

Crimean Congo Haemorrhagic fever; An emerging viral haemorrhagic disease

Ali Mirazimi, *Professor*

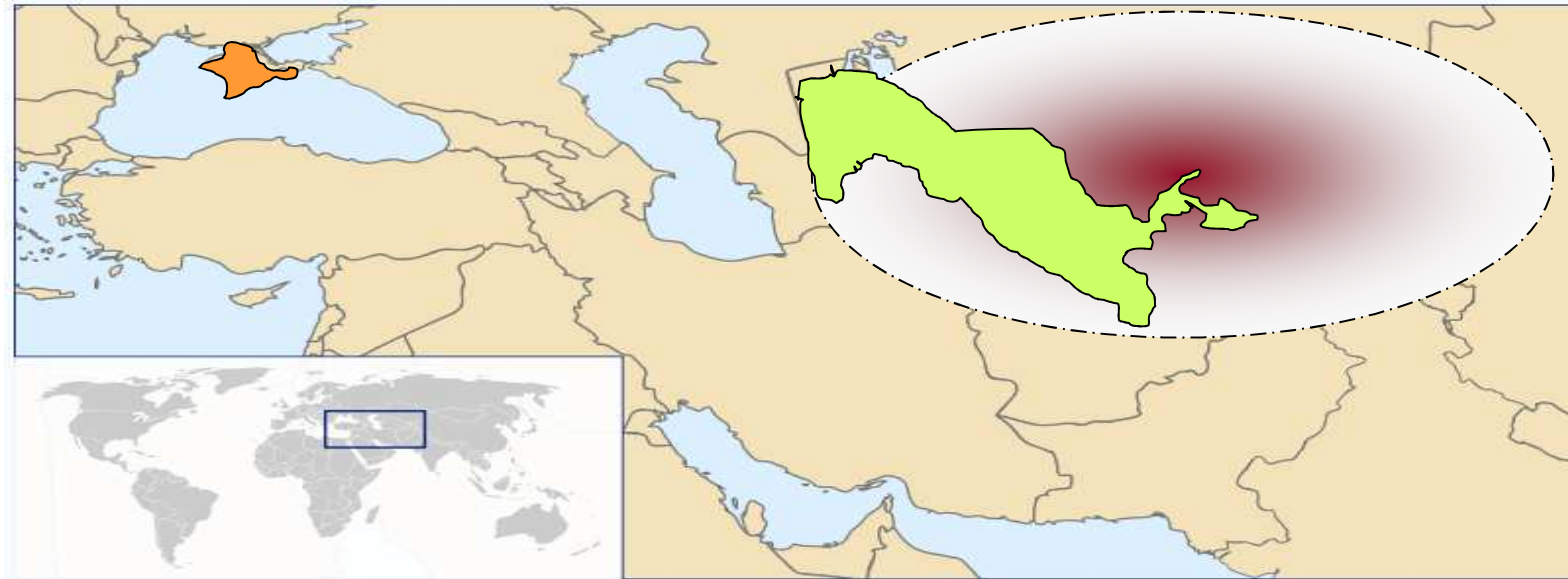
Karolinska Institute

Public Health agency of Sweden

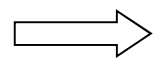
National veterinary Institute

CCHF – Historical Perspective

1st Descriptions of Central Asian / Crimean Haemorrhagic fever



1944 Viral origin - passage through human volunteers (they could not Isolate the virus by using the mice model, most probably due to that they used Adult Mice)

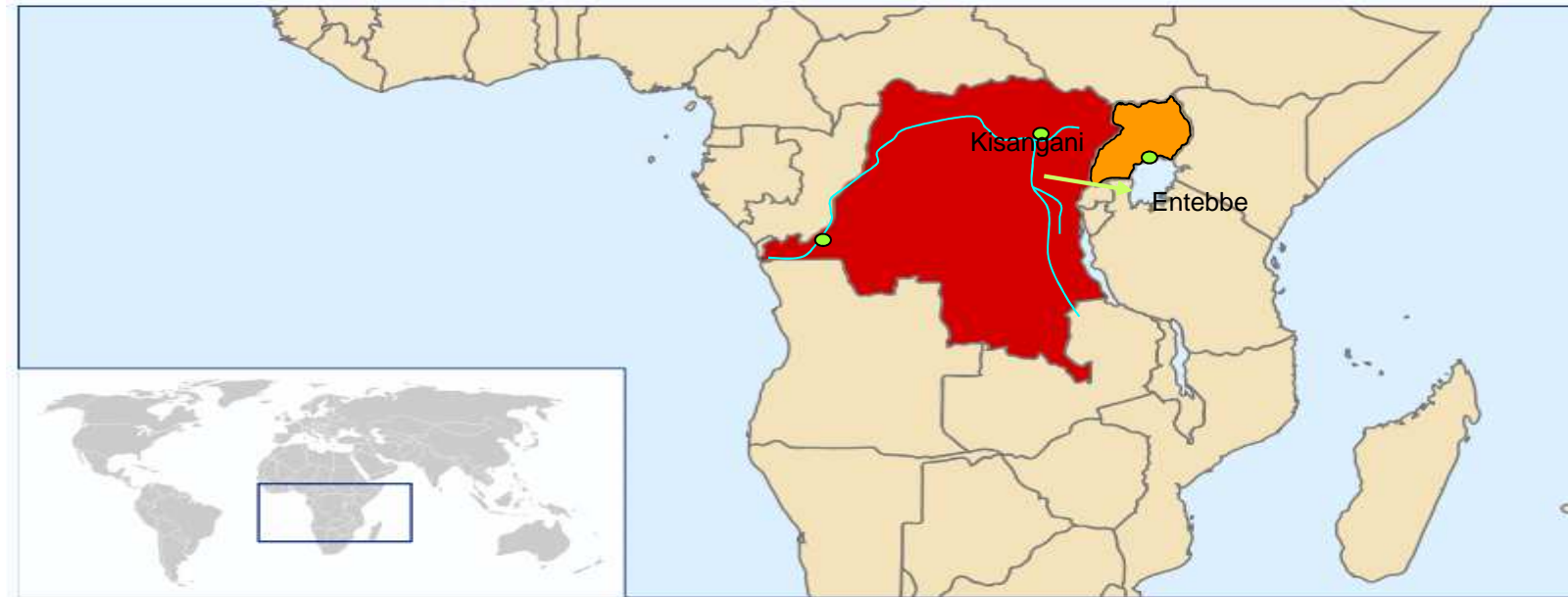


Isolation / registration - Yale 1968 (Crimean HF)

M.P Chumakove et al.,

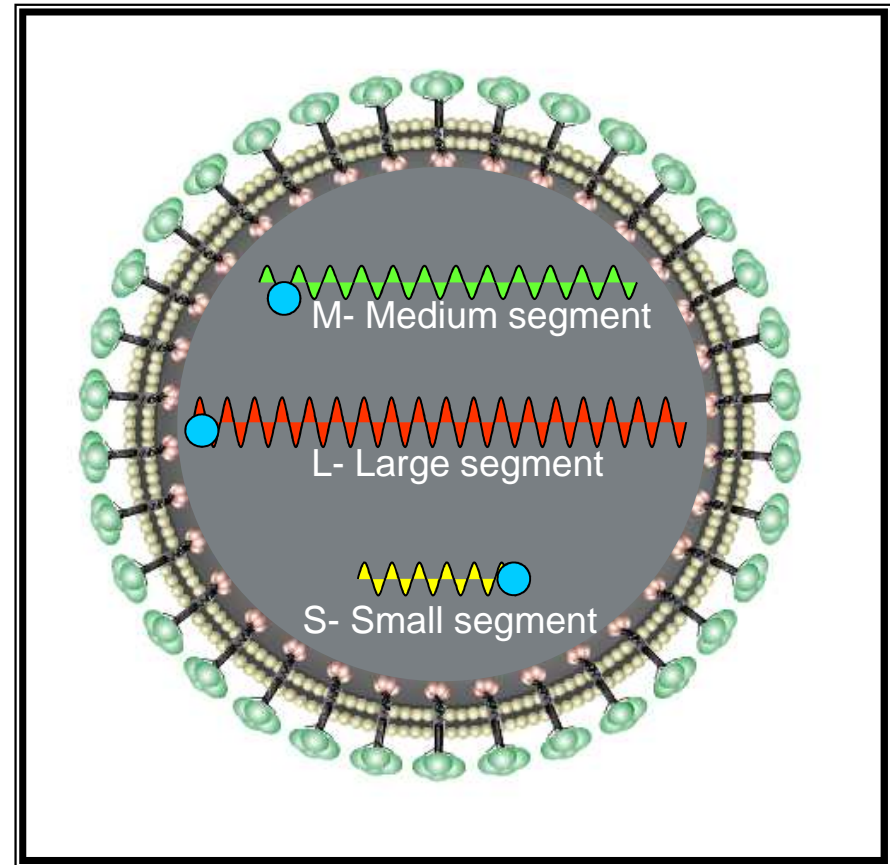
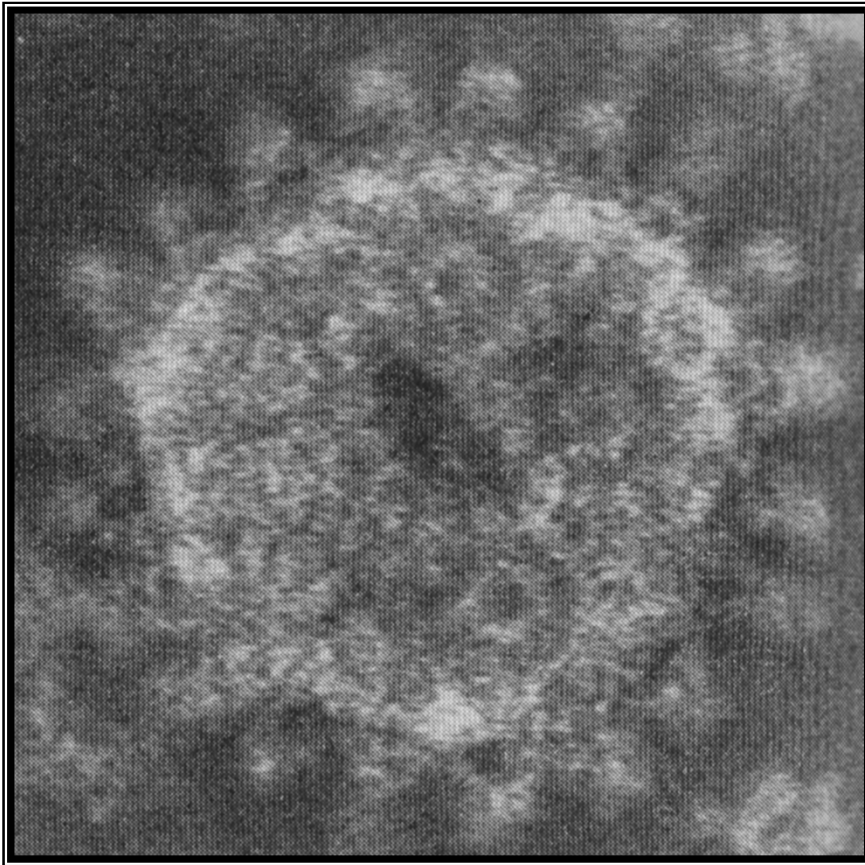
CCHF – Historical Perspective (ii)

