DENGUE

RED SPOTS OR PATCHES ON THE SKIN

RESTLESSNESS

LOSS OF APPETITE

BLEEDING FROM GUMS OR NOSE

JOINT PAIN

HEADACHES

HIGH FEVER

PAIN BEHIND EYES

NAUSEA AND VOMITING

CHIKUNGUNYA

SEVERE JOINT PAIN MAINLY IN THE ARMS AND LEGS

HEADACHES

MUSCLE PAIN

RED SPOTS OR PATCHES ON THE SKIN

HIGH FEVER

ZIKA

JOINT AND MUSCLE PAINS

BACK PAIN

MILD FEVER

HEADACHES

RED EYES

RED AND WHITE PATCHY SKIN RASH

Mousavi Nasab , Ph.D

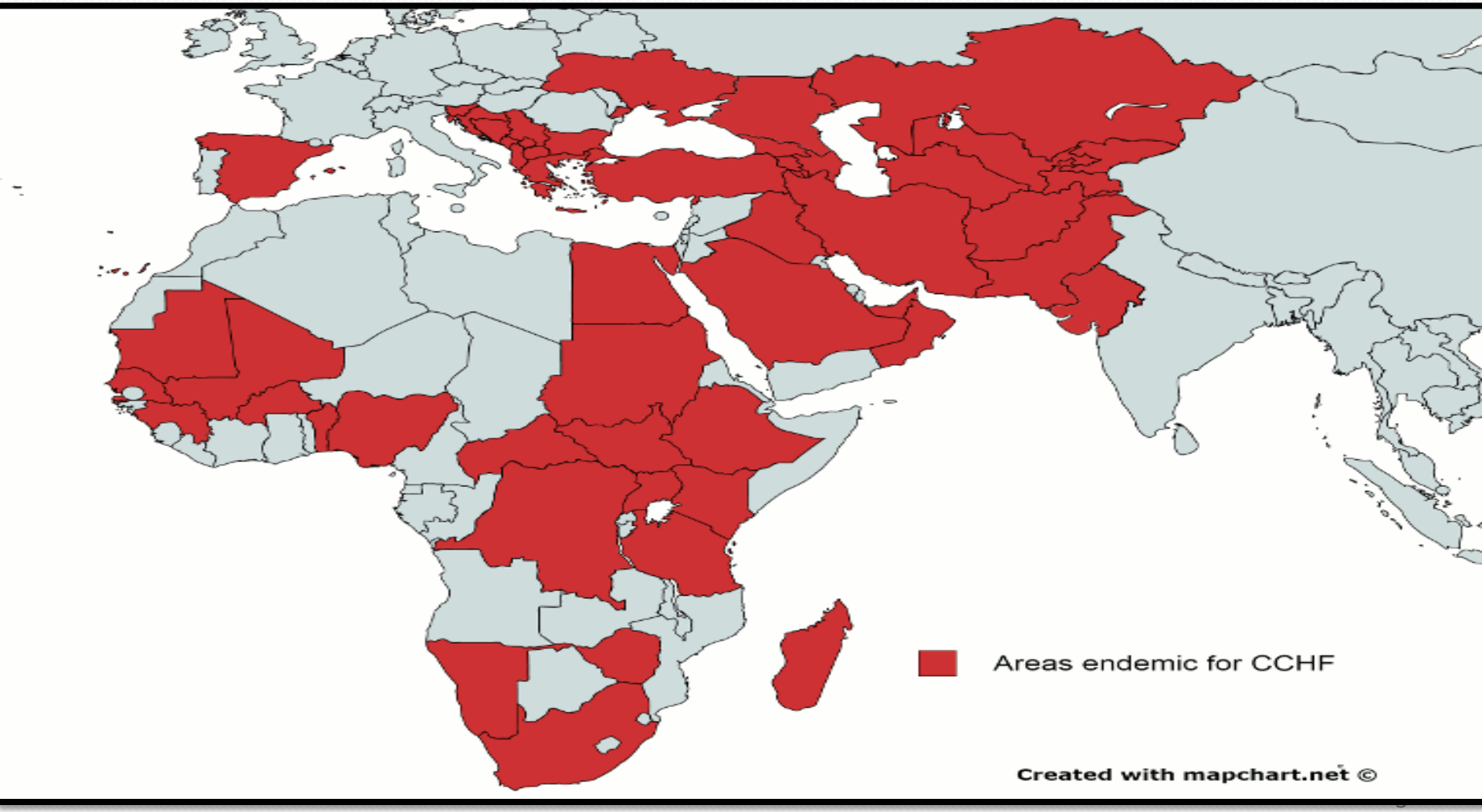
Department of arboviruses & viral hemorrhagic fevers

Pasteur Institute of Iran

Crimean-Congo hemorrhagic fever

- Crimean–Congo hemorrhagic fever (CCHF):
  - Is the **most important tick-borne viral disease** of humans
  - Is endemic across a huge geographic area:
    - From **western China** to the **Middle East** and **southeastern Europe** and throughout most of **Africa**

Geographic Distribution of CCHF



CCHF is a high-priority pathogens

- Crimean-Congo Haemorrhagic Fever (CCHF) is one of the high-priority pathogens identified in the WHO R&D Blueprint because of **its high case fatality rate**, **its potential for nosocomial outbreaks** and the **difficulties in treatment and prevention**.

Worldwide, the number of potential pathogens is very large, while the resources for disease research and development (R&D) is limited. To ensure efforts under WHO's R&D Blueprint are focused and productive, a list of diseases and pathogens are prioritized for R&D in public health emergency contexts.

A WHO tool distinguishes which diseases pose the greatest public health risk due to their epidemic potential and/or whether there is no or insufficient countermeasures.

