentiated febrile illness outbreak in the Federal Republic of Sudan: A retrospective epidemiological and diagnostic cohort study

Hilary Bower[1,2‡*], Mubarak El Karsany[3,4‡], Mazza Alzain[5], Benedict Gannon[1,6], Rehab Mohamed[4], Iman Mahmoud[4], Mawahib Eldegail[4], Rihab Taha[4], Abdalla Osman[4], Salim Mohamednour[5¤a], Amanda Semper[7], Barry Atkinson[7¤b], Daniel Carter[7], Stuart Dowall[7], Jenna Furneaux[7], Victoria Graham[7], Jack Mellors[7], Jane Osborne[7], Steven T. Pullan[7], Gillian S. Slack[7], Tim Brooks[7], Roger Hewson[7], Nicholas J. Beeching[8], Jimmy Whitworth[1,2], Daniel G. Bausch[1,6,9], Tom E. Fletcher[8‡]

Crimean-Congo haemorrhagic fever

Mail Online News

Man, 38, dies from deadly tropical disease after returning to the UK from Afghanistan

By Anthony Bond
12:08, 06 Oct 2012, updated 18:14, 14 Oct 2012

Health Care Response to CCHF in US Soldier and Nosocomial Transmission to Health Care Providers, Germany, 2009[1]

Nicholas G. Conger, Kristopher M. Paolino, Erik C. Osborn, Janice M. Rusnak, Stephan Günther, Jane Pool, Pierre E. Rollin, Patrick F. Allan, Jonas Schmidt-Chanasit, Toni Rieger, and Mark G. Kortepeter

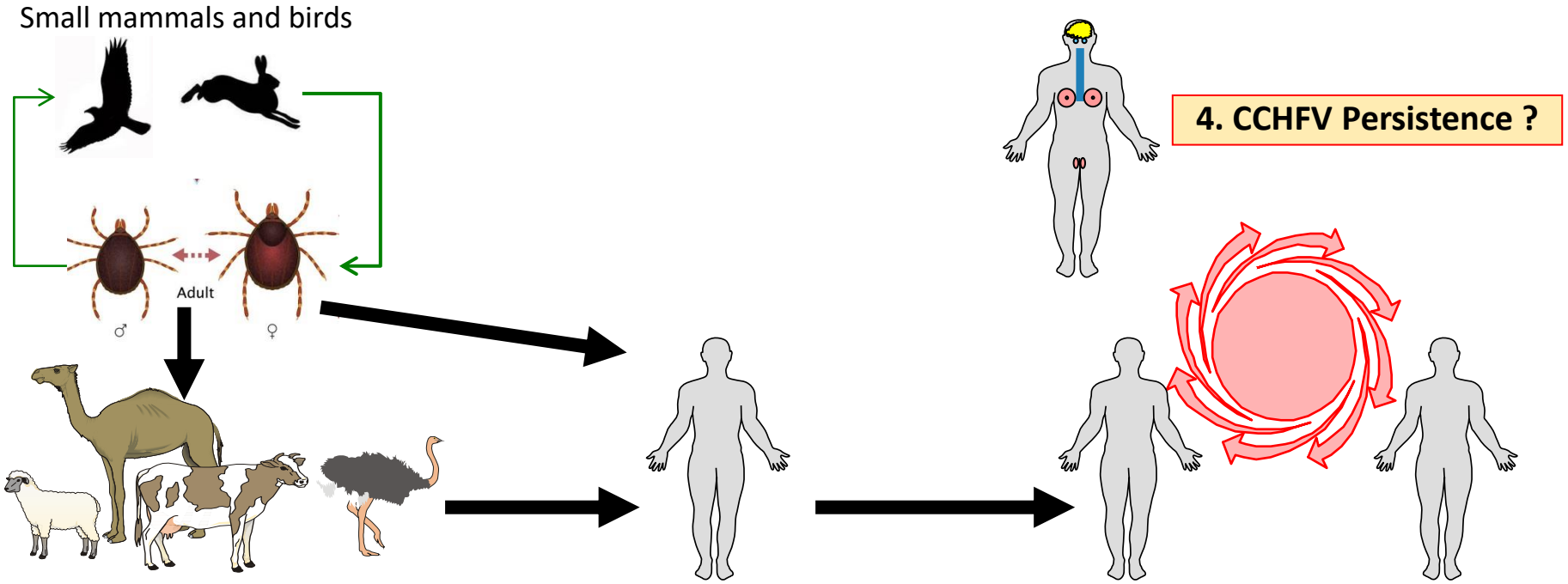
In 2009, a lethal case of Crimean–Congo hemorrhagic fever (CCHF), acquired by a US soldier in Afghanistan, was treated at a medical center in Germany and resulted in nosocomial transmission to 2 health care providers (HCPs). After his arrival at the medical center (day 6 of illness) by aeromedical evacuation, the patient required repetitive bronchoscopies to control severe pulmonary hemorrhage and renal and hepatic dialysis for hepatorenal failure. After showing clinical improvement, the patient died suddenly on day 11 of illness from cerebellar tonsil herniation caused by cerebral/cerebellar edema. The 2 infected HCPs were among 16 HCPs who received ribavirin postexposure prophylaxis. The infected HCPs had mild or no CCHF symptoms. Transmission may have occurred during bag-valve-mask ventilation, breaches in personal protective equipment during resuscitations, or bronchoscopies generating infectious aerosols. This case highlights the critical care and infection control challenges presented by severe CCHF cases, including the need for experience with ribavirin treatment and postexposure prophylaxis.

blood or body fluids of infected animals (*1*–*3*). The disease is characterized by the abrupt onset of a febrile illness usually 2–7 d (range 2–14) after exposure to the virus and by subsequent severe changes in mental status, hemorrhagic manifestations, and hepatorenal failure (*1*,*4*). Case-fatality rates vary by region but are 30%–50% (range 1%–73%) in most regions; death generally occurs 5–14 d after symptom onset and is most commonly a result of multi-organ failure, shock, severe anemia, cerebral hemorrhage, and/or pulmonary edema (*1*,*5*).

We report a fatal case of CCHF in a US soldier deployed to Afghanistan, who was aero-evacuated to Germany for treatment, and the documented nosocomial infection of 2 health care providers (HCPs) who were at risk for exposure and had received ribavirin postexposure prophylaxis (PEP). We also review infection control interventions and contact surveillance, both of which were required because of the patient's severe bleeding and the risk for aerosol production. Research on human subjects was conducted

CCHF transmission and maintenance

EDPLN



1. Maintenance in nature	2. Primary human infection	3. Secondary transmission
In nature, CCHF virus maintains itself in unobserved enzootic tick-vertebrate-tick cycles.	Humans are infected either by ticks bite or through direct contact with blood or tissues of infected ticks or viraemic vertebrates including wild animals and livestock.	Secondary human-to-human transmission occurs through direct contact with the blood, secretions, organs or other body fluids of infected persons. High transmission risk when providing direct patient care or handling dead bodies (funerals).

Know our history: NAMRU Russian translations……

TRANSLATION 721 (T721)
MEDICAL ZOOLOGY DEPARTMENT
UNITED STATES NAVAL MEDICAL RESEARCH UNIT No. 3
CAIRO, EGYPT

TRANSLATION FROM RUSSIAN. BEREZIN, V. V., CHUMAKOV, M. P., RESHETNIKOV, I. A., & ZGURSKAYA, G. N. (1971)*. Study of the role of birds in the ecology of Crimean hemorrhagic fever virus. Mater. 6. Simp. Izuch. Virus. Ekol. Svyazan. Ptits. (Omsk, 1971), pp. 94-95.

Birds are the chief hosts of immature Hyalomma plumbeum plumbeum** tick vectors of Crimean hemorrhagic fever (CHF) in Astrakhan Oblast. In 1968, CHF virus was isolated from nymphs collected from rooks. Thus, we aimed to clarify the role of birds in CHF virus ecology.

More than 500 bird blood sera, chiefly of Corvidae which are the main infection donors to immature H. plumbeum, were examined by serological tests (DPRA and CF). All were negative. No CHF virus was isolated from blood and organs of 360 birds belonging to 35 species.