1st Descriptions of Congo fever



- Stanleyville March 1956: 13 year old presented with fever.
- Dr. Courtios Isolated / adapted to mice ("2-3 days old, Intraperitoneal/ maintained by passage.
- He get also the disease but survived.
- Sent to EAVRI / Entebbe 1957

Crimean-Congo hemorrhagic fever virus

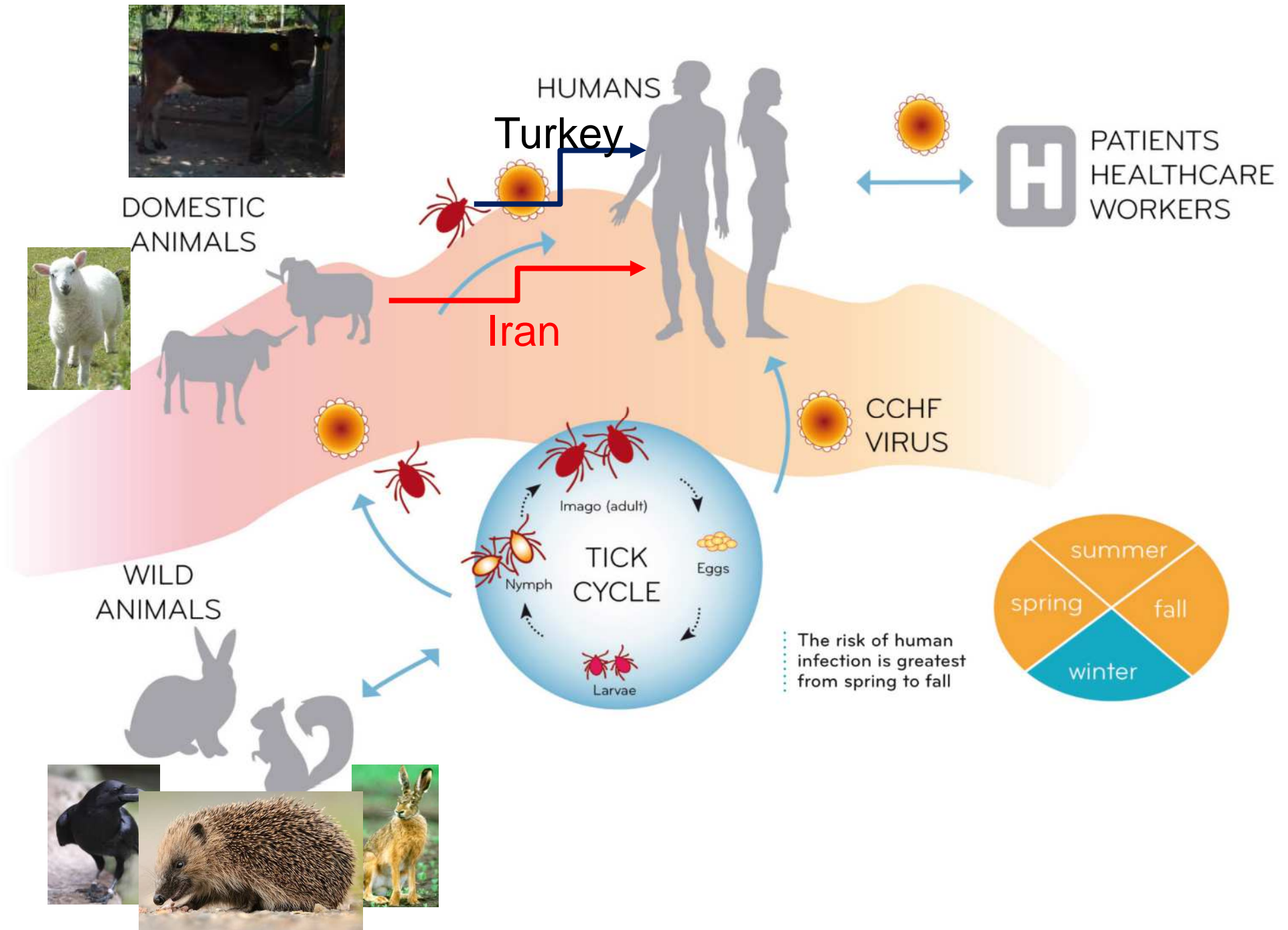


Crimean – Congo Haemorrhagic fever



CCHF virus
(Nairovirus genus of
the family
Bunyaviridae)

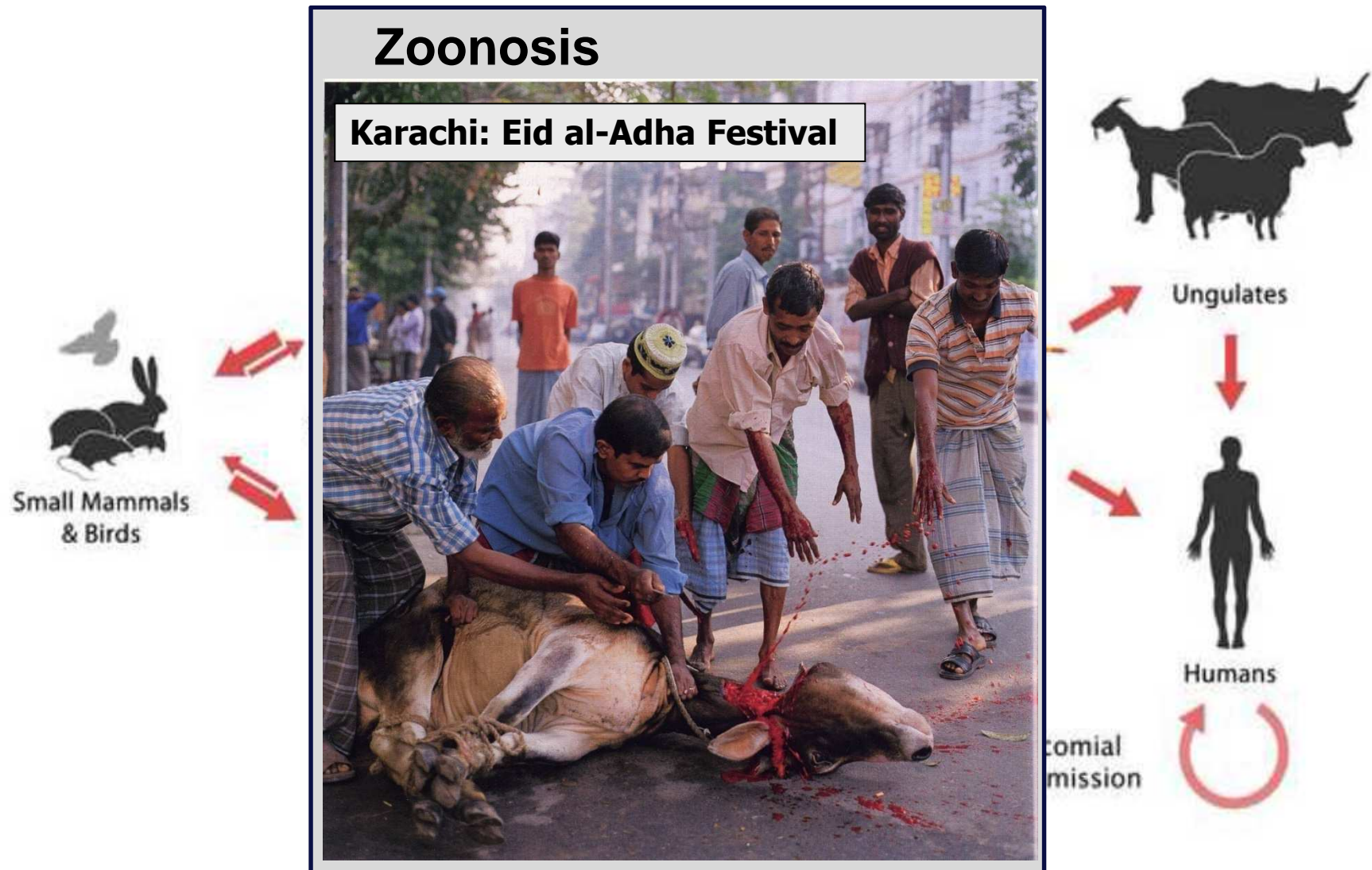
30% mortality rate
(but can approach
80% in some
circumstances)
[WHO]





***Hyalomma marginatum*, are “two-host” ticks**
***Hyalomma* are “hunting” ticks, which can quest up to 400 m to find their hosts (including humans).**