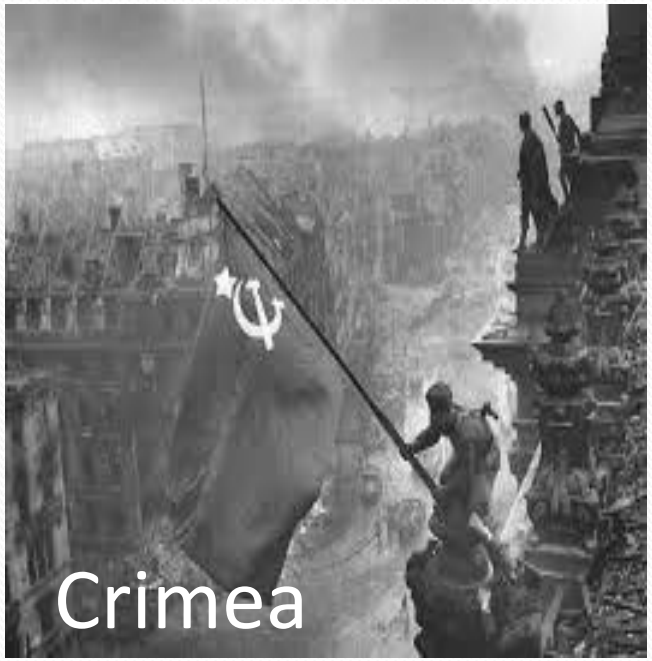
At present, the priority diseases are:

- COVID-19
- 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"*

Discovery of the virus

The disease was first described in the Crimea in 1944 and given the name **Crimean hemorrhagic fever**

When Soviet troops re-occupying the Crimean peninsula developed an acute febrile illness with a high incidence of bleeding and shock



Discovery of the virus

An investigative team was dispatched from Moscow, led by **Mikhail Chumakov**.

The researchers were quickly able to link cases of the new disease to **tick exposure**

Chumakov and his colleagues soon succeeded in proving that "**Crimean hemorrhagic fever**" (CHF) was a **tick-borne <u>viral</u> infection** by:

inoculating people with ultrafiltrates of patient serum or extracts of pooled ticks(Chumakov, 1965, 1974).

Mikhail Chumakov

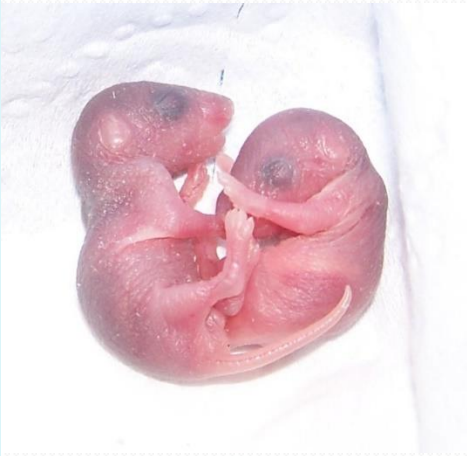
Discovery of the virus

In 1967, a breakthrough in CHF research came when **Chumakov** and his colleagues first used newborn white mice for CHF virus isolation

The resulting Drosdov strain, isolated by this method from a patient (Drosdov) became the prototype strain.

Using the suckling mouse method and immunologic assays, in 1969 **Casals** discovered that the Drosdov virus, was identical to an agent that had been isolated in the Congo in 1956 **(Congo virus)**

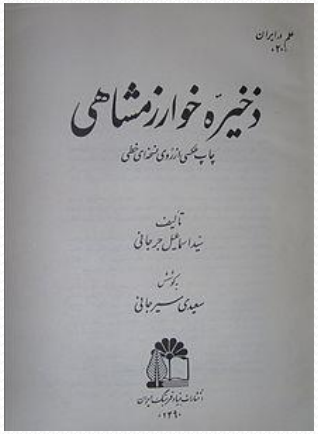
The realization lead to the new name, **CHF–Congo virus**.



History of CCHF in Iran

The **oldest known reference** to a hemorrhagic febrile illness (now considered to have been CCHF) dates to the **Zakhirayi Kharazmshahi**, written by **Jorjani** in the late **12th century**

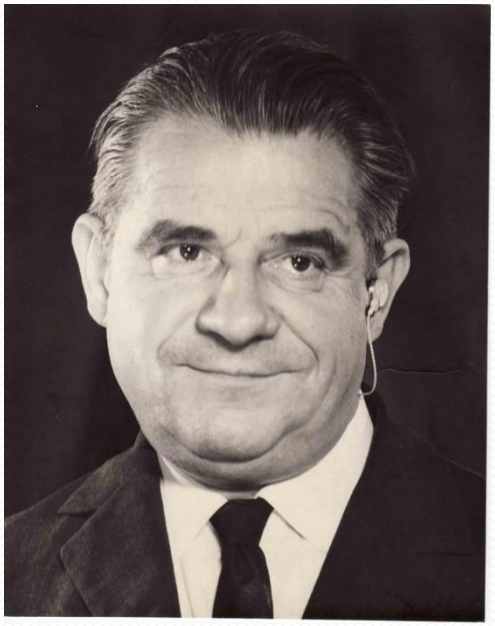
The description was of **a hemorrhagic disease** with the presence **of blood in the urine**, **rectum**, **gums**, and **abdominal cavity** and was said to be **caused by an insect bite**



History of CCHF in Iran

Crimean-Congo hemorrhagic fever in Iran was first reported in **1970** by **Chumakov,**

45 of 100 sheep sera that were sent from Tehran abattoir to Moscow reacted positively for CCHF virus infection