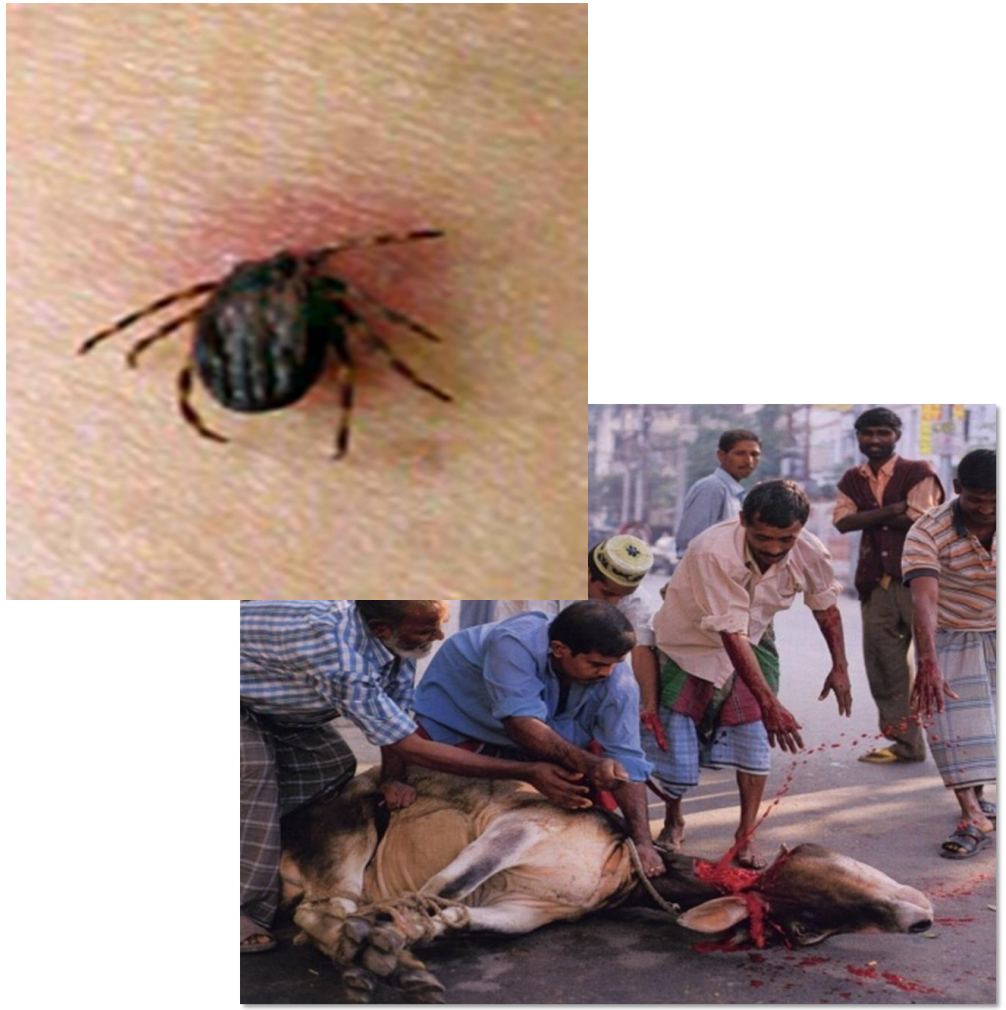
TRANSLATION 876 (T876)
MEDICAL ZOOLOGY DEPARTMENT
UNITED STATES NAVAL MEDICAL
RESEARCH UNIT NUMBER THREE
CAIRO, EGYPT

TRANSLATION FROM RUSSIAN. CHUMAKOV, M.P. (1972)*. Investigations of arboviruses in the USSR and the question of possible association through migratory birds between natural arbovirus infection foci in the USSR and warm-climate countries. In: Transcontinental connections of migratory birds and their role in distribution of arboviruses edited by Cherepanov, A. I. Mater. 5. Simp. Izuch. Roli Pereletn. Ptits. Rasp. Arbovirus. (Novosibirsk, July 1969), pp. 133-138.

When Hammon et al (1942) first suggested the term "arthropod-borne viruses" (abbreviated to arboviruses), it was considered that these agents (for example those of seasonal encephalitis) always reproduce in certain arthropod tissue (mosquitoes, ticks, and other bloodsucking species) and are transmitted to other susceptible organisms only by bloodsucking arthropods.

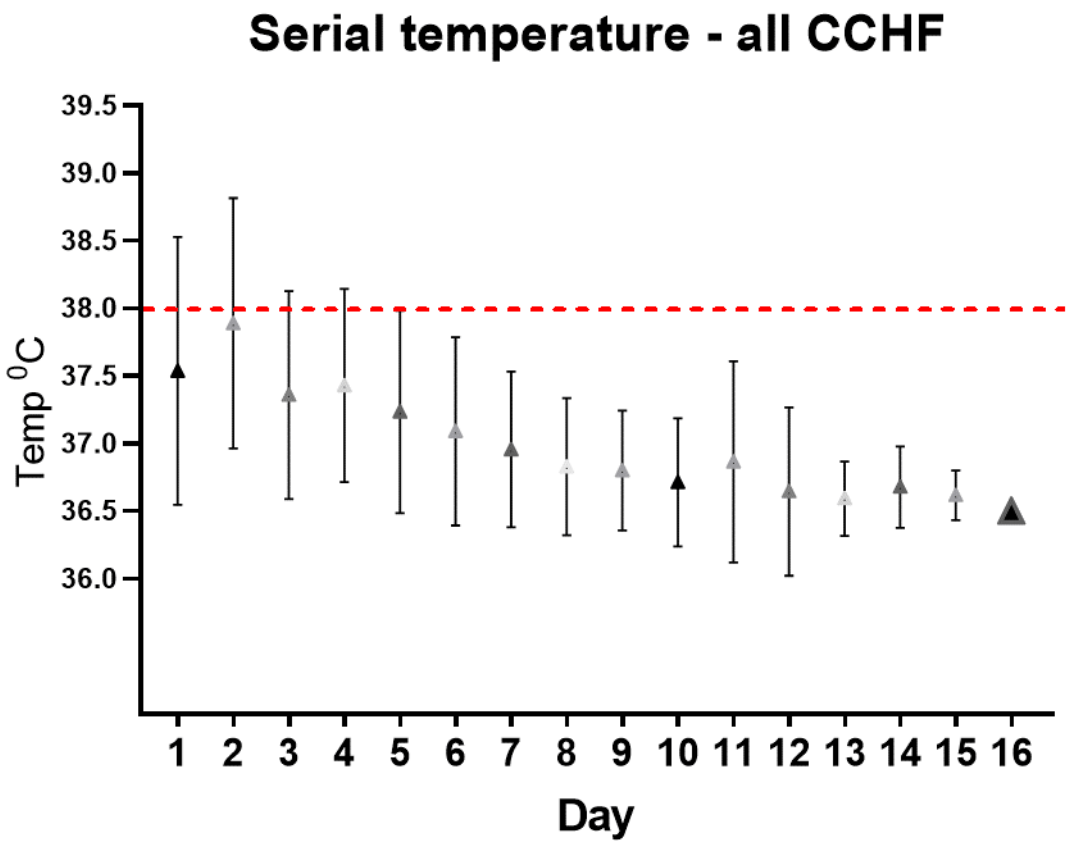
CCHF Clinical features – clinical trial case definitions

- The clinical spectrum of illness and disease severity in patients with CCHF is broad, and it is estimated that up to 88% of infections may be sub-clinical (Bodur 2012).
- In highly endemic areas such as Tokat and Sivas provinces in Turkey, the CCHF IgG seroprevalence has been shown to be as high as 12.8% in rural populations (Gunes 2009).
- The majority of the patients with CCHF in Turkey report a history of tick bite (70%) (Yilmaz 2009) .
- The incubation period ranges from 1-13 days (typically 1-3 days after tick bite), and has been shown to be shorter in fatal cases (Nabeth 2004 & Vorou 2007)



CCHF Clinical features

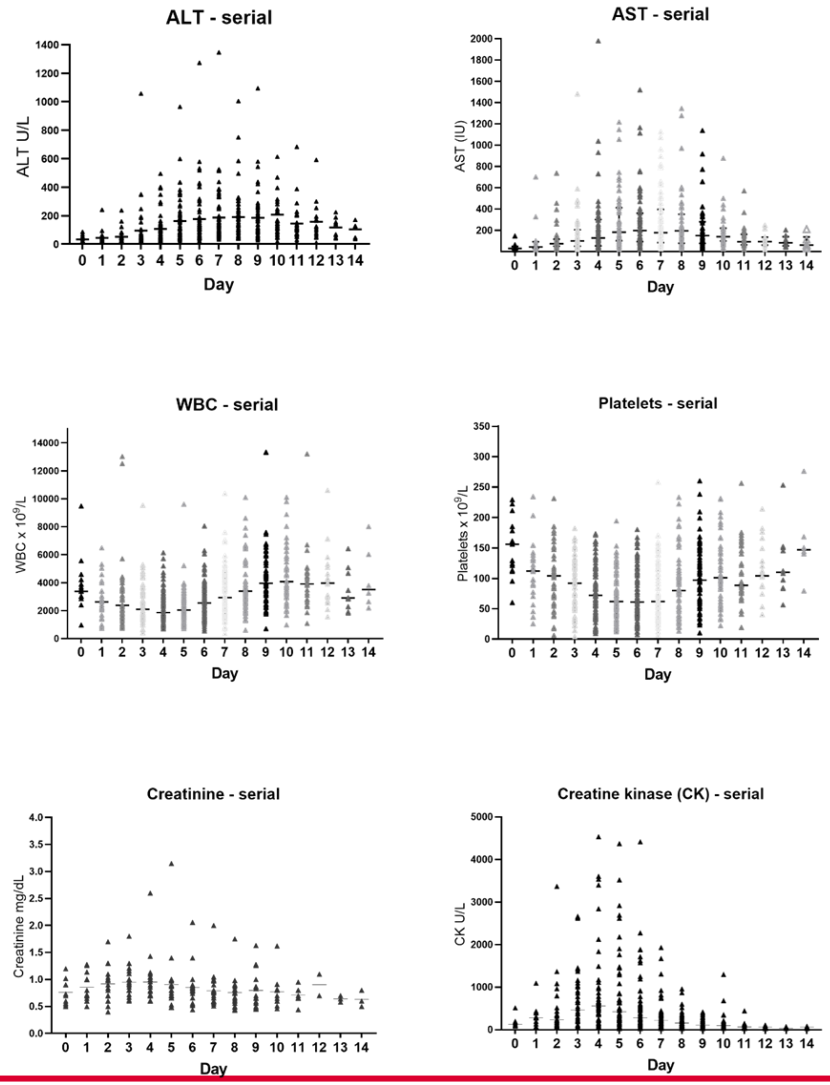
- Data from a large cohort in Turkey (n=1670) showed that the most common complaints at presentation were fever (90%), fatigue (90%), headache (70%), myalgia (70%) and nausea (65%).
- Haemorrhagic manifestations were reported in 23% of patients at admission (Haematomas, ecchymosis, epistaxis, vaginal bleeding)
- Leucopenia (88.9%), thrombocytopenia (93.2%) and elevated transaminases (85.9%), LDH (75.8%) and CK (65.9) were the most common laboratory abnormalities at presentation (Yilmaz 2009)