CCHFV Transmission Cycle

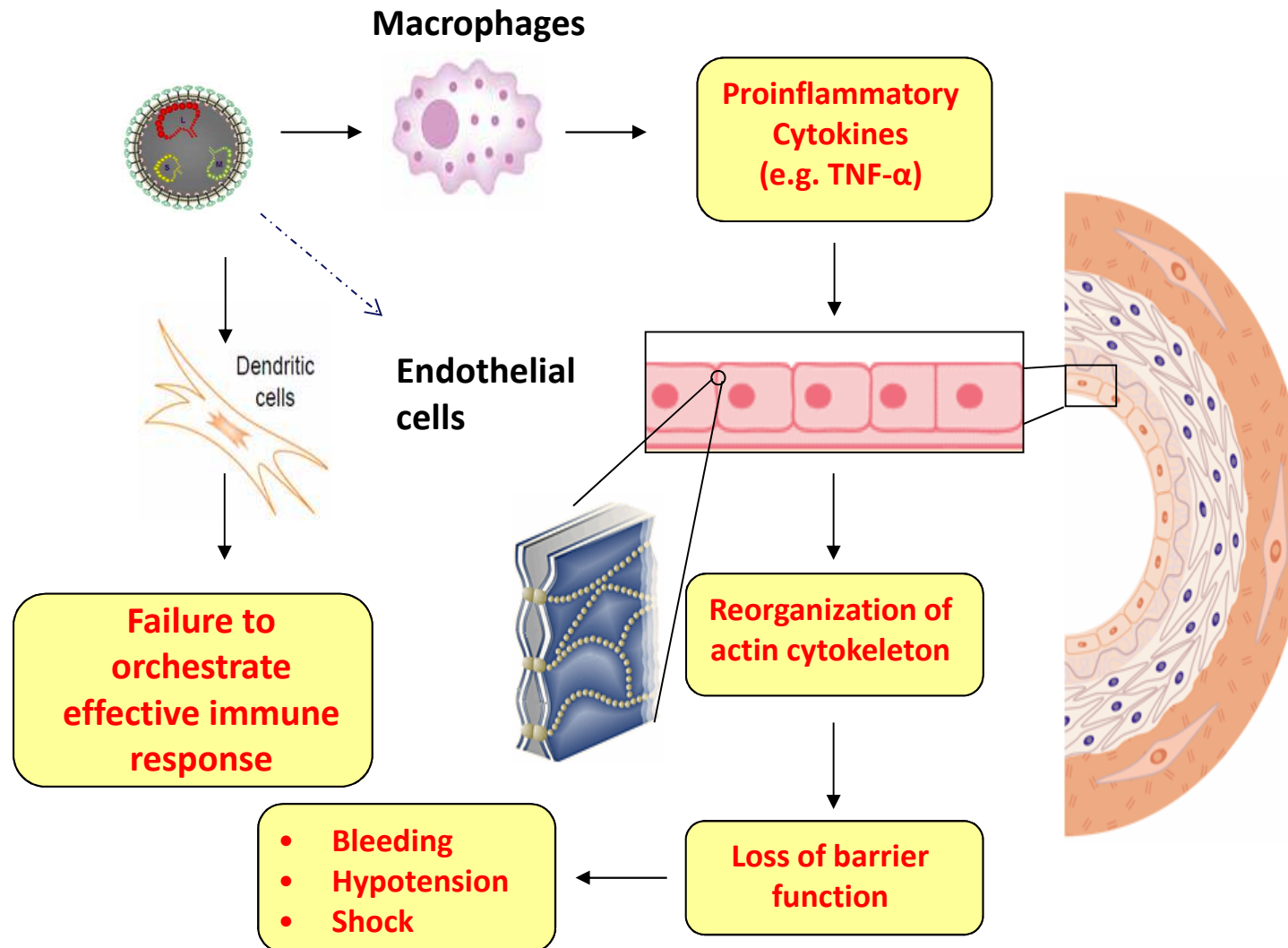


CCHF - Clinical Disease



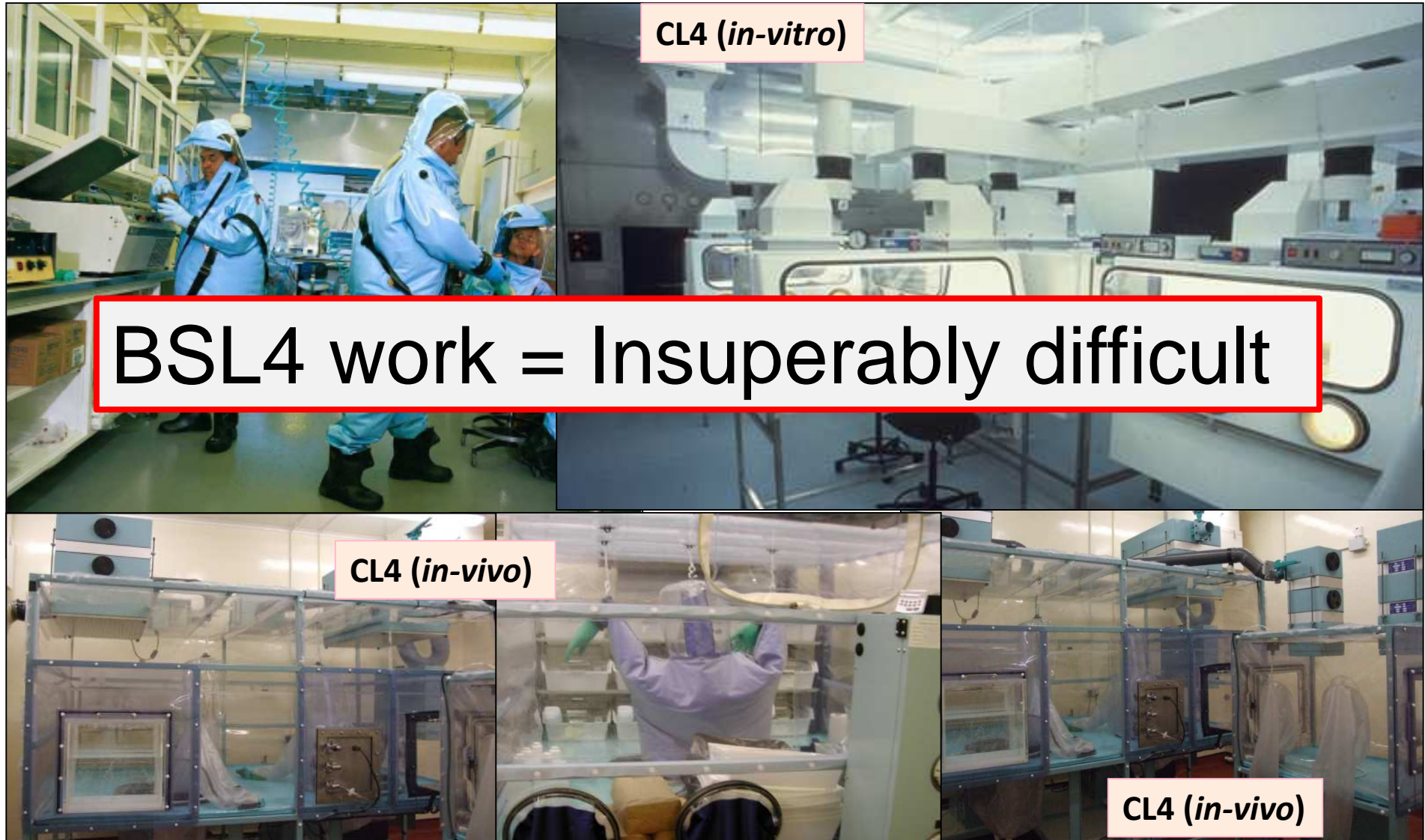
- Incubation period 2-7 days (depends on the Transmission)
- Haemorrhagic state develops 3 - 5 days
- Petechial rash / ecchymoses in the skin
- Bleeding from the mucous membranes
Epitaxis, Haematuria, Haemoptysis
- Loss of blood pressure - shock
- Death 7-9 days
[massive bleeding / cardiac arrest]

Pathogenesis of VHF disease



ACDP
HG4

High Containment BSL4 / CL4 labs



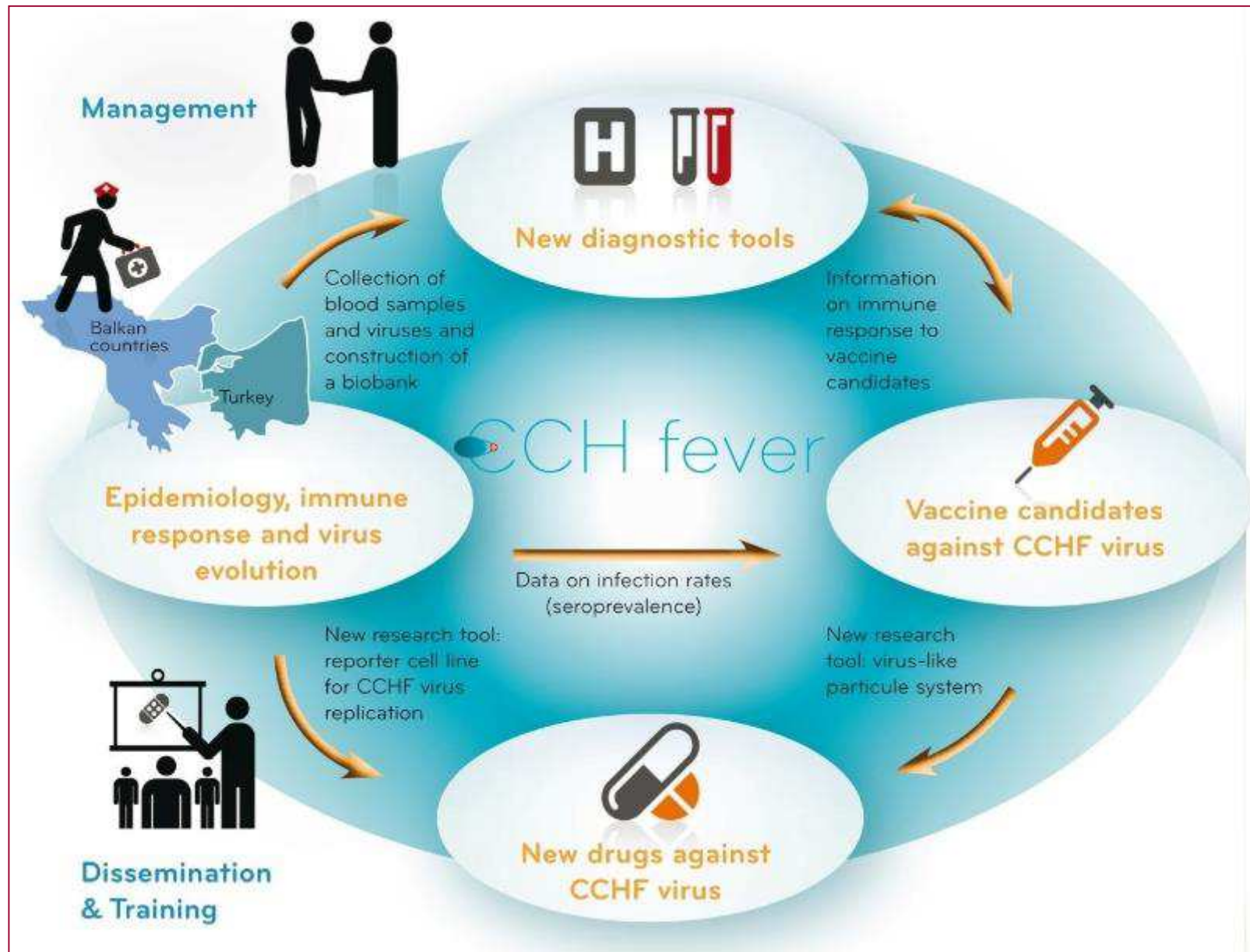
Years	Country/region	Total cases	Case fatality rate	Clade
1944	Crimea	161	11	
1953–1963	Astrakhan	104	17	Europe-V
1953–1968	Stavropol	25	44	Europe-V
1963–1969	Rostov	323	15	
1953–2009	Bulgaria	2431	17	Europe-V
1995–2010	Kosovo	216	19	Europe-V
1999–2008	Russia	>1150	3.2	Europe-V
2001–2006	Albania	32	3	Europe-V
2008	Greece	1	100	Europe-V