History of CCHF in Iran

First suspected cases of CCHF in **humans** by **Dr. Asefi** in **1974**

Report of 60 cases of hemorrhagic fever from East Azerbaijan, Iran

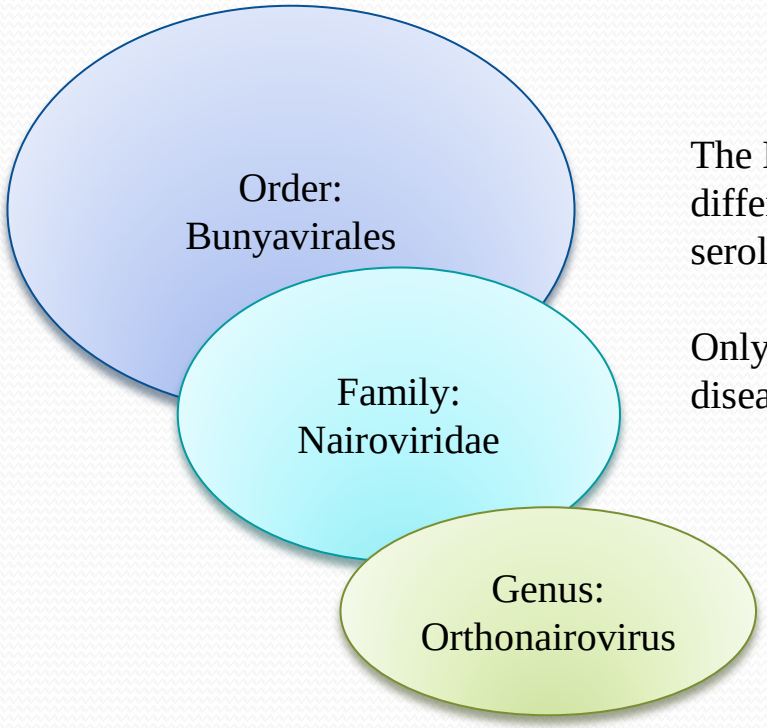
Dr. Ardoin (Pasteur Institute of Paris) and Dr. Y. Karimi (Pasteur Institute of Iran) reported more clinical cases in this area (1974-1975).

First documentation of CCHFV infection in human by **Dr. Saidi** in **1975:**

Sera of humans in northern Iran tested positive for anti-CCHFV antibodies

Dr. Sureau (Pasteur Institute of Paris) with collaboration of Pasteur Institute of Iran isolated CCHF virus from infected ticks collected from Khorassan province [north east of Iran] (1978).

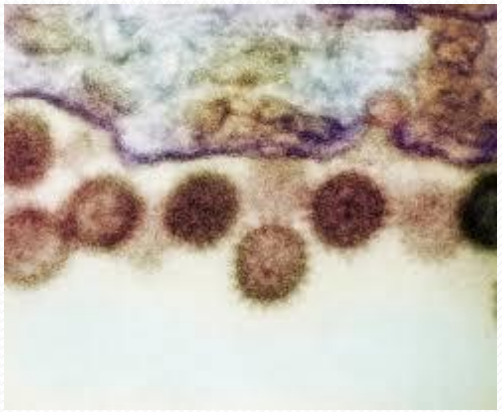
Classification of CCHFV

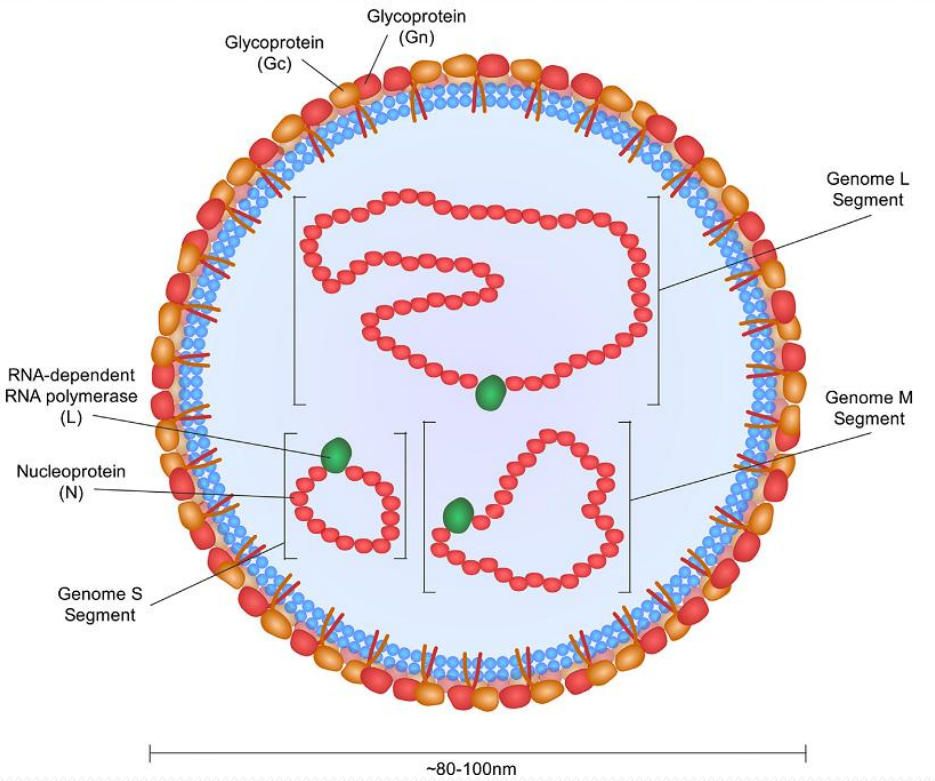


The Nairovirus genus comprises 34 different viruses divided into 7 distinct serological subgroups.

Only CCHF viruses can cause a serious disease in humans.

Structure of the CCHFV





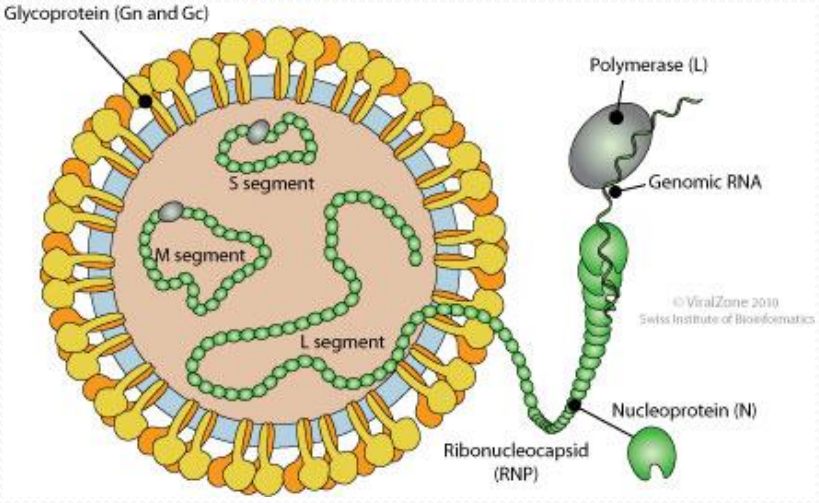
The CCHF virion is **spherical** and approximately **80–100 nm** in diameter. Its lipid **envelope** is studded with spikes consisting of the glycoproteins **G_N and G_C**, which are responsible for virion **binding** to cellular receptors. **Neutralizing antibodies** to GN and GC are produced during the course of infection