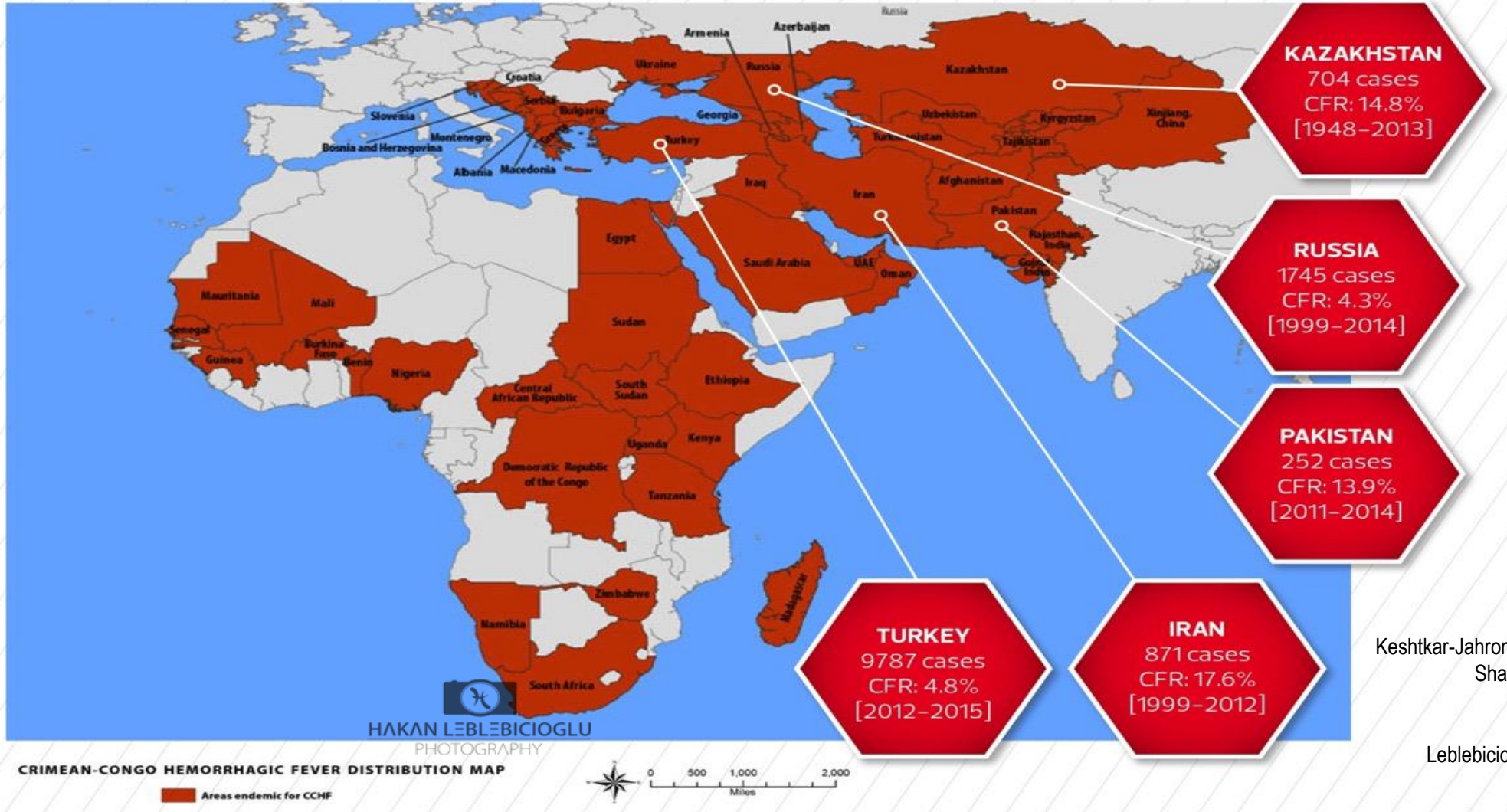
CCHF clinical features

- Median time to presentation/hospital admission 3-4 days
- Median duration of hospitalisation 8 days
- Median age 50 years

- Alanine transaminase and aspartate transaminase (ALT/AST) reach peak levels at day 7/8 of illness.
- The lowest median white blood count was at day 4 with the median lowest platelet count occurring at day 6 of illness.
- The highest median/peak of creatine kinase and APTT observed was at Day 4.
- Acute renal impairment occurred by RIFLE criteria uncommon (4%) - at the time of the AKI stage 3 creatinine kinase levels were elevated at 688/685 U/L.
- Critical care admission 5-10%.



Varying CCHF Case fatality rates……



Keshtkar-Jahromi M et al. Antiviral Research 2013;100(1):20-8
Shaikh MA et al. J Pak Med Assoc 2015;65(5):576
Nurmakhanov T, et al. IJID 2015;38:19-23
Volynkina AS et al. Plague , 2015: no. 1
Leblebicioglu H et al. Antiviral Research 2016;126:21-34

SOCIAL MOBILIZATION

Key Messages for Social Mobilization and Community Engagement in Intense Transmission Areas

September 2014

CCHF Prognostic indicators

- The first study evaluating prognostic indicators in CCHF was by Swanepoel et al in South Africa in 1989. They reported that the occurrence of any of the following factors during the first 5 days of illness was >90% predictive of a fatal outcome:

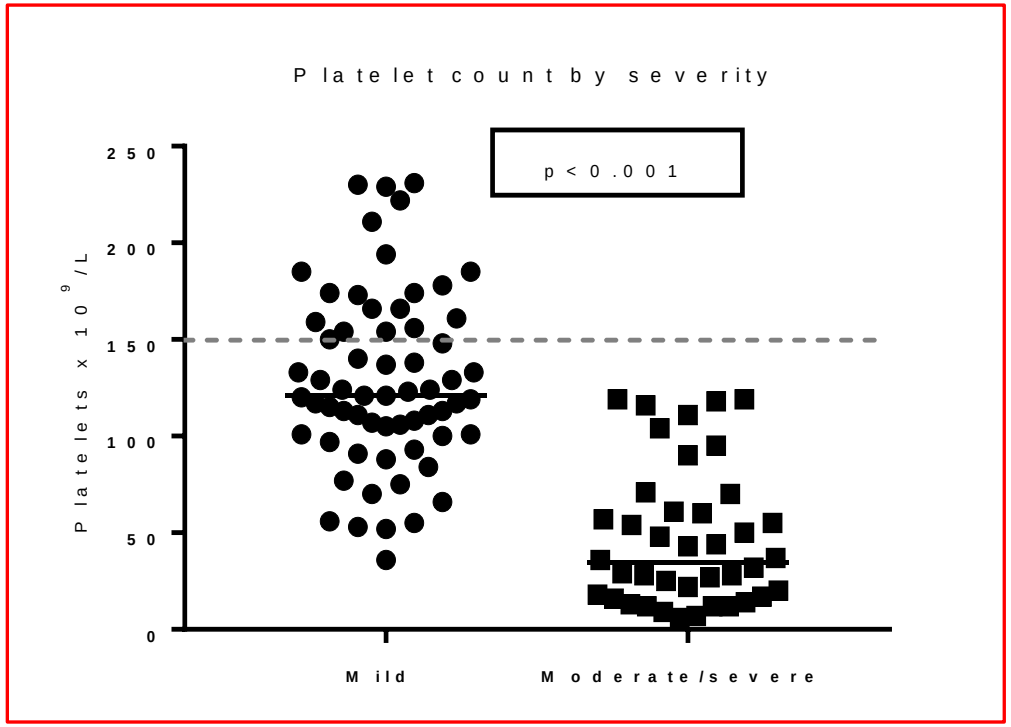
Leucocyte counts >10 x 10^9/L; platelet counts <20 x 10^9/L; AST >200 IU/L; ALT >150IU/L; APTT >60 seconds; and fibrinogen <110 mg/dL.