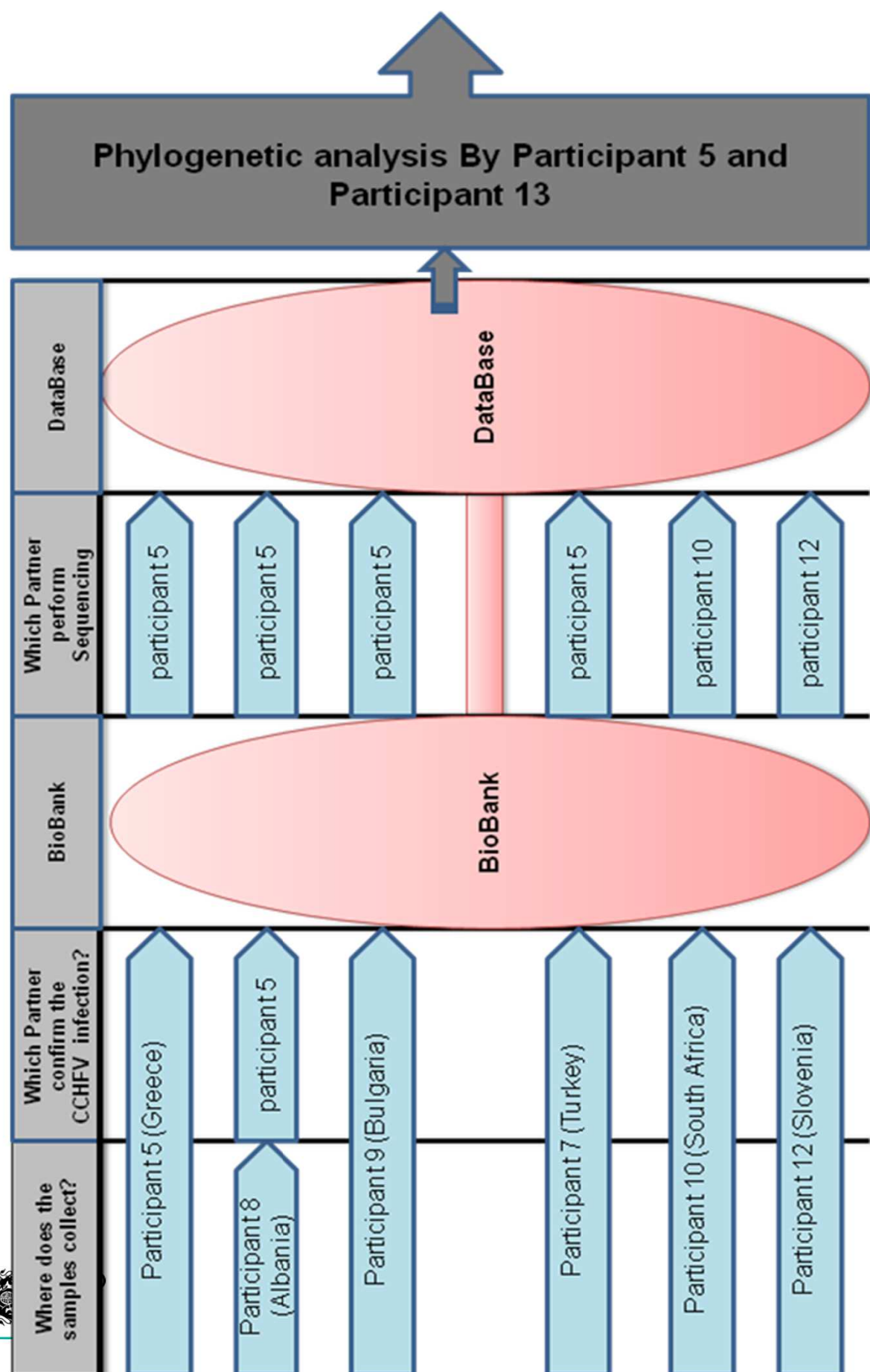
Years	Country/region	Cases	Case fatality rate	Clade
1965–1997	China	286	21	Asia-2 IV; M1; M2; M3
1948–2000	Khazakhstan	108	35	
1943–2010	Tajikistan	237	16	Asia-2 IV; M2
1976–2000	Pakistan	23	39	Asia-1 IV; M1; M2; Asia-IV
2011	India	6	83	Asia-2 IV; M2; Asia-IV

Years	Country/region	Cases	Case fatality rate	Clade
1979–1995	United Arab Emirates	18	61	Asia-2 IV
1990	Saudi Arabia	7	0	
1995–1997	Oman	4		Asia-1 IV; M1; Asia-IV
1979–1980	Iraq	55	64	Asia-1 IV; M2; Asia-IV
2000–2008	Iran	534	15	Asia-1 IV; Africa-3; Europe-1 V.
2008–2012	Afghanistan	51	47	Asia-1 IV; M2; Asia-IV
2002–2009	Turkey	4431	5	Europe-V

Years	Country/region	Cases	Case fatality rate	Clade
1956	Zaire (DRC)	2	0	Central Africa-II
1958–1977	Uganda	12	8	Central Africa-II
1983–2004	Mauritania	39	28	
1983	Burkina Faso	1	0	
1981–1986	South Africa	32	31	S Africa/W Africa-III; M1; M2
1986	Tanzania	1	0	
2000	Kenya	1	100	
2008–2010	Sudan	12	75	S Africa/W Africa-III; M2

CCH fever project



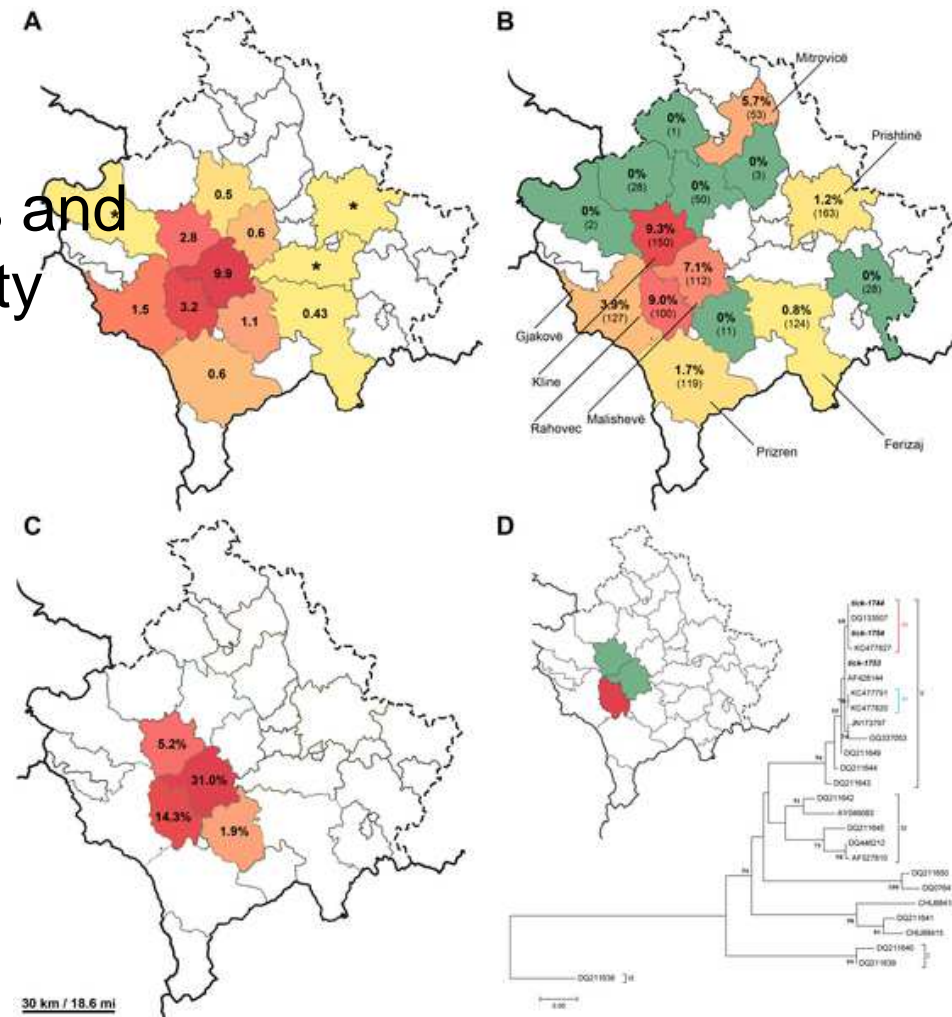


CCHFV seroprevalence in Greece



Figure 1. Prevalence of CCHF in Kosovo A. Cumulative incidence (per 100,000) of CCHF (from 1995 to 2013) in each municipality of Kosovo.

Severe cases and
High Mortality



Fajš L, Humolli I, Saksida A, Knap N, Jelovšek M, et al. (2014) Prevalence of Crimean-Congo Hemorrhagic Fever Virus in Healthy Population, Livestock and Ticks in Kosovo. PLoS ONE 9(11): e110982. doi:10.1371/journal.pone.0110982
<http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0110982>

CCHFV seroprevalence in Albania

Less cases and Mild Symptoms!?