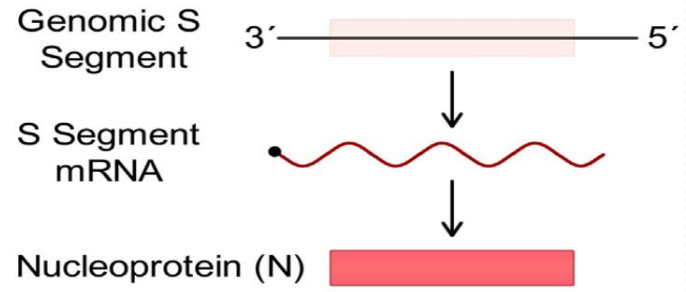
Antiviral Research 100 (2013) 159–189

Genome Organization of CCHFV

The **S-segment** is about **1.7 Kb** and contains a **single ORF** that encodes the nucleoprotein (NP) responsible for the **encapsidation** of the viral RNA

The S segment is the **most conserved** viral gene: The first priority for **molecular** diagnosis (S segment) and **Serological** diagnosis (NP) as well as **phylogenetic** analysis.





Antiviral Research 100 (2013) 159–189

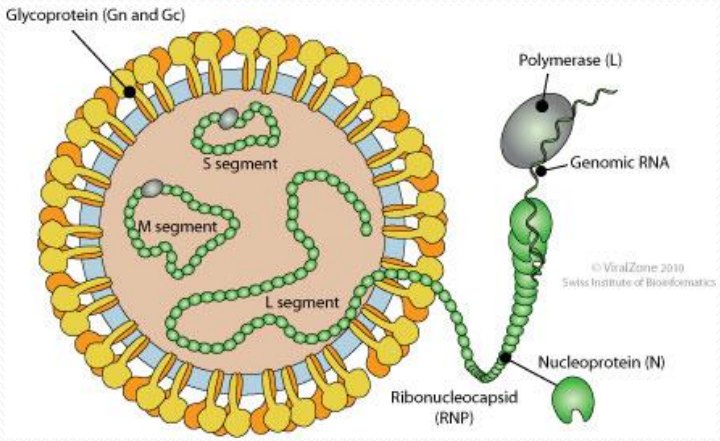
Genome Organization of CCHFV

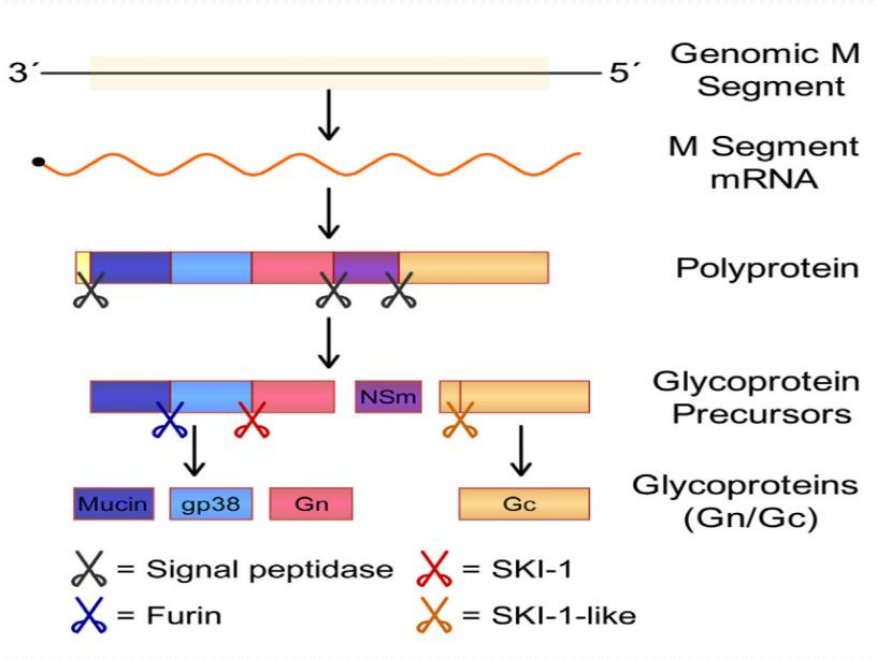
The **M-segment** is approximately **5.4 Kb** long with **a single ORF** that encodes a **precursor protein (1,684 amino acids in length**) from which two glycoproteins, G_N and G_C, are produced through **cotranslational cleavage** and **post-translational processing**, beginning in the endoplasmic reticulum (ER) and concluding in the Golgi body.

Gn performs a chaperone-like function for Gc, and must be present for correct folding to occur.

Gn and Gc are responsible for Viral attachment and entry.

Gc is the primary target-cell binding protein (nucleolin) for CCHFV and also mediates virus entry through endocytosis.