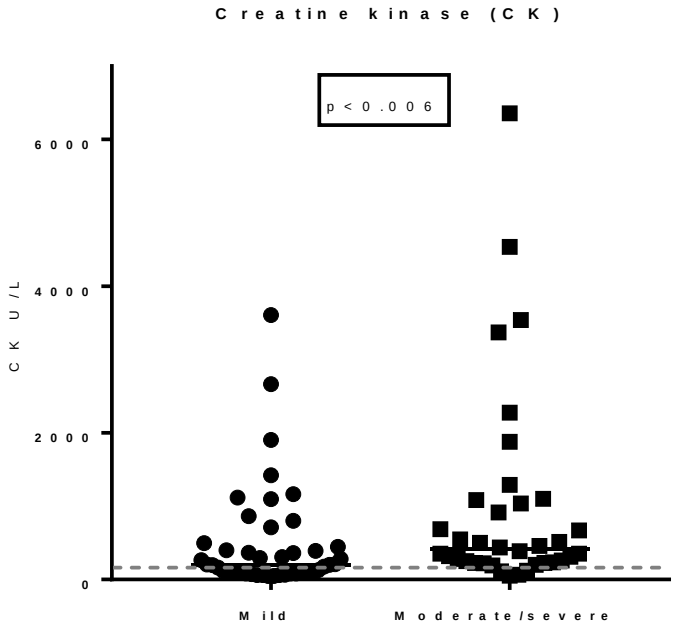
- Subsequent studies have evaluated a range of clinical and laboratory valuables prognostically (Bakir 2005, Cevik 2008, Kazancioglu 2016 , Hatipoglu 2010, Ergonul 2006, Bastug 2015)

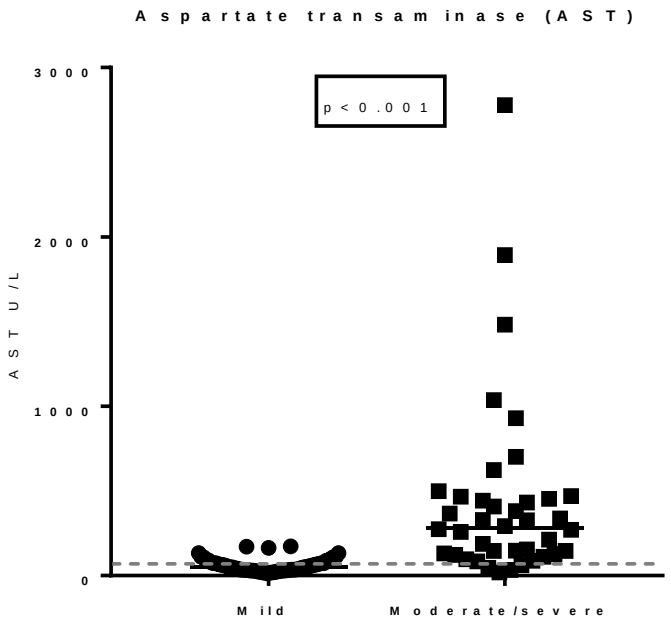
Clinical features associated with mortality by multivariate analysis: Impaired consciousness; diarrhoea; and haemorrhagic manifestations

The most consistently abnormal **laboratory parameters** in multivariate analysis: Elevated APTT ; Elevated ALT; with raised LDH an independent predictor of death in 2 studies; and platelet count <20 x 10^9/L a predictor in one study.

CCHF standard laboratory measurements by severity







There are a number of CCHF severity scoring systems

Swanepoel criteria

Platelet count ≤20 X 109 /L
aPTT ≥ 60 seconds
Aspartate transaminase ≥200 U/L
Alanine transaminase ≥150 U/L
White blood cells ≥10,000 cells/μL
Fibrinogen <110 mg/dL.

Table 1 Variables of the severity grading score (SGS) system

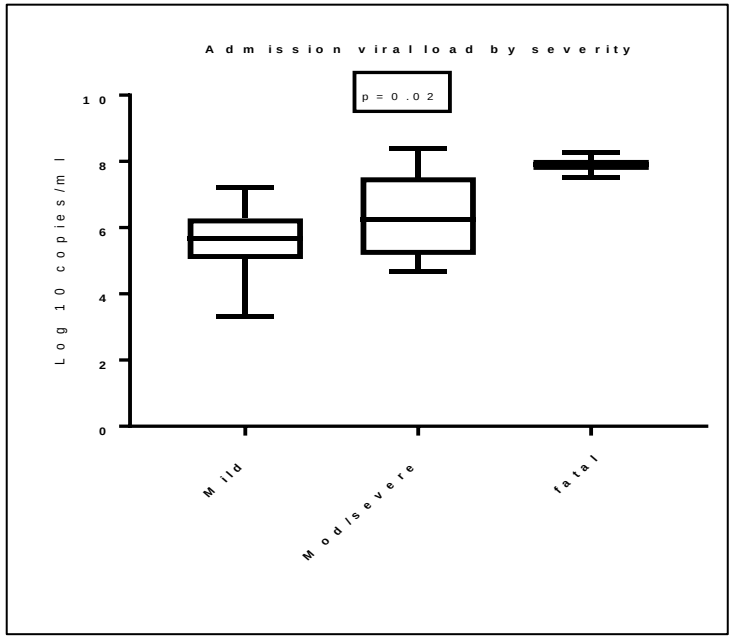
Items	Classification	SGS points
Aspartate transaminase	<5×ULNV	0
	≥5×ULNV	1
Alanine transaminase	<ULNV	0
	≥ULNV	1
Lactate dehydrogenase	<3×ULNV	0
	≥3×ULNV	1
White blood cells	<10,000 cells/μL	0
	≥10,000 cells/μL	1
Hepatomegaly	No	0
	Yes	1
Organ failure	No	0
	Yes	1
Bleeding	No	0
	Yes	1
Age	<60 years	0
	≥60 years	1
Platelets	≥100,000 cells/μL	0
	≥50,000, <100,000 cells/μL	1
	<50,000 cells/μL	2
Prolongation of PT	<3 s	0
	≥3 s, <6 s	1
	≥6 s	2
aPTT	<70	0
	≥70	1
INR	<1.6	0
	≥1.6	1

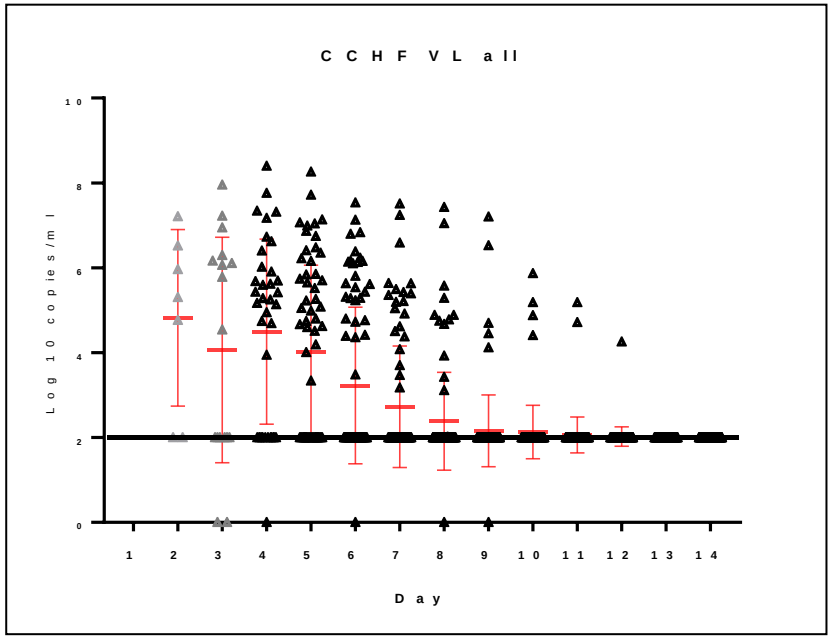
Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

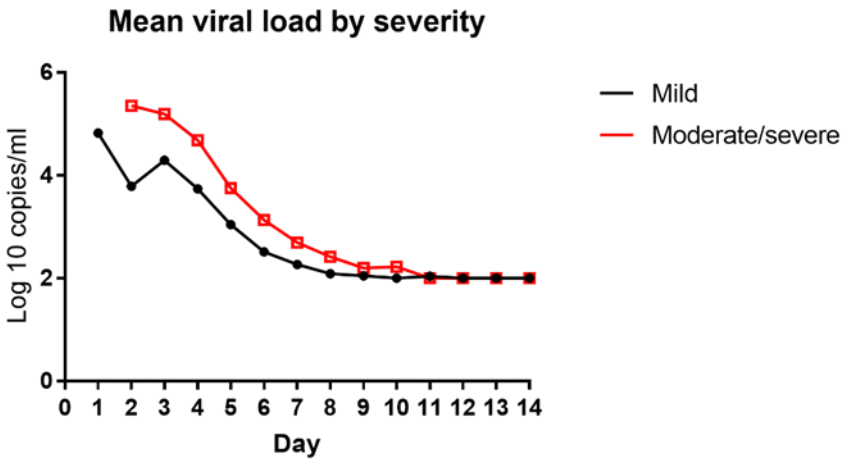
SSI Parameter	Score
Platelet count, $\times 10^3$ platelets/mm^3	
>150	0
150–50	1
49–20	2
<20	3
aPTT, sec	
≤34	0
35–45	1
46–59	2
>60	3
Fibrinogen level, mg/dL	
≥180	0
179–160	1
159–120	2
<120	3
Bleeding	
No	0
Petechia	1
Ecchymosis	2
Bleeding	3
Somnolence	
No	0
Yes	1