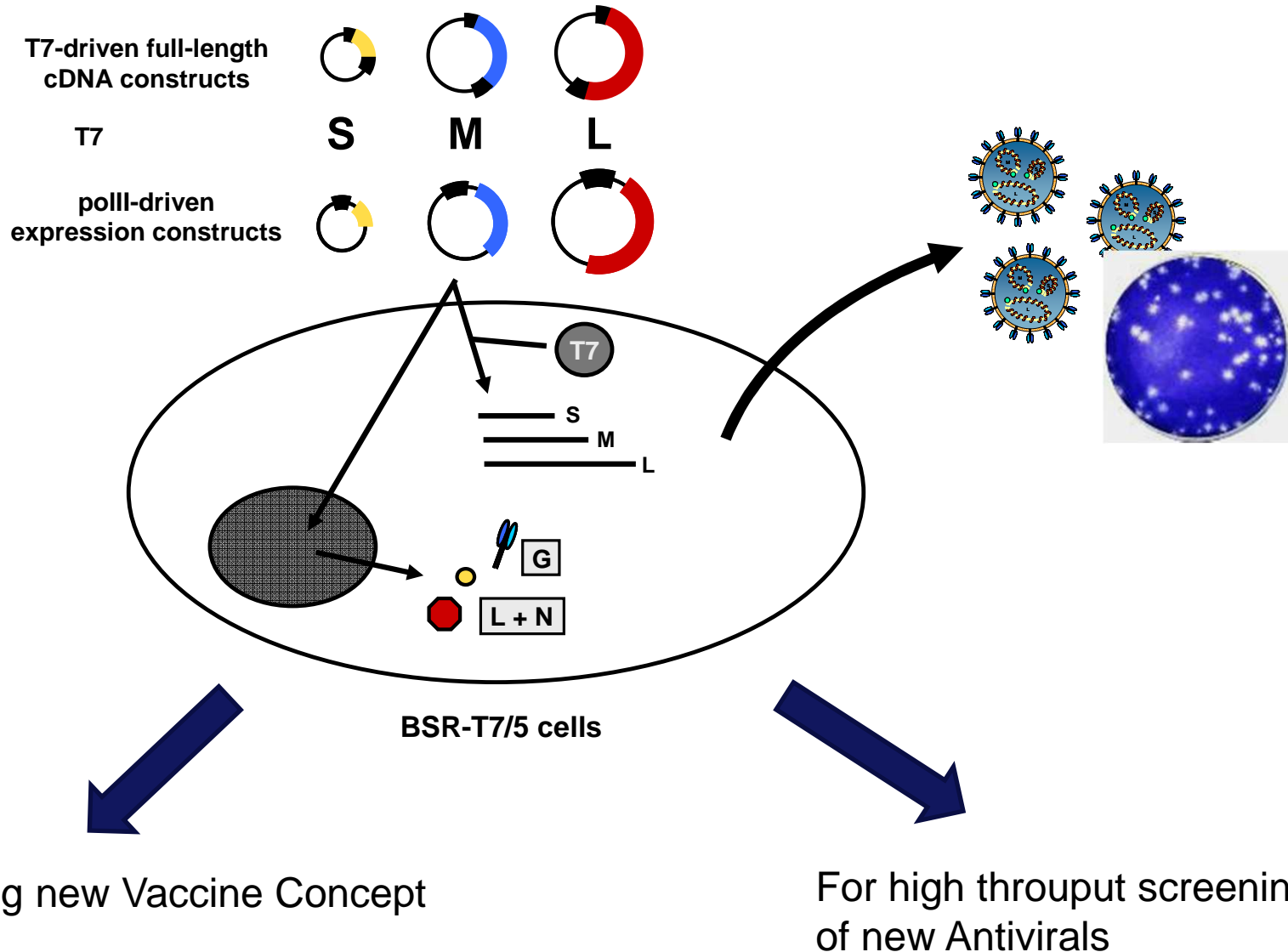
Conclusions

- High sero-prevalence at Greece and Generally Very low nr of reported cases
- Mild cases at Albania compared to Kosvo.
- High Sero-pervalence in animals at endemic Area (up to 79%)

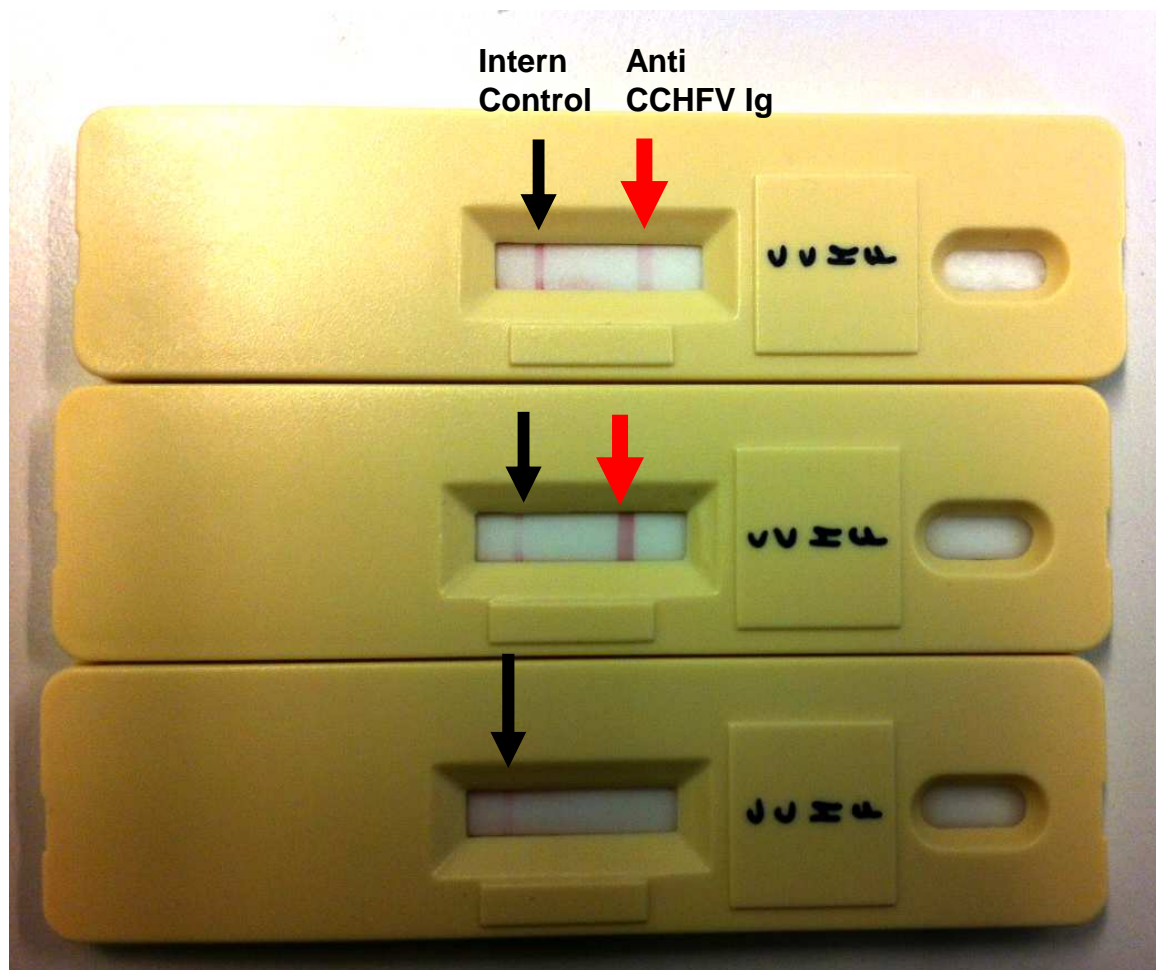
Diagnostic

- EQA for validation of the tests
- Developing New Field/bedside Diagnostic
- VLP based ELISA (no need for BSL4).
- Inactivation of Samples (No need for BSL4).

Using tools (Reverse Genetic) to produce VLPs



Field Diagnostic

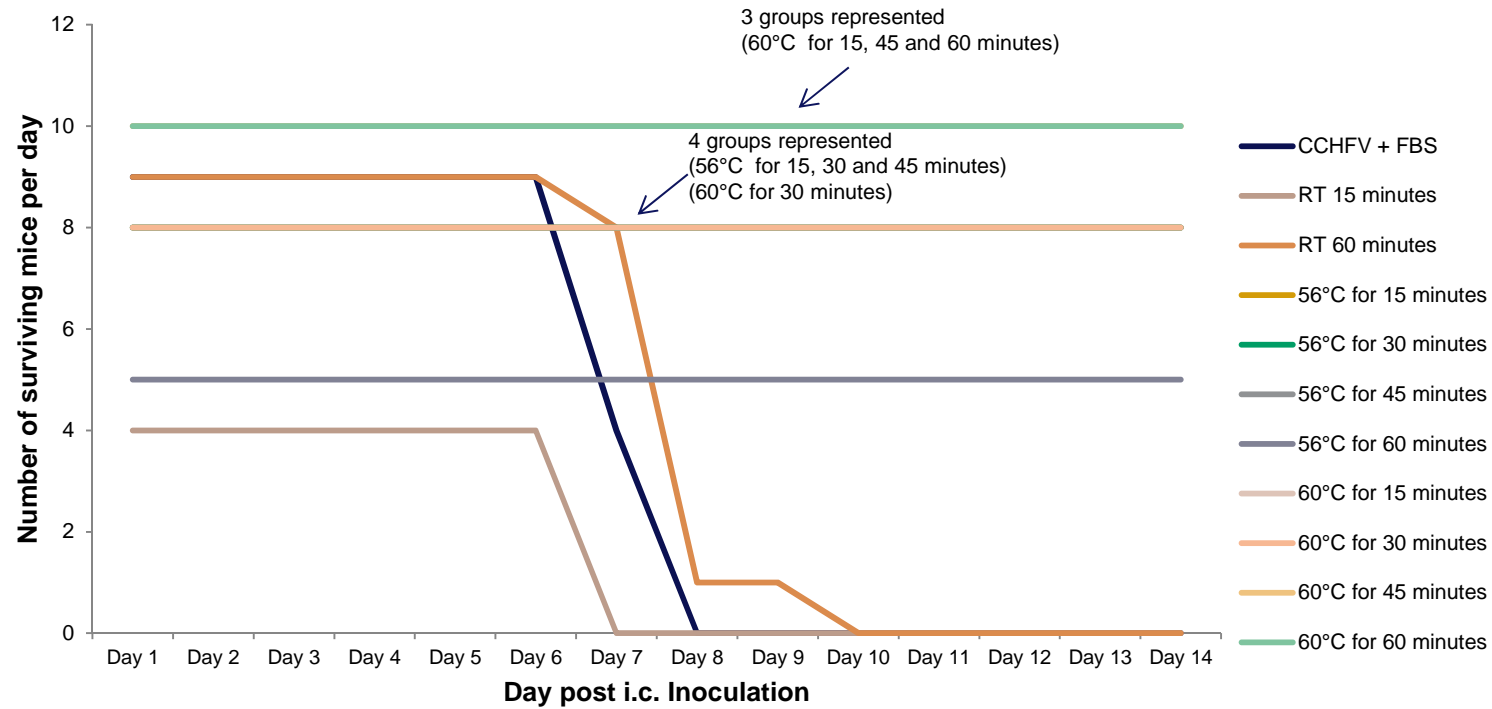


Patient 211 Weak Positive

Patient 262 Positive

Patient Rumania Negative

Mouse survival curve



Diagnostic

Multi-center evaluation of available Commercial diagnostic Kits.