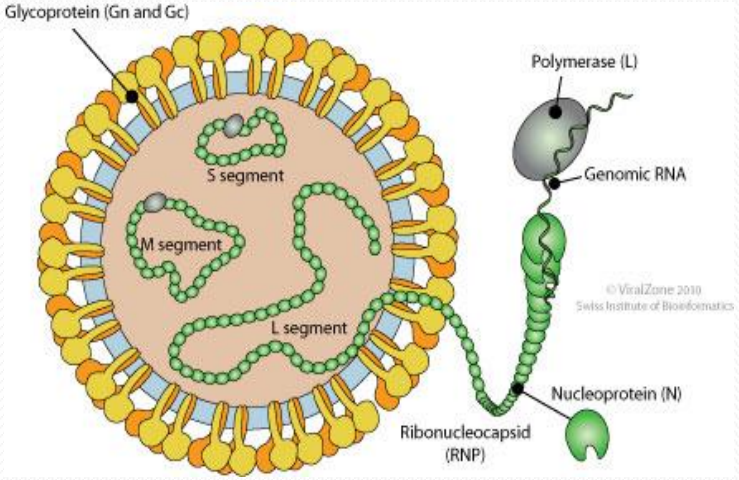


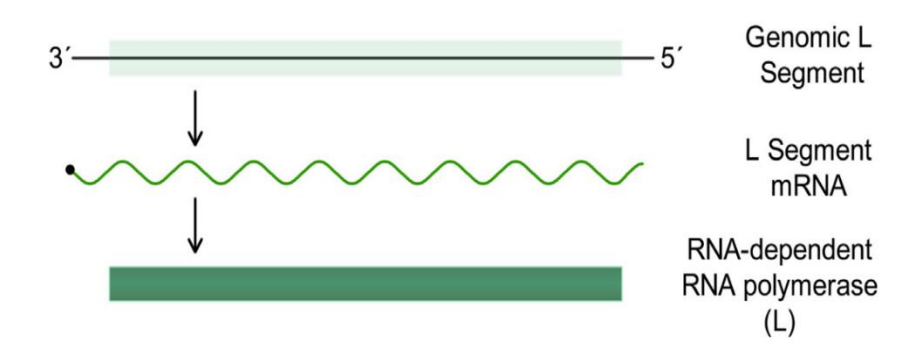
Genome Organization of CCHFV

The **L segment** is about **12 Kb** and contains **a single ORF** that encodes a **4000-amino acid polyprotein** which contains an **ovarian tumor protease (OTU) domain** near its N-terminus and a **RdRp catalytic domain** near the C-terminus.

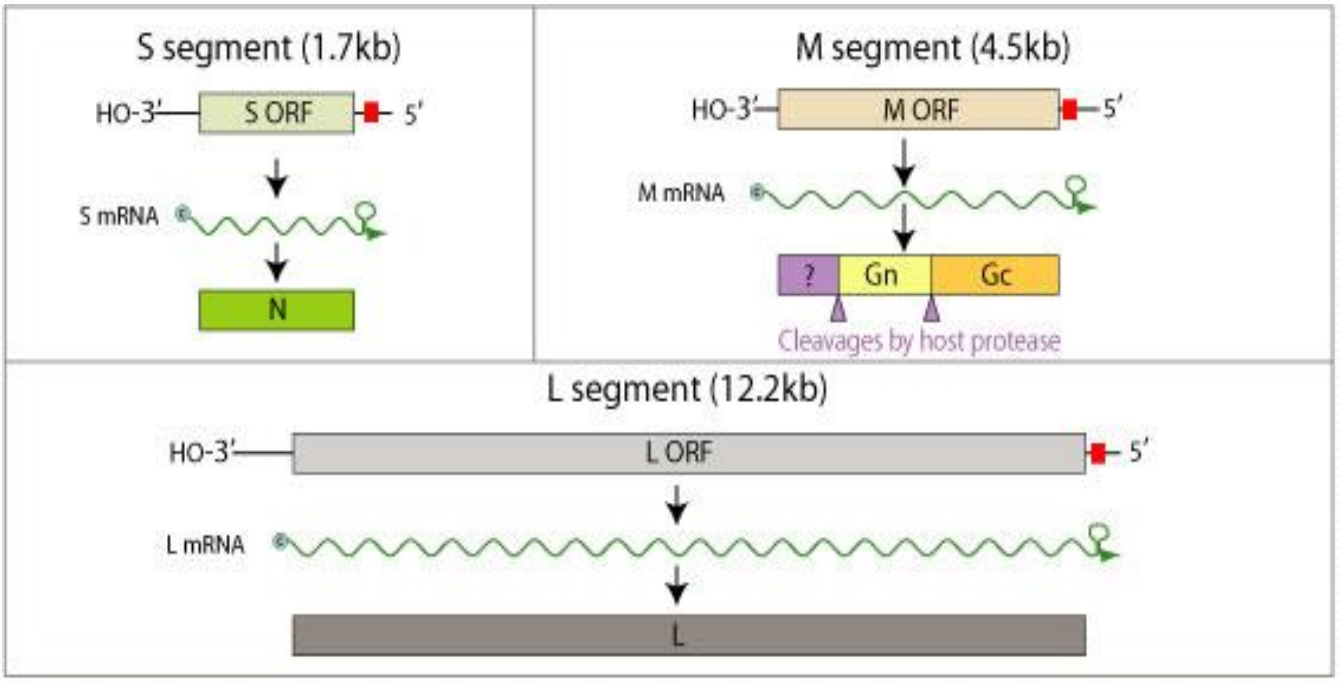
RdRp domain is responsible for viral RNA synthesis (Transcription & Replication).