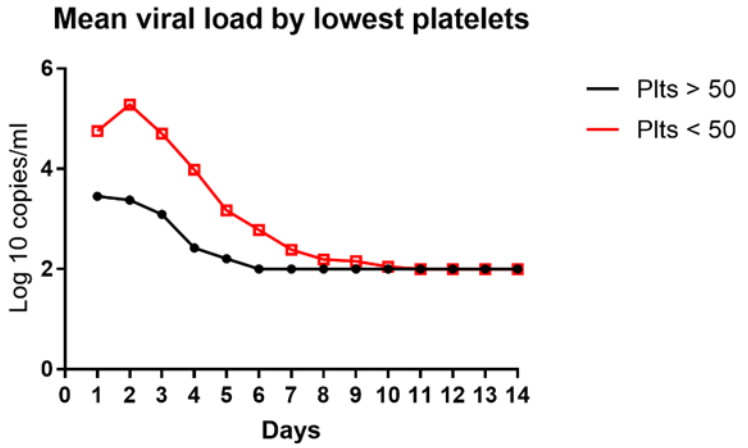
Bakir M Eur J Clin Microbiol Infect Dis 2015;34(2):325-30
Dokuzoguz B, et al. Clin Infect Dis 2013;57(9):1270-4

CCHF Viral dynamics in plasma



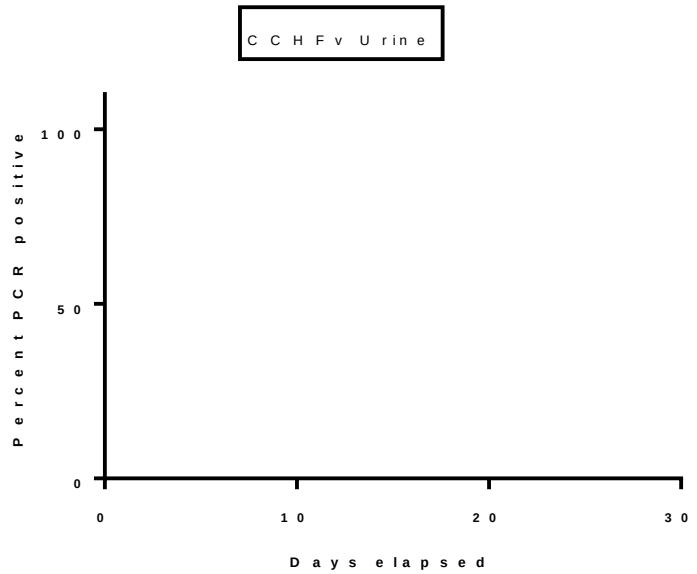






CCHF Viral dynamics – urine

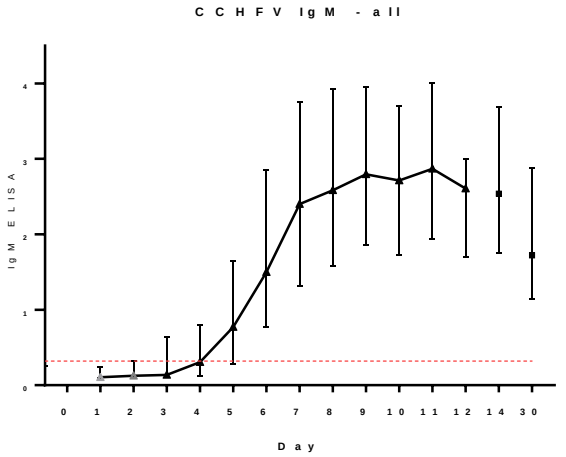
- Prolonged urine CCHFv PCR positivity had been demonstrated in one previous study from Kosovo 2009 – 36 days!
- 679 urines screened from 103 plasma CCHFV PCR positive patients
- ……

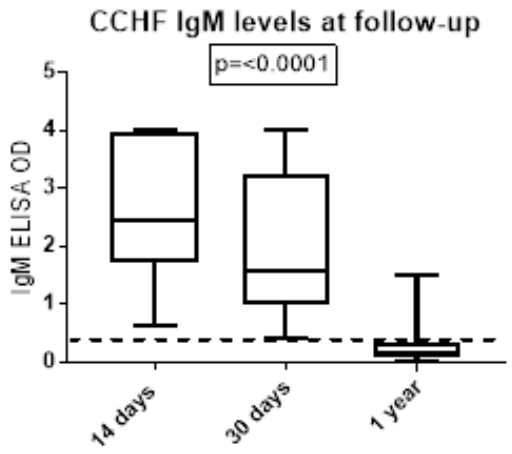


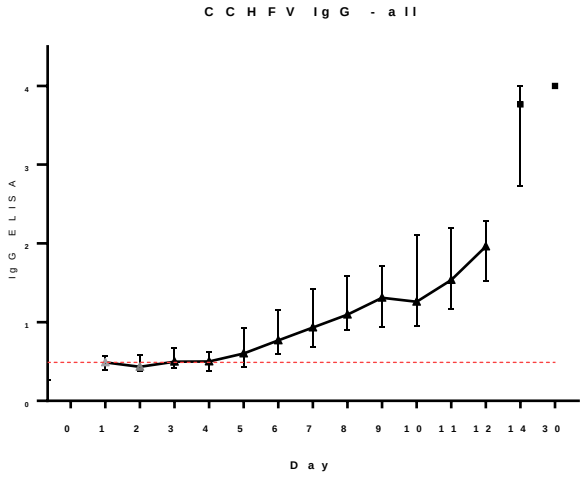
CCHF antibody responses

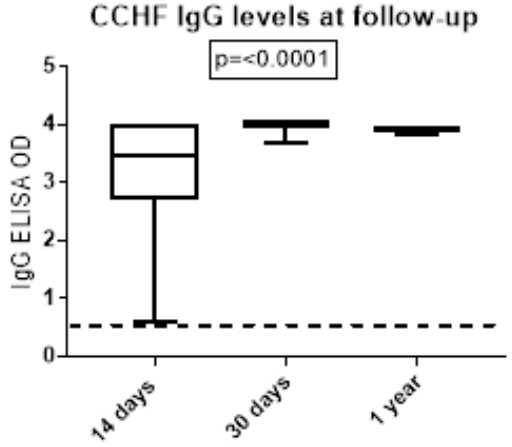
- Antibody production in CCHF has been suggested as an important early survival factor, with reduced antibody response demonstrated in fatal cases
- No correlation with IgM titre and death or severity has been demonstrated. Previous studies have not undertaken serial daily ELISA but mainly focussed on analysis of diagnostic samples.
- At admission:

- 42% of patients are IgM positive, with all patients IgM positive by day 8 of illness, continuing to 30 days.
- 50% of patients are IgG positive, with >95% positive by day 8 of illness.



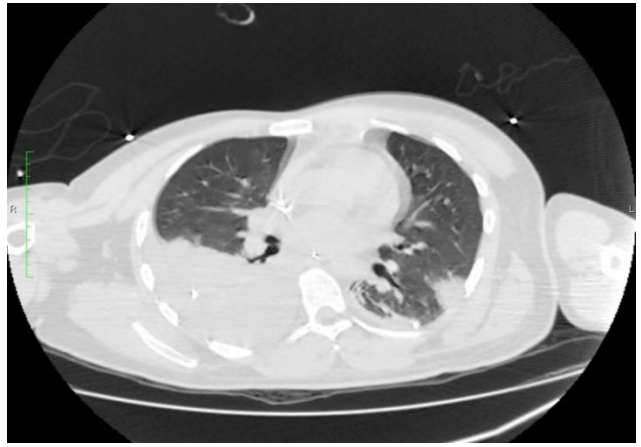






Treatment

- **Standard treatment is supportive therapy +/- Antiviral**
- Early aggressive intensive care support
- Support of coagulation system with blood component therapy
- Careful monitoring
  - Oxygenation
  - Fluid & electrolyte balance
  - Blood pressure
- Early use of inotropic/vasopressor agents
- Ventilatory and renal replacement support for severe cases
- Pain management
- Parenteral nutrition



Leblebicioglu H, et al. Vector Borne Zoonotic Dis 2012;12(9):805-11

Current recommendations in guidelines (with methods)

- WHO Clinical management of patients with viral haemorrhagic fever 2016
- Ribavirin can be used to treat patients with CCHF and Lassa fever and considered for patient contacts.
- Observational data from Lassa fever, suggest that ribavirin is most effective if given in the first 6 days of illness.
- The main side-effect is a dose-dependent, mild-to-moderate haemolytic anaemia that infrequently necessitates transfusion and disappears with cessation of treatment.
- Afghanistan 2012; India 2011; Pakistan 2013; United Kingdom 2016; South Africa 2014; San Francisco Department of Public Health 2008
- All recommend early treatment with ribavirin based on weak evidence