EQA panel to 20 laboratories around the Europe.

Evaluation of several developed new diagnostic Tools and Field trials of new bed site Diagnostic.



European Preparedness

Vaccine

Bulgarian Vaccine

Healthy individuals' immune response to the Bulgarian **Crimean-Congo** hemorrhagic fever virus vaccine.

Mousavi-Jazi M, Karlberg H, Papa A, Christova I, Mirazimi A.

Vaccine. 2012 Sep 28;30(44):6225-9.

<i>Individs vaccinated 4 times</i>	ELISA	NT titer
1	pos	168
2	pos	32
3	pos	168
4	pos	168
<i>Individs vaccinated once</i>		
5	+	32
6	+	8
7	+	8
8	+	32

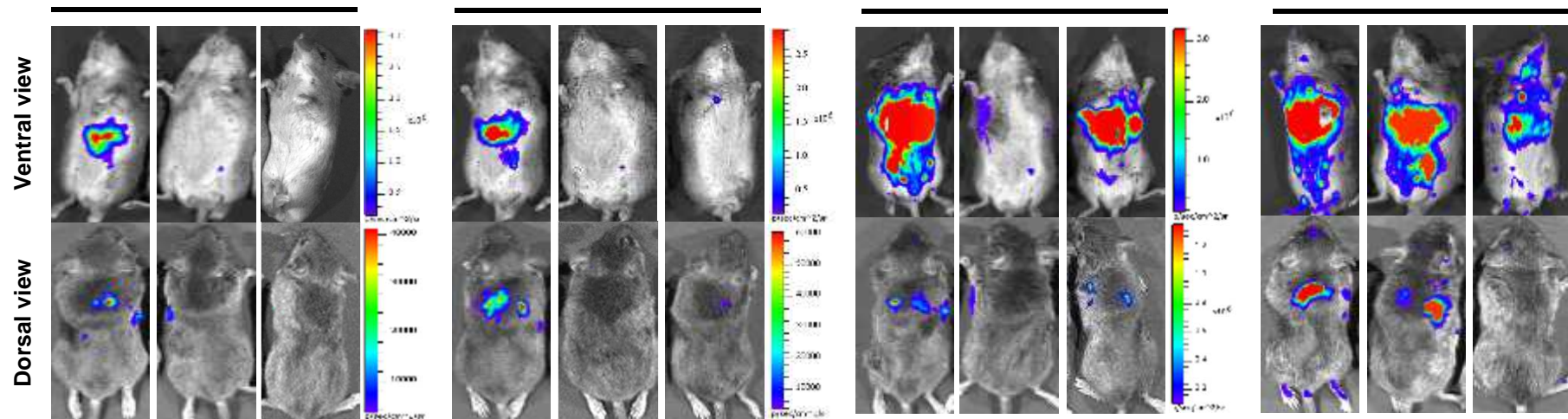
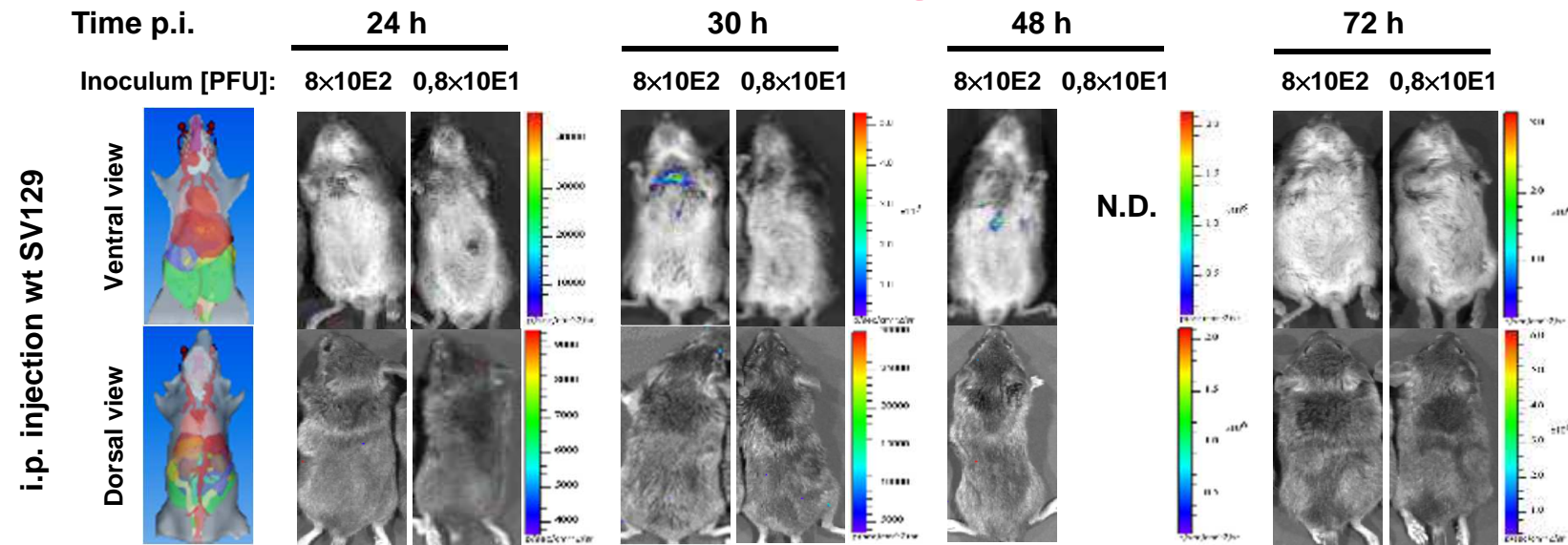
Conclusion

- Needs more than one immunization before any T-cell activity.
- Low NT-antibody titer

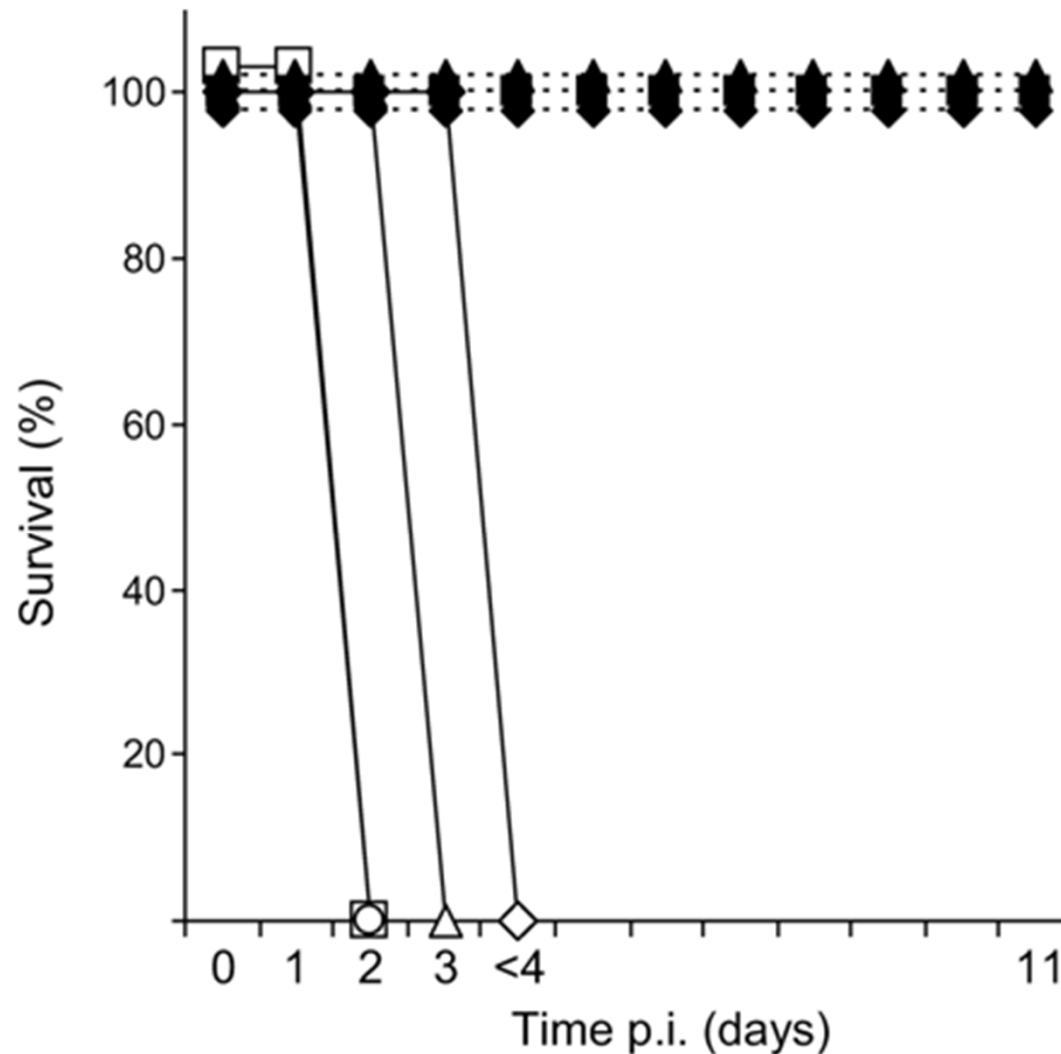
Animals get infected but do
NOT develop Disease!