OUT domain suppresses the antiviral interferon response in infected cells

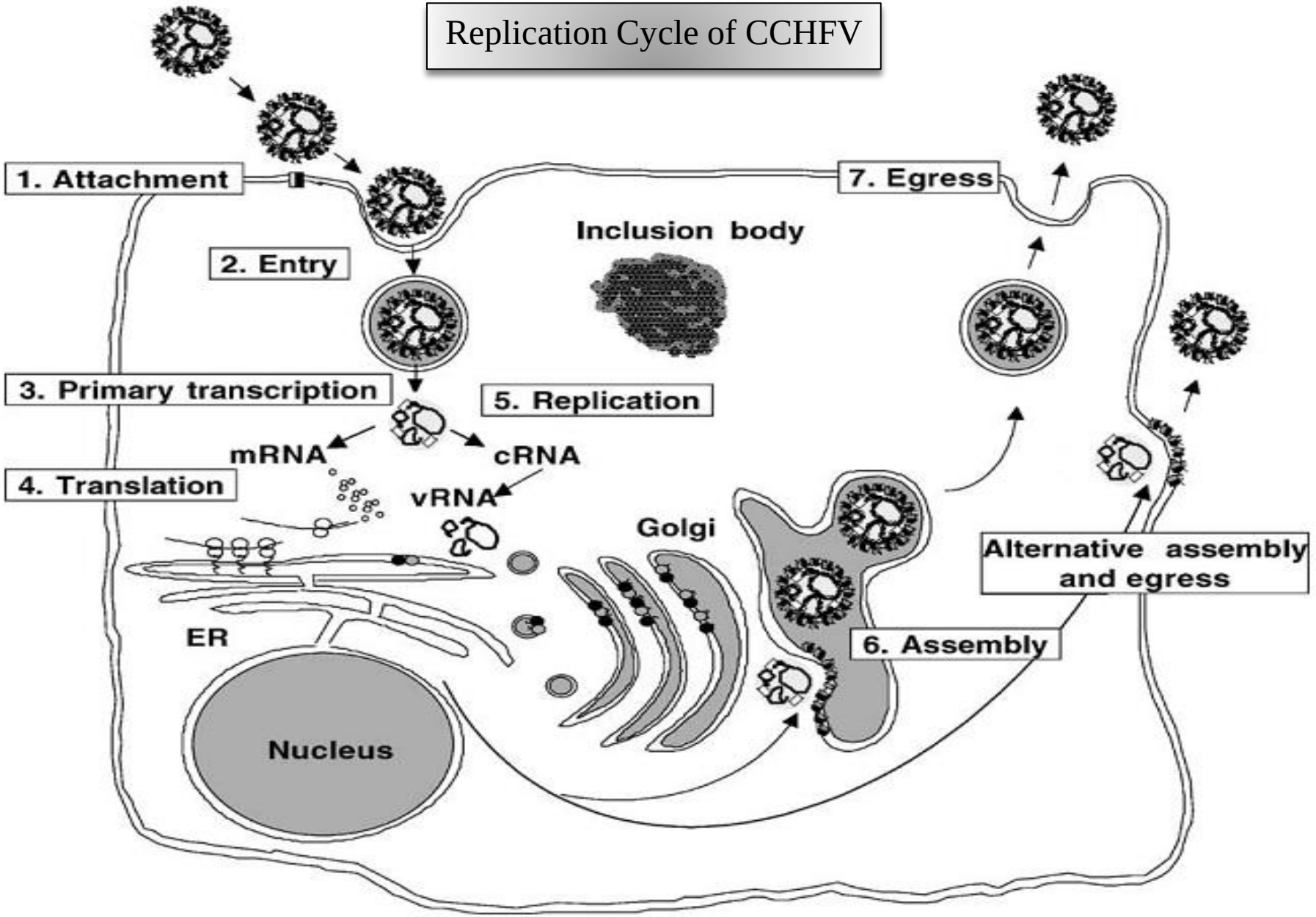




Genome Organization of CCHFV



Replication Cycle of CCHFV



Genetic diversity of CCHFV

CCHFV displays the greatest degree of sequence diversity of any arbovirus, with divergence of :

20% in S-segment--- > 8% in NP

22% in L-segment --- > 10% in L protein

31% in M-segment --- > 27% in precursor (GPC)

Genetic diversity of CCHFV

Variation in sequence diversity of the CCHFV genome arises from:

1- **Genetic drift**, results from the accumulation of copying errors by the error-prone RdRp

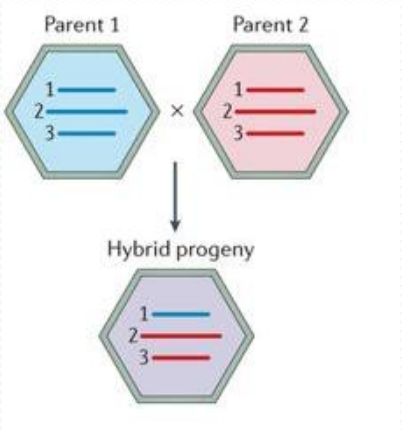
- It has been estimated that all 3 genome segments undergo **changes per nucleotide per year**

2- **Genetic recombination**

2- **Genetic reassortment**

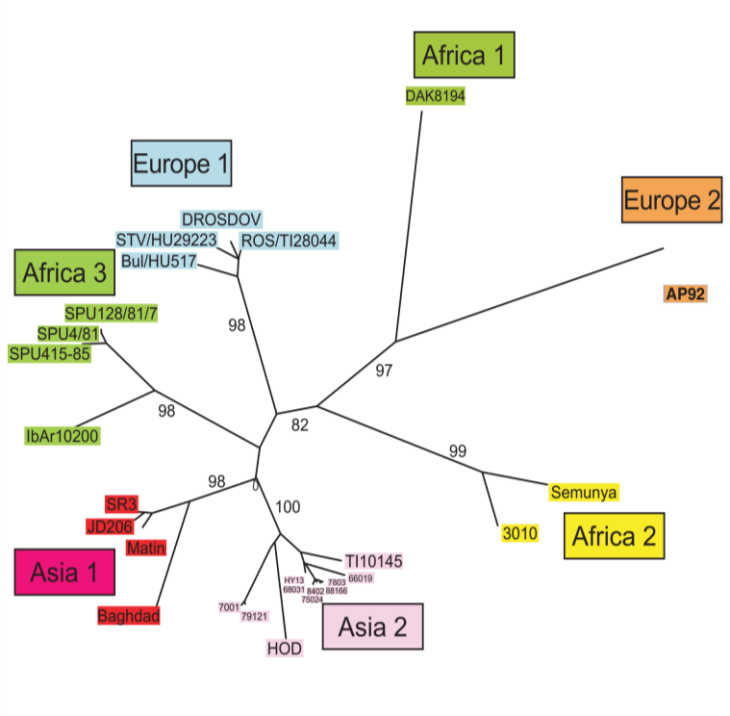
A median rate of reassortment of "**once in 100 years**" has been proposed for CCHFV