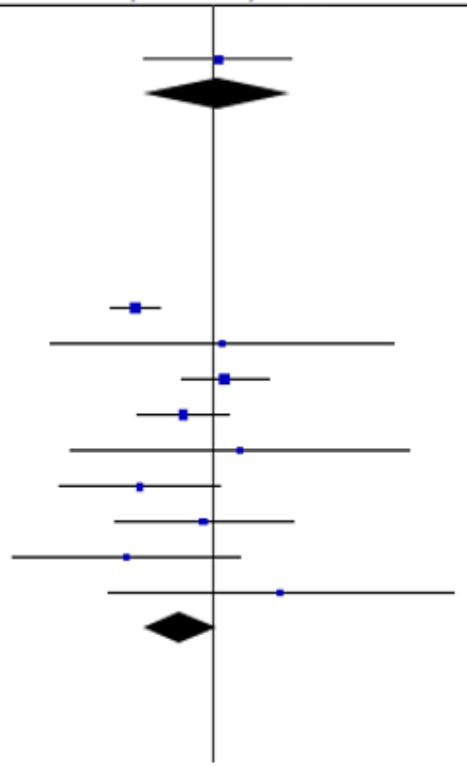
Risk of bias of included studies

	Selection bias	Baseline confounding	Bias in classification of interventions	Deviation from intended intervention	Incomplete outcome data	Risk in measurement of outcomes	Selective outcome reporting	Other bias
Belet 2014	Unclear	High	Low	Unclear	Low	Low	High	Unclear
Elaldi 2009	Low	High	Low	Unclear	Low	Low	Low	Unclear
Alavi-Naini 2006	Unclear	High	Low	Unclear	Low	Low	High	Unclear
Ertem 2016	High	High	Low	Unclear	Low	Low	High	Unclear
Ertugrul 2009	Unclear	High	Unclear	Unclear	Low	Low	High	Unclear
Fisgin 2009	Unclear	High	Low	Low	Low	Low	Unclear	Unclear
Kalin 2014	Unclear	High	Unclear	Unclear	Low	Low	Unclear	Unclear
Ozkurt 2006	High	High	Low	Unclear	Low	Low	High	Unclear
Tulek 2012	Unclear	High	Unclear	Unclear	Low	Low	Low	Unclear
Tuygun 2012	Unclear	High	Low	Unclear	Low	Low	Unclear	Unclear
Tezer 2016	Unclear	High	Unclear	Unclear	Low	Low	Unclear	Unclear
Bodur 2011	Low	High	Low	Unclear	Low	Low	Unclear	Unclear
Cevik 2008	High	High	Unclear	Unclear	Low	Low	Unclear	Unclear
Ergonul 2004	Unclear	High	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Ergonul 2006	Unclear	High	Unclear	Unclear	Low	Low	Unclear	Unclear
Dokuzoguz 2013	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Unclear

- 25 studies included
- 1 RCT (Koksal 2010 J Clin Virol)
- 23 observational studies
- 1 ongoing study

Ribavirin Vs No Ribavirin – Mortality

Study or Subgroup	Ribavirin Events	Total	No ribavirin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 RCT						
Koksal 2010	4	64	4	72	11.1%	1.13 [0.29, 4.32]
Subtotal (95% CI)		**64**		**72**	**11.1%**	**1.13 [0.29, 4.32]**
Total events	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.86)						
1.1.2 Non-RCTs						
Alavi-Naini 2006	37	236	12	19	20.1%	0.25 [0.16, 0.39]
Belet 2014	1	39	0	15	3.4%	1.20 [0.05, 27.94]
Cevik 2008 (1)	5	9	7	16	16.4%	1.27 [0.57, 2.84]
Elaldi 2009	9	126	11	92	16.1%	0.60 [0.26, 1.38]
Ertugrul 2009	1	17	0	9	3.5%	1.67 [0.07, 37.21]
Fisgin 2009 (2)	3	41	3	11	10.2%	0.27 [0.06, 1.15]
Ozkurt 2006	2	22	4	38	9.1%	0.86 [0.17, 4.34]
Tulek 2016	1	91	8	152	6.6%	0.21 [0.03, 1.64]
Tuygun 2012	1	23	0	27	3.4%	3.50 [0.15, 81.99]
Subtotal (95% CI)		**604**		**379**	**88.9%**	**0.56 [0.29, 1.10]**
Total events	60		45			
Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 18.82$, df = 8 (P = 0.02); $I^2 = 57\%$						
Test for overall effect: Z = 1.68 (P = 0.09)						



Footnotes

(1) I.v. ribavirin

(2) Early and late ribavirin groups combined

‘Current’ Ribavirin treatment recommendations

World Health Organization

The antiviral drug ribavirin has been used in treatment of established CCHF infection with apparent benefit. Both oral and intravenous formulations seem to be effective

ecdc

Although there is some evidence for its effectiveness in vitro, clinical efficacy needs to be assessed

CDC

The virus is sensitive in vitro to the antiviral drug ribavirin. It has been used in the treatment of CCHF patients reportedly with some benefit

CCHF IP&C

PLOS ONE

RESEARCH ARTICLE

Infection prevention and control practice for Crimean-Congo hemorrhagic fever—A multi-center cross-sectional survey in Eurasia

Tom E. Fletcher[1,2], Abuova Gulzhan[3], Salih Ahmeti[4], Seif S. Al-Abri[5], Zahide Asik[6], Aynur Atilla[7], Nick J. Beeching[1], Heval Bilek[8], Ilkay Bozkurt[2], Iva Christova[9], Fazilet Duygu[10], Saban Esen[2], Arjun Khanna[11], Çiğdem Kader[12], Masoud Mardani[13], Faisal Mahmood[14], Nana Mamuchishvili[15], Natalia Pshenichnaya[16], Mustafa Sunbul[2], Tuğba Y. Yalcin[17], Hakan Leblebicioglu[2]*

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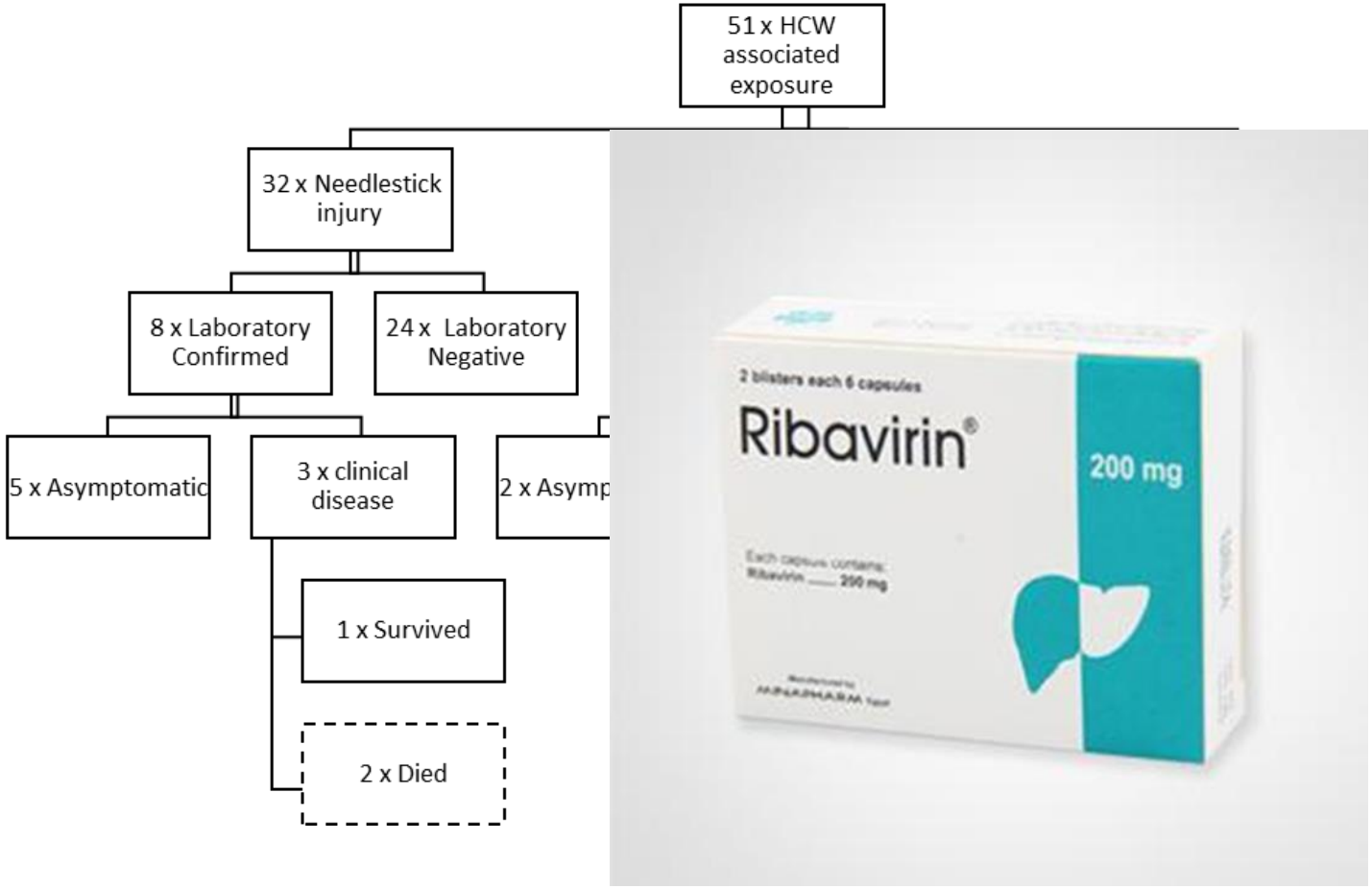
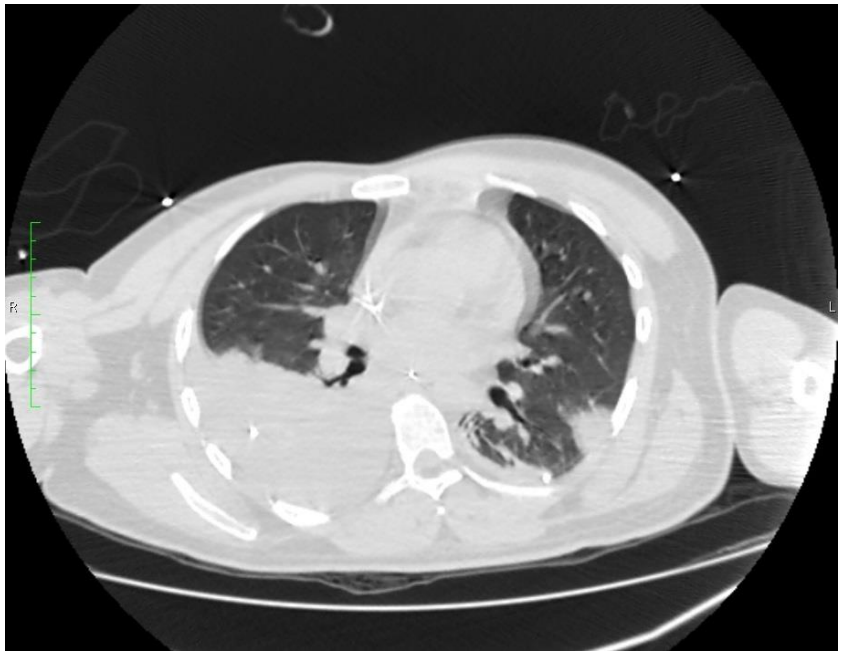
Table 2. CCHF infection prevention and control responses (23 centers).