IFNAR^{-/-} dies within 48 hpi with 10 Virus Particles by developing disease as has been demonstrated in Humans developed at the P4

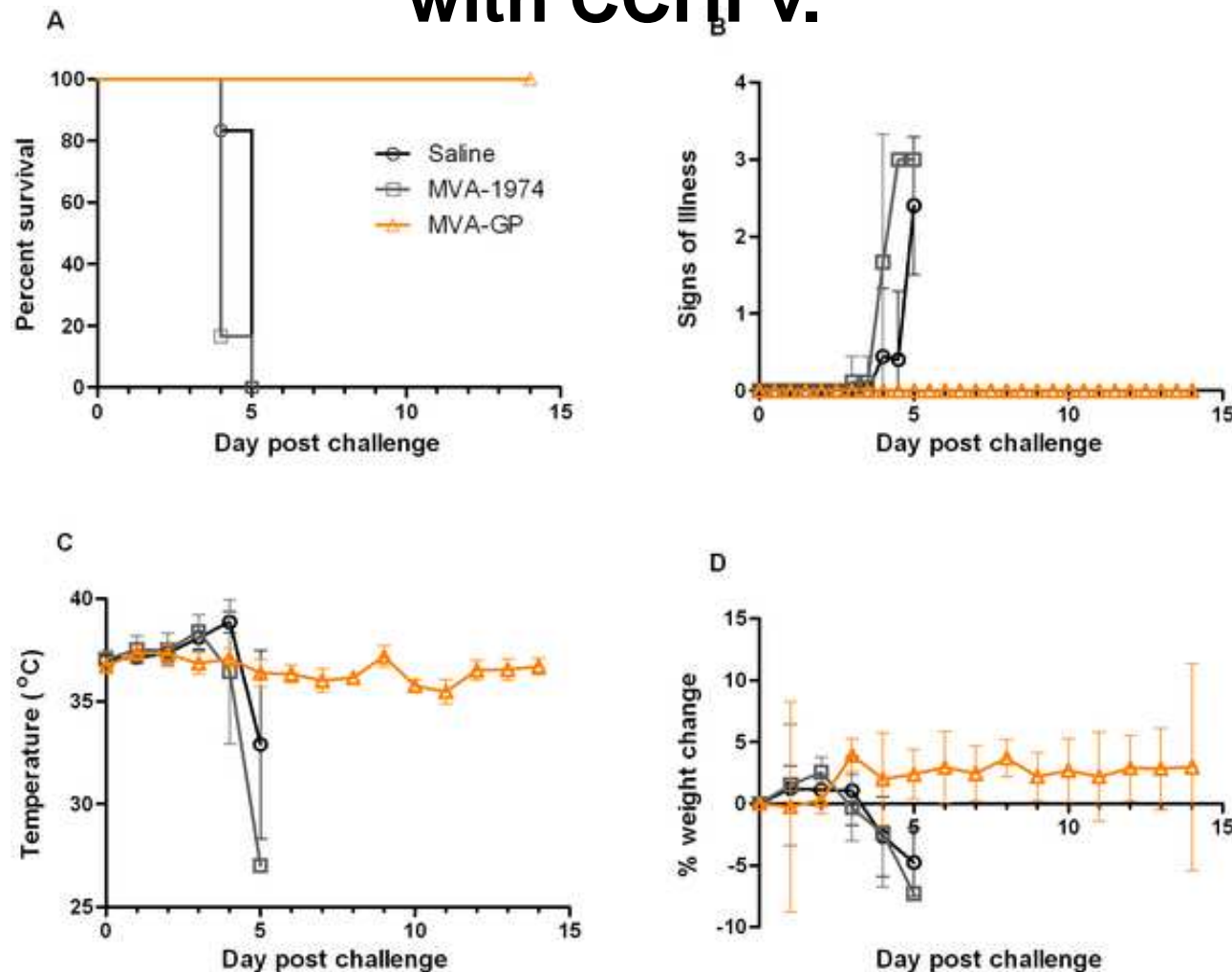
Lab at Solna



IFNAR^{-/-} and STAT-1^{-/-} Mice are sensitive to CCHFv Just with 10 Virus...



Efficacy of MVA-GP in A129 mice challenged with CCHFv.

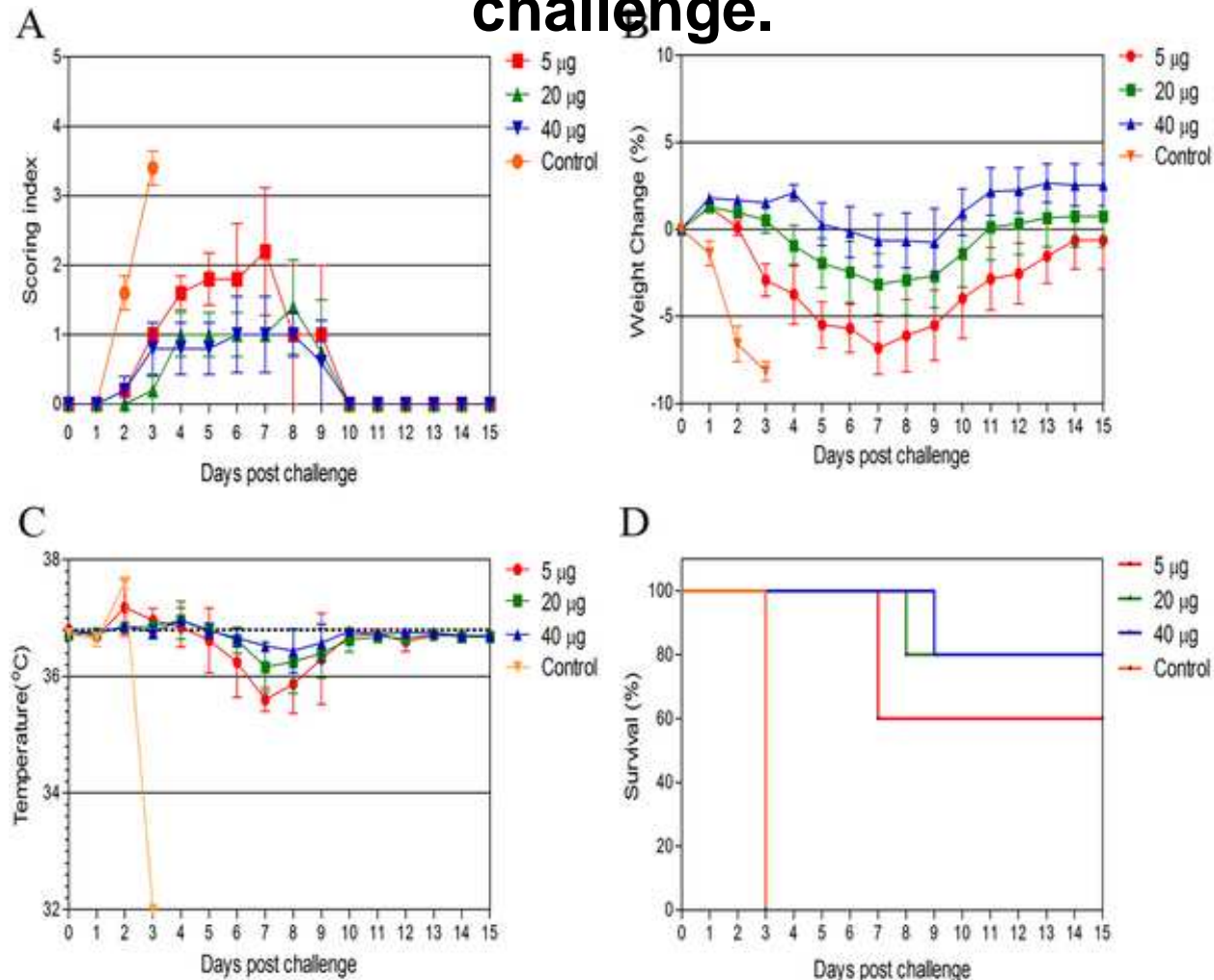


Buttigieg KR, Dowall SD, Findlay-Wilson S, Miloszevska A, Rayner E, et al. (2014) A Novel Vaccine against Crimean-Congo Haemorrhagic Fever Protects 100% of Animals against Lethal Challenge in a Mouse Model. PLoS ONE 9(3): e91516.

doi:10.1371/journal.pone.0091516

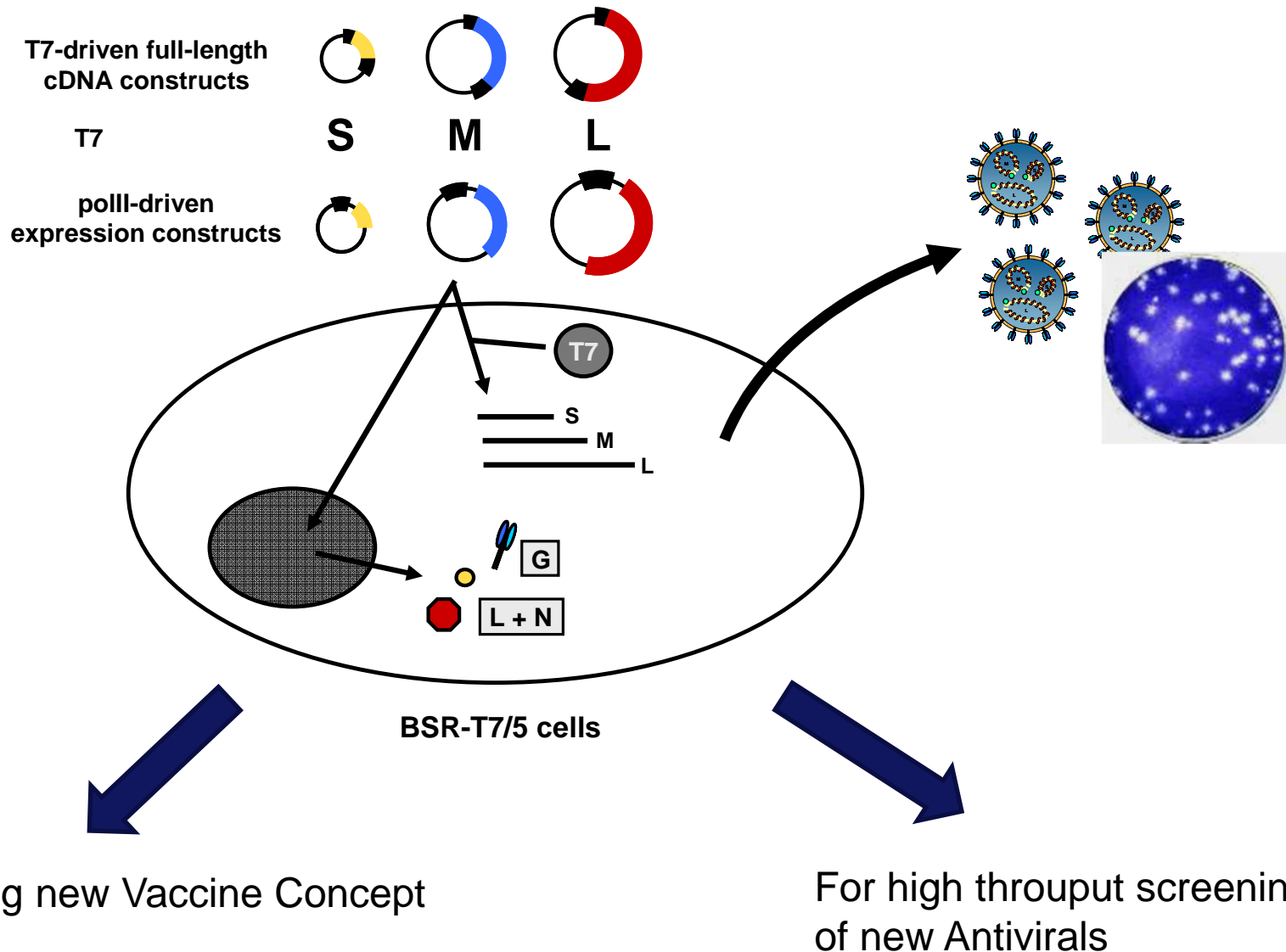
<http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0091516>

Protection of IFNAR^{-/-} mice immunized with the cell culture based vaccine against CCHF virus Turkey-Kelkit06 strain challenge.