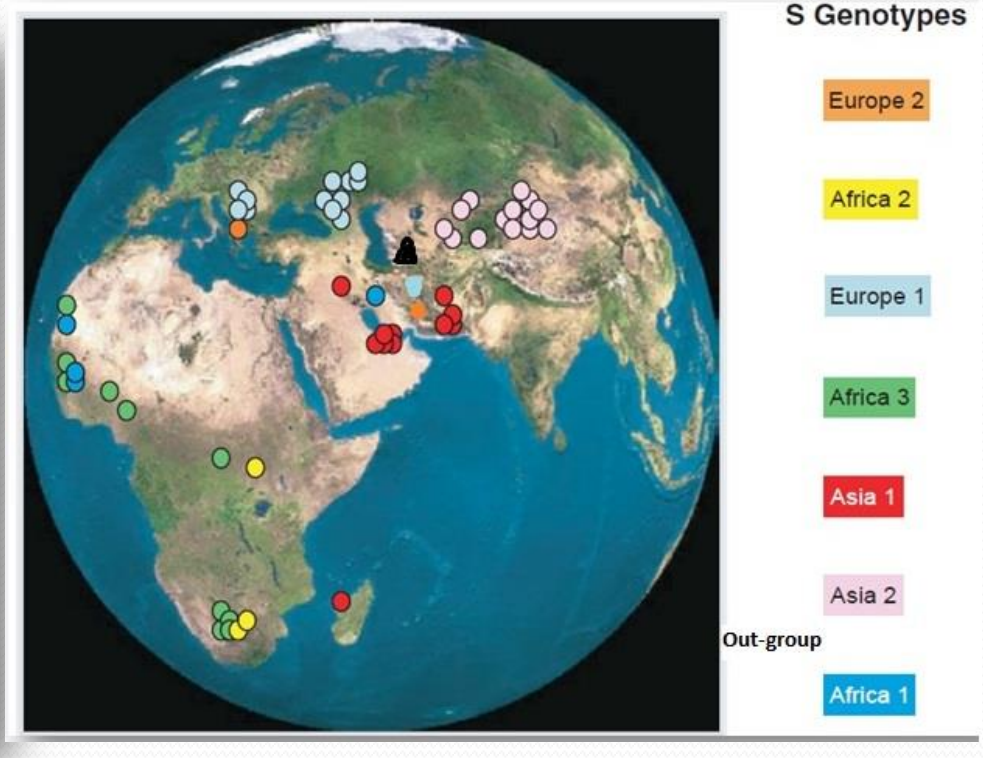
Reassortment or recombination is more likely to occur in **ticks** than vertebrate hosts



Reassortant progeny can have different phenotypes

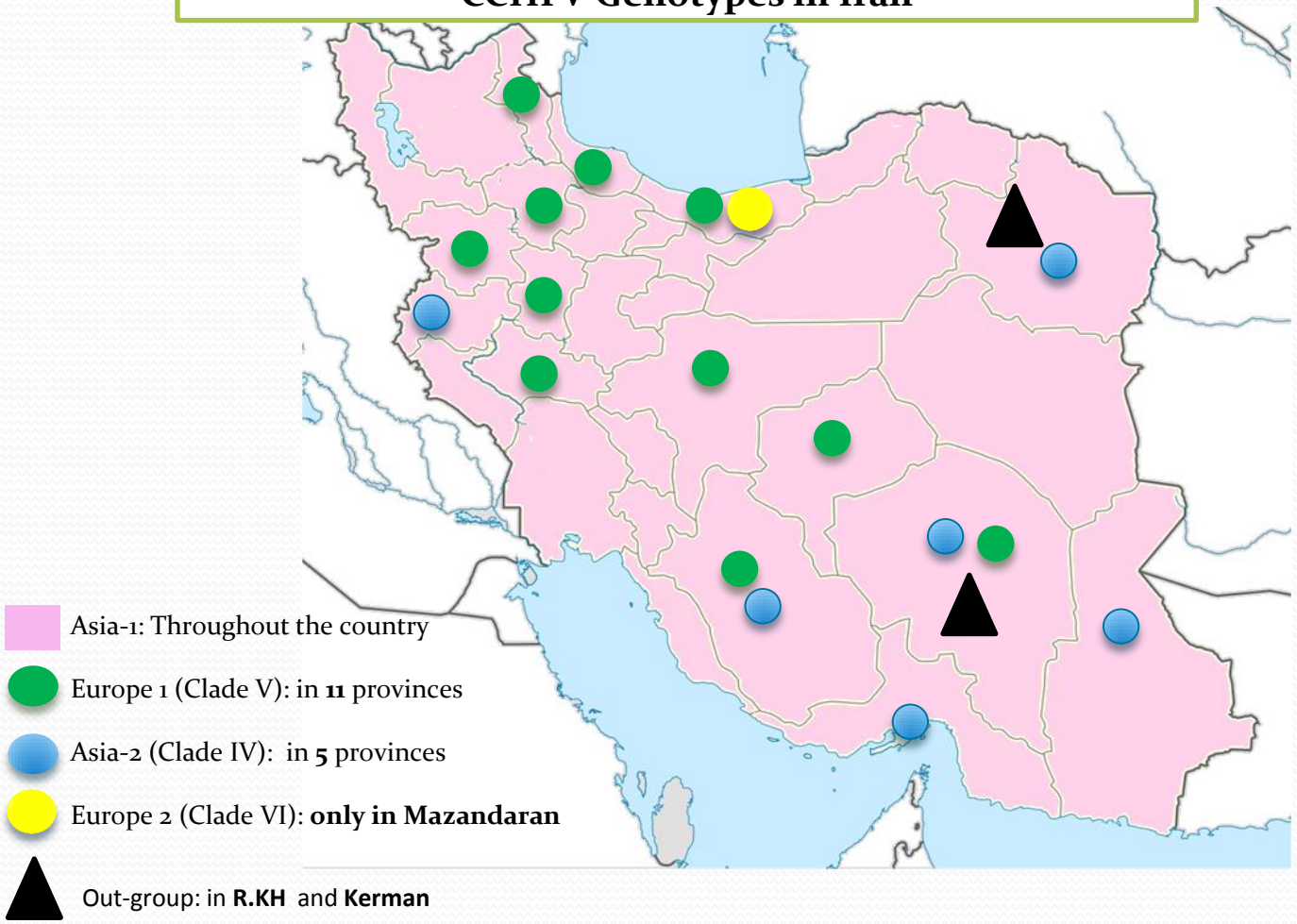
CCHFV is the most genetically diverse of the Arboviruses with 8 distinct genotypes