Characteristics	*Yes, number (%)*
HCWs specifically allocated to CCHF patients	10/23 (43.5)
Adequate staffing to provide care to CCHF patients	14/23 (60.9)
Reduction in nursing staff levels for CCHF in-patients overnight	19/23 (82.6)
Isolation rooms for CCHF patients in the Emergency Department	17/23 (74)
Isolation rooms for CCHF patients in the Intensive Care Unit	17/23 (74)
Isolation rooms in the Infectious diseases have:	
- Anterooms	10/23 (43.5)
- Dedicated ventilation systems	8/23 (34.8)
- Negative pressure ventilation	5/23 (21.7)
- HEPA filtration	4/23 (17.4)
Cohorting of confirmed CCHF cases	16/23 (69.6)
Cohorting of suspect and confirmed CCHF cases together	9/23 (39.1)
Relatives allowed to enter CCHF patient rooms	7 /23 (30.4)
Adequate personal protective equipment (PPE) in the facility	22/23 (95.7)
Routine use of PPE when entering CCHF patient's rooms	21/23 (91.3)
Adequate training in donning & doffing of PPE	20/23 (87)
Supervised donning & doffing of PPE	14/23 (60.9)
PPE donning & doffing posters available	18/23 (78.3)
Number of healthcare worker CCHF exposures in the last 5 years?	
- 1–5	18/23 (78.3)
- >5	5/23 (21.7)
Special burial protocol for fatal CCHF cases	18/23 (78.3)
Terminal cleaning of CCHF patient's rooms	20/23 (87)
Needle safe devices used in CCHF patients	16/23 (69.6)
Frequency of Healthcare worker CCHF education:	
- Annually	13/21 (61.9)
- Monthly	1/21 (4.8)
- Once	(7/21) (33.3)

Understand and mitigate the nosocomial risk



Leblebibioglu H, et al. Clin Microbiol Infect. 2016



Sunbul M, Esen S, Fletcher TE, et al. A fatal case of healthcare associated Crimean-Congo haemorrhagic fever with severe disease and multi-organ failure. J Infect. 2015 Oct 19

CCHF R&D Roadmap: Vision

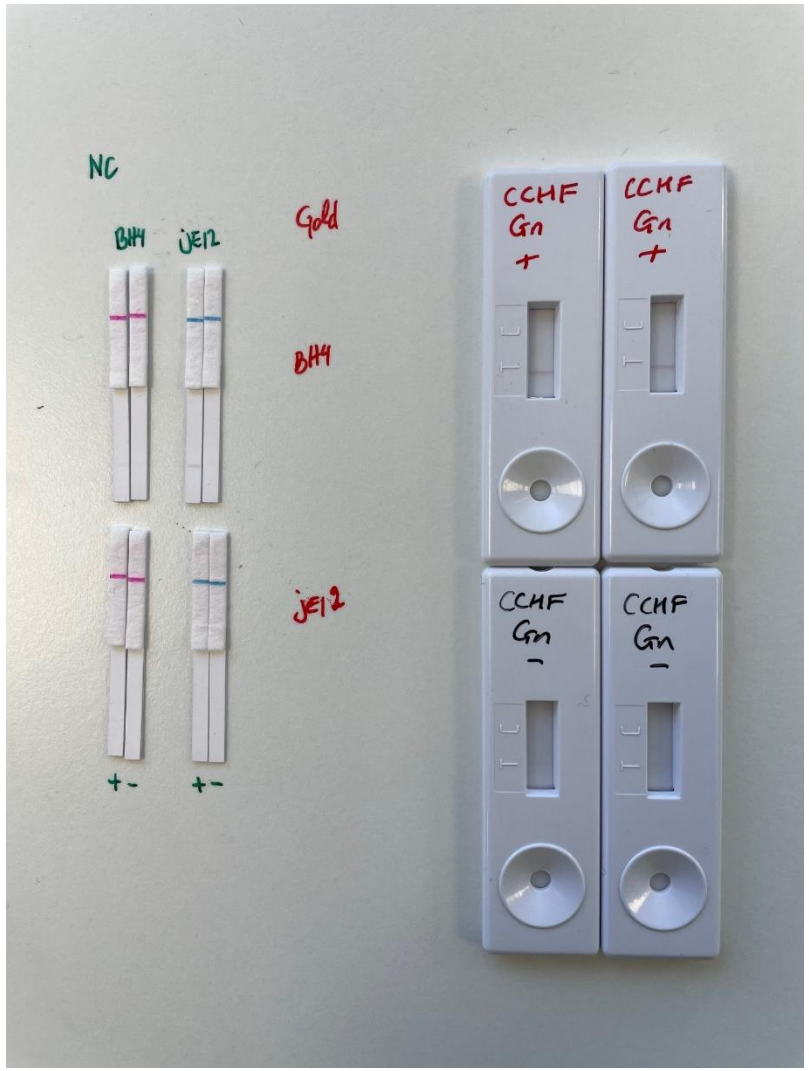
- **Prioritises the development of countermeasures – diagnostics, therapeutics and vaccines for human or animal use - that are most needed by CCHF-affected countries and sets the direction and timelines for future CCHF product research and development activities.**

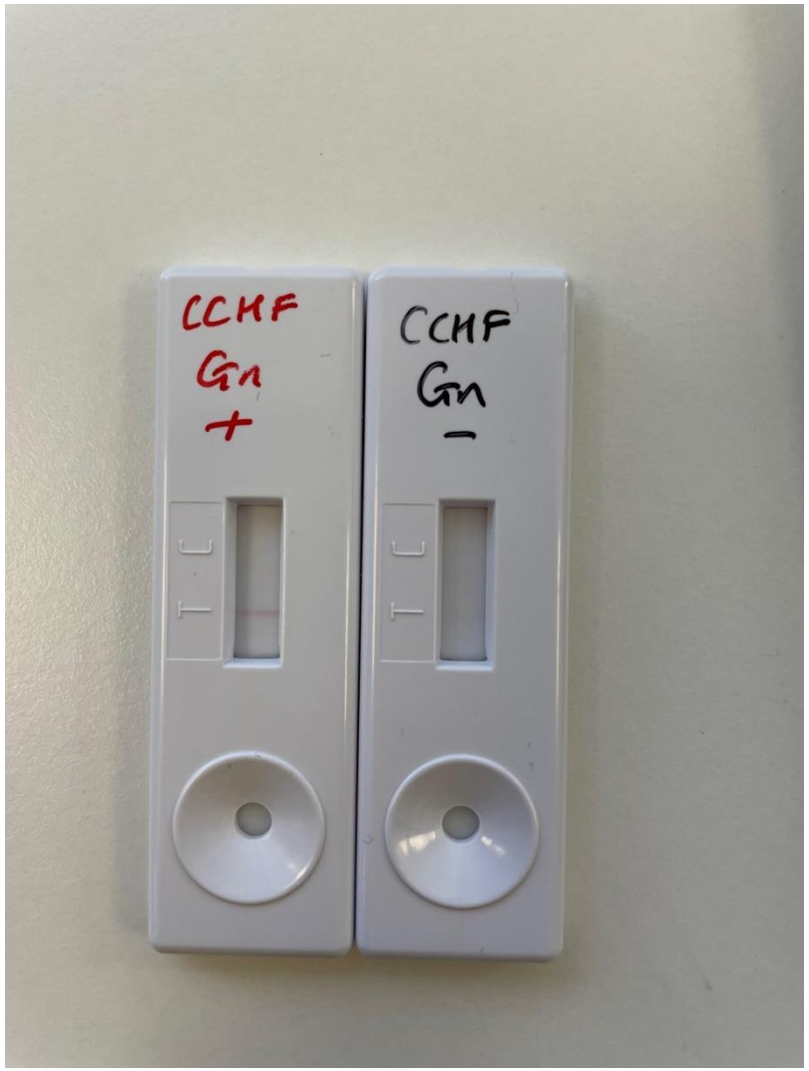
- **Vision**
- **To be able to reduce death and morbidity from CCHF through safe and affordable effective treatments informed by rapid, reliable, simple-to-use and easily accessible diagnostics by 2023**
- **and**
- **To be able to prevent or mitigate CCHF disease through deployment of safe, affordable and effective vaccines or other preventive measures by 2030**

Near patient PCR platforms

- Portable real-time PCR
- Simplified sample preparation
- Commercial and new platforms
- Currently being evaluated with PHE Porton, BNITM
- Trials with MoH Turkey in 2/12

CCHF LFT prototype development





CCHF Prototype 001

Native Antigen Company

Gn Monoclonal Antibodies
- BH14
- JE12

The ‘UMIT-1’ trial

Cohort 1: IV Favipiravir low dose
Day 1: Favipiravir 1800mg BD
Day 2-10: Favipiravir 800mg BD
N=6 (4 IMP:2 SoC)

Safety Review Committee 1
Evaluate safety up to day 8 (Bayesian dose escalation model)
Decision:
- Halt study due to safety
- Randomise more patients to cohort 1 or progress cohort 2a & 2b.