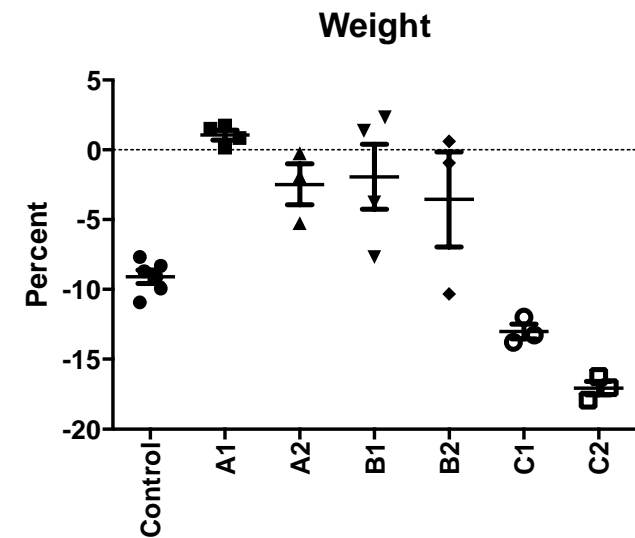
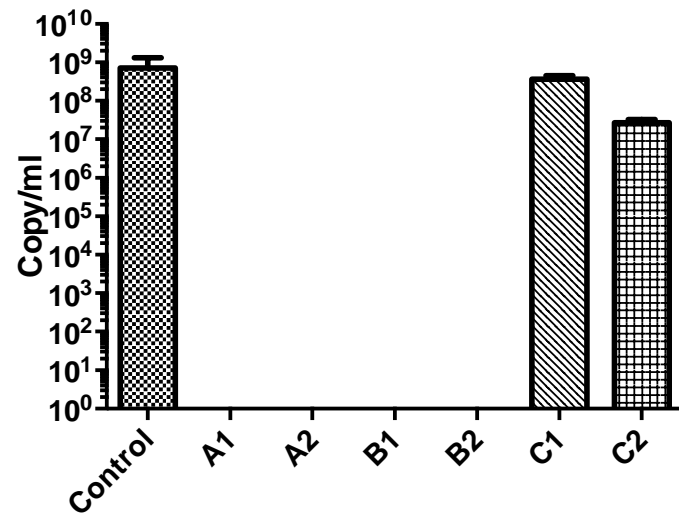
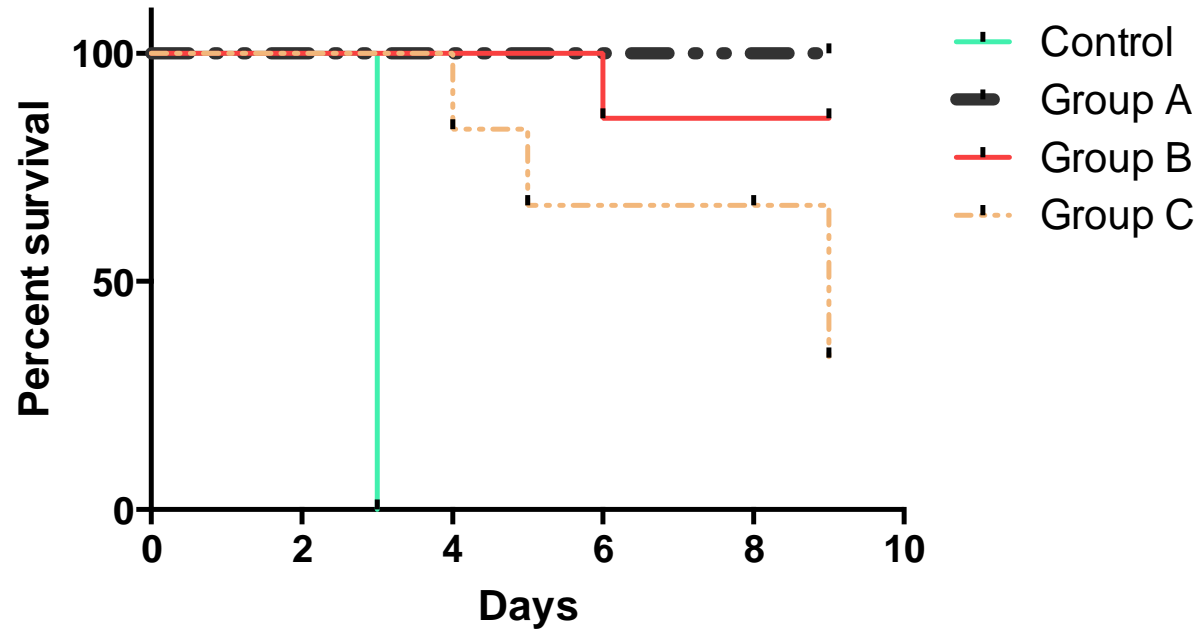


Canakoglu N, Berber E, Tonbak S, Ertek M, Sozdutmaz I, et al. (2015) Immunization of Knock-Out α/β Interferon Receptor Mice against High Lethal Dose of Crimean-Congo Hemorrhagic Fever Virus with a Cell Culture Based Vaccine. PLoS Negl Trop Dis 9(3):

Using tools (Reverse Genetic) to produce VLPs



Survival proportions: Survival of Three groups



Conclusion

Vaccine Candidates:

- **MVA**
- **Adenovirus based Vaccine**
- **VLP**
- **DNA?**
- **Inactivated Virus !?**

There is a need for Vaccine

Treatment

Ribavirin

(effective or Not?)

Maybe new one such as Favipiravir (T-705)?

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of Comments the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	ribavirin			
Mortality (RCT) Follow-up: mean 8 weeks	56 per 1000	63 per 1000 (16 to 242)	RR 1.13 (0.29 to 4.32)	136 (1 study)	⊕⊕⊕⊖ low ^{1,2}
Mortality (Observational studies) Follow-up: 1-12 months	254 per 1000	142 per 1000 (89 to 229)	RR 0.56 (0.35 to 0.9)	955 (11 studies)	⊕⊕⊕⊖ Very low ^{3,4,5,6}
Length of Hospital stay (RCT) Days in hospital Follow-up: mean 8 weeks	The mean length of hospital stay (rct) in the control groups was 6.3 days	The mean Length of hospital stay (RCT) in the intervention groups was 0.21 standard deviations lower (0.55 lower to 0.12 higher)		136 (1 study)	⊕⊕⊕⊖ very low ^{1,2}
Length of Hospital Stay (Observational studies) days in hospital Follow-up: mean 4-24 months	The mean length of hospital stay (observational studies) in the control groups was 6.4 days	The mean Length of hospital stay (Observational studies) in the intervention groups was 0.60 standard deviations lower (1.21 lower to 0 higher)		303 (3 studies)	⊕⊕⊕⊖ Very low ³

Capacity Building

Training of Medical doctors and other health workers

CCHF virus and pathogenesis, Sweden

Clinical features of CCHF, Turkey

Case reports (Group-work), Turkey

Infection control and prevention: standard and isolation precautions Turkey,

Case Definition in Turkey, Turkey

Laboratory diagnosis of CCHF, Turkey

Prognostic factors in CCHF, Turkey

Treatment of CCHF, Turkey

Evolution of CCHFv and other HF viruses - CDC

Ticks and CCHFv - Turkey)

....



W-shop 20th Oct 2011

Joint action with Turkish Public Health Agency

(Over 90 participant)

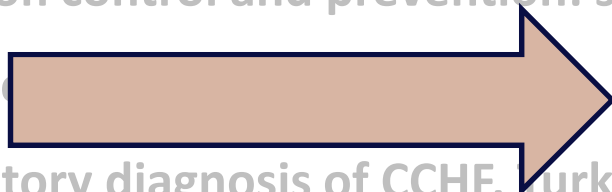
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Evolution of CCHFv and other HF viruses - CDC

Ticks and CCHFv - Turkey)

CCHF in Europe Sweden

Challenges for prevention and control of CCHF outbreaks - WHO

A new Platform for Health
Care workers from
North and West Europé
to do Training program
At Endemic Area in
Turkey during epidemic
Period

Outbreak response Joint Action with WHO/EUROPE

General overview on Outbreak Response (WHO)

Investigation of an outbreak (NICD, South Africa)

Risk assessment (WHO)

Risk matrix (WHO)

Treatment (Turkey)

Field and entomological investigation (Turkey)

Infection Control (Russia)

Outbreaks versus endemic activities (WHO)

Crises Communication (WHO)



For Clinical microbiologist- a technical w-shops

**Clinical diagnostic, Molecular diagnostic, Serology , Sample
Collection, Shipment, Biosafety issues and Waste management,
Available kits**

**Reference laboratories had opportunities to test their diagnostic tools on Clinical
samples from Turkey in Wet Lab and also evaluate the commercially available
diagnostic tools as the same time. The results were analysed and discussed
during this event (Over 30 participants from all the national (from endemic
Countries) and European ref laboratories)**

Subject for capacity building at Central ASIA

- * Training of clinical microbiologist on bedside/field diagnostic.**
- * Establish a EQA system at region**
- * Training and w-shop on Biosafety for Health care workers, Microbiologist and etc.**
- * Establish a monitoring system on survey of CCHF.**
- * Establish and co-organize of Bio-Bank and Database over CCHFV cases**
- * Build a regional center for CCHF diagnostic refernce center**
- * Etc**

Thank You

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