Cohort 2a: IV Favipiravir high dose
Day 1: Favipiravir 2600mg BD
Day 2-10: Favipiravir 1200mg BD
N=6 (4 IMP:2 SoC)

Cohort 2b: Combo low dose IV FAVI/Ribavirin
Day 1: Favipiravir 2600mg BD AND Ribavirin 33mg/kg load then 16mg/kg QDS
Day 2-5: Favipiravir 1200mgBD AND Ribavirin 16mg/kg QDS
Day 6-10: Favipiravir 1200mg BD AND Ribavirin 8mg/kg TDS
N=6 (4 IMP:2 SoC)

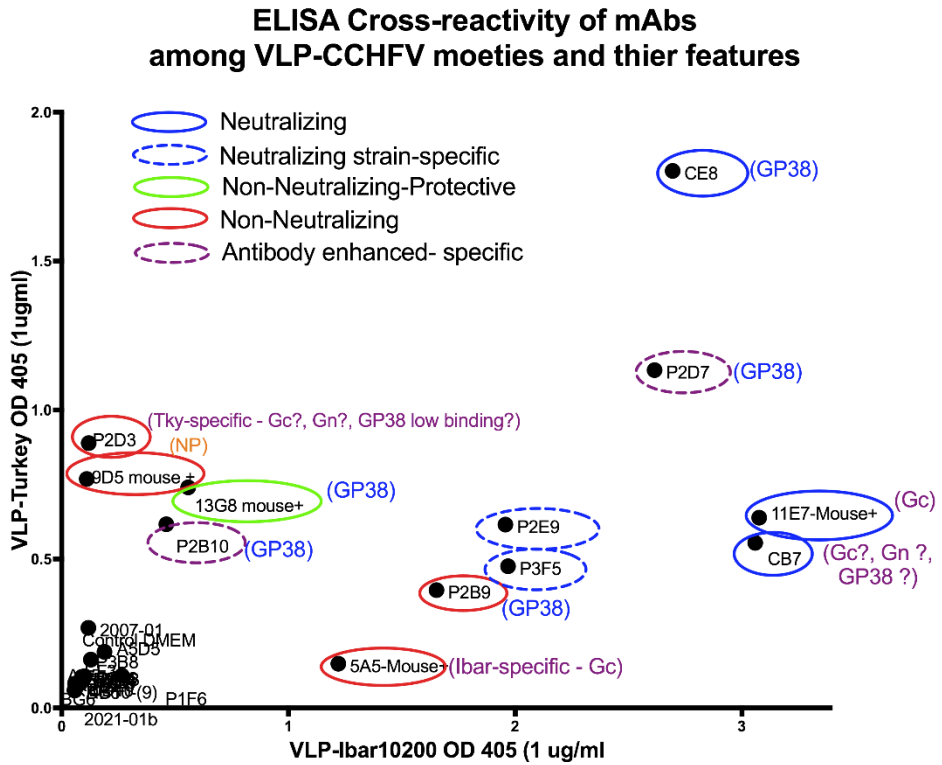
Safety Review Committee 2
Evaluate safety up to day 8 (Bayesian dose escalation model)
Decision:
- Halt study due to safety
- Randomise more patients to existing cohorts or cohort 3.

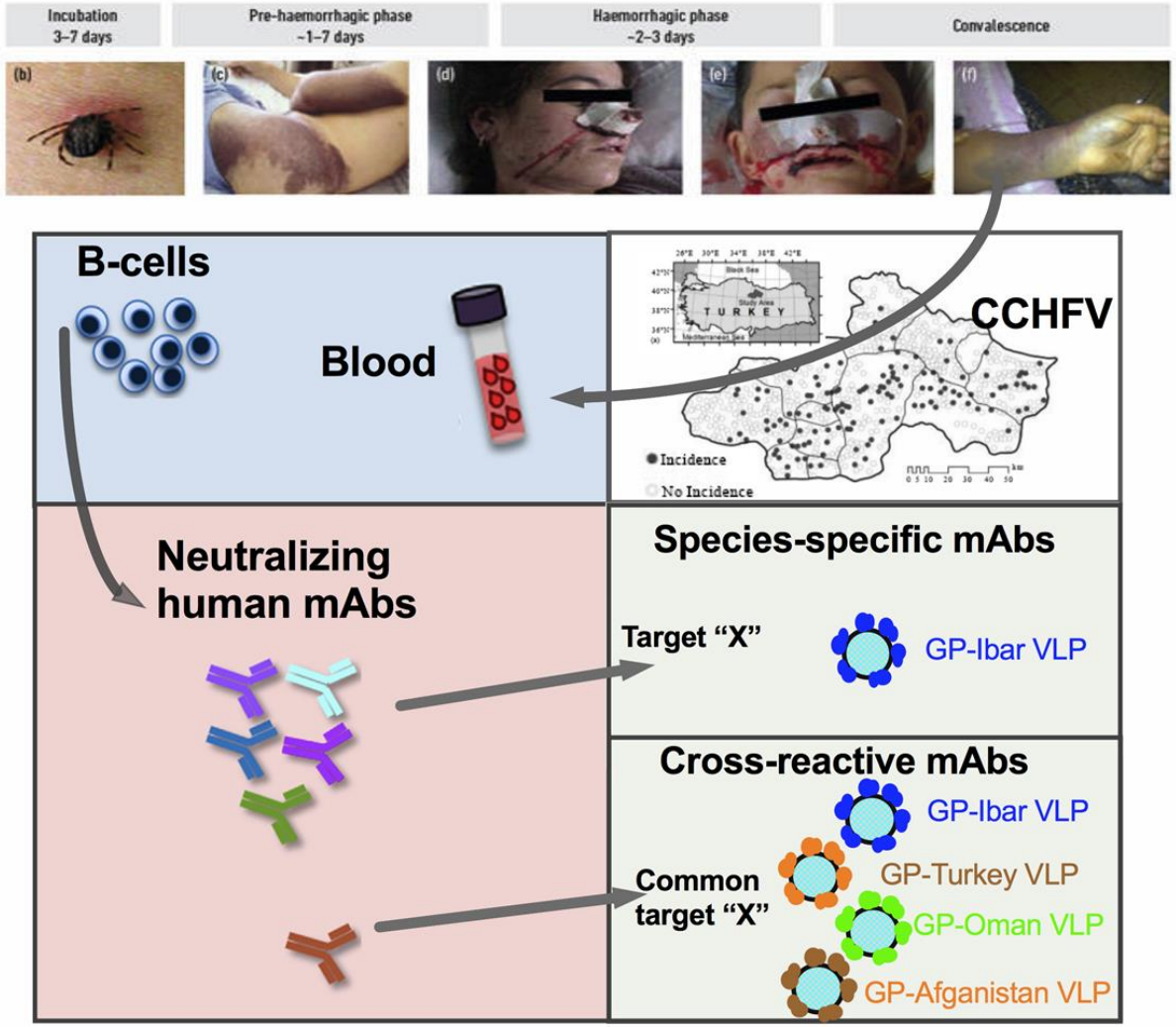
Cohort 3: Combo high dose IV FAVI/Ribavirin
Day 1: Favipiravir 2600mg BD AND Ribavirin: 33mg/kg load then 16mg/kg QDS
Day 2-5: Favipiravir 1200mgBD AND Ribavirin 16mg/kg QDS,
Day 6-10: Favipiravir 1200mg BD Day 6-10 AND Ribavirin 8mg/kg TDS
N=6 (4 IMP:2 SoC)

Safety Review Committee 3
Evaluate safety up to day 8 (Bayesian dose escalation model)
Decision:
- Halt study due to safety or select dose for Phase 2
- Randomise more patients to existing cohorts.

CCHF mAb development KOBINGER (UTMB & GuardRX)

- 21 CCHFv survivors
- Two mAbs selected with broad-neutralising activity





Thank you & Questions

Republic of Turkey
Ministry of Health

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ONDOKUZ MAYIS ÜNİVERSİTESİ

GuardRX

UTMB
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