O. Ergonul and C. A. Whitehouse (eds.), Crimean-Congo Hemorrhagic Fever, 45–55.
© 2007 *Springer.*

CCHFV Genotypes in Iran



Maintenance and transmission of CCHFV

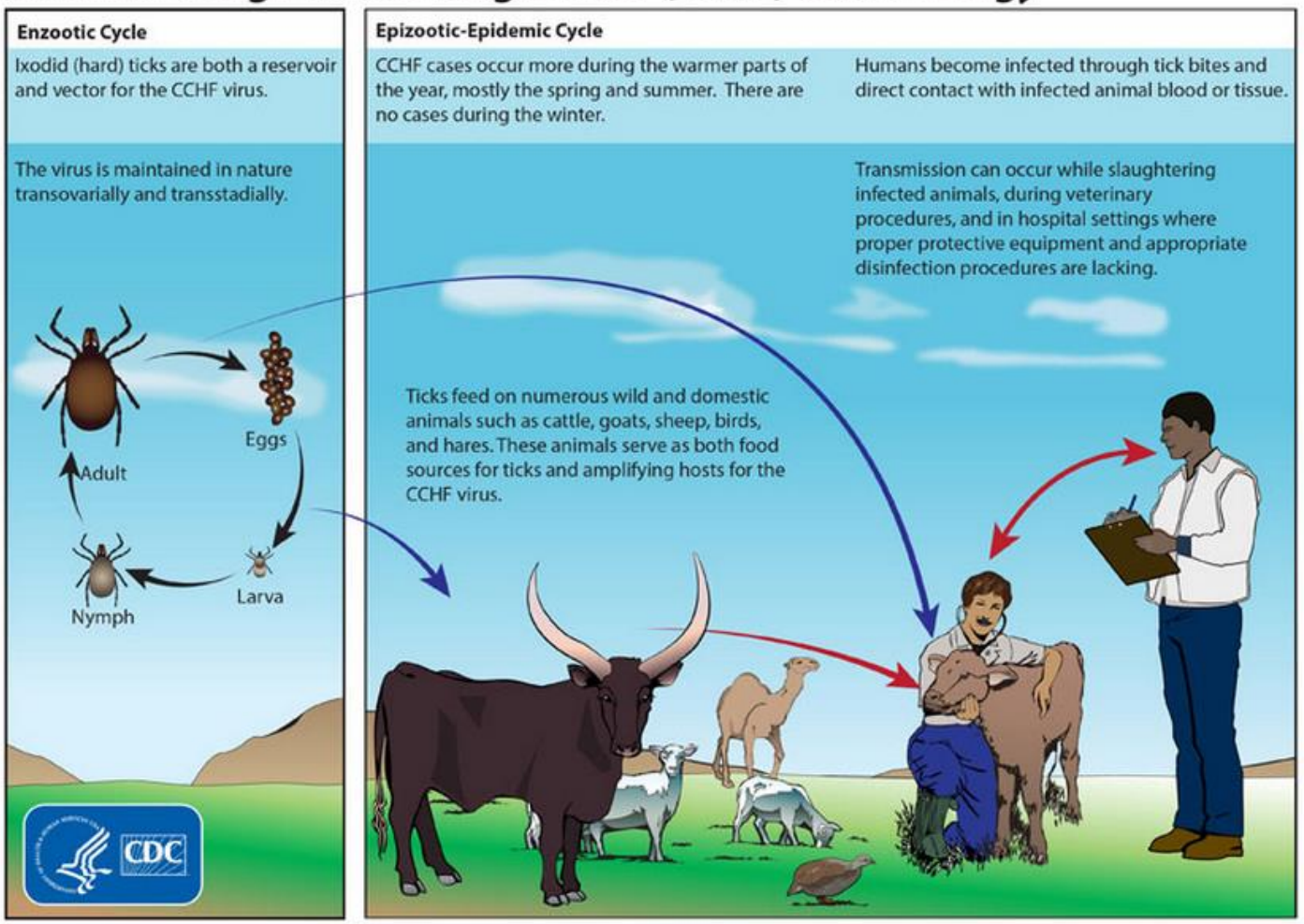
- Ticks are both **reservoirs** and **vectors** of CCHFV
  - CCHFV has been isolated from at least 31 species of ticks
  - Although **Hyalomma** spp. ticks are considered the most important in the epidemiology of CCHF, the virus has been isolated from ticks in other genera:
    - **Rhipicephalus**,
    - **Dermacentor**


Hyalomma


Rhipicephalus


Dermacentor

Crimean-Congo Hemorrhagic Fever (CCHF) Virus Ecology

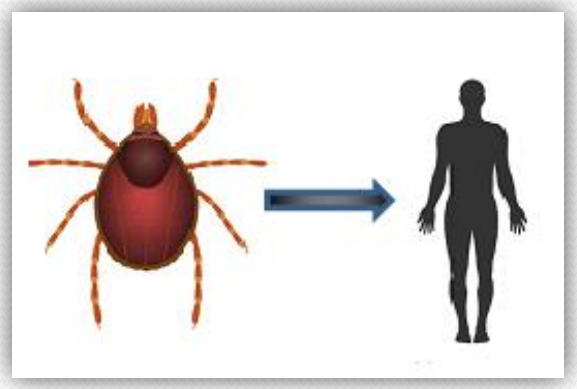


Clinical features of CCHF

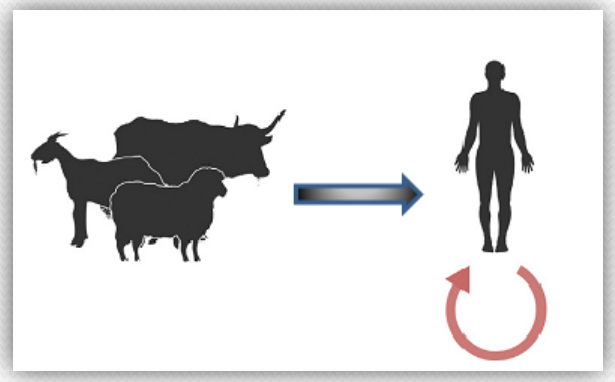
- The course of CCHF can be divided into four phases:

Clinical features of CCHF

- The length of the **incubation period** appears to depend in part on the **mode of acquisition of virus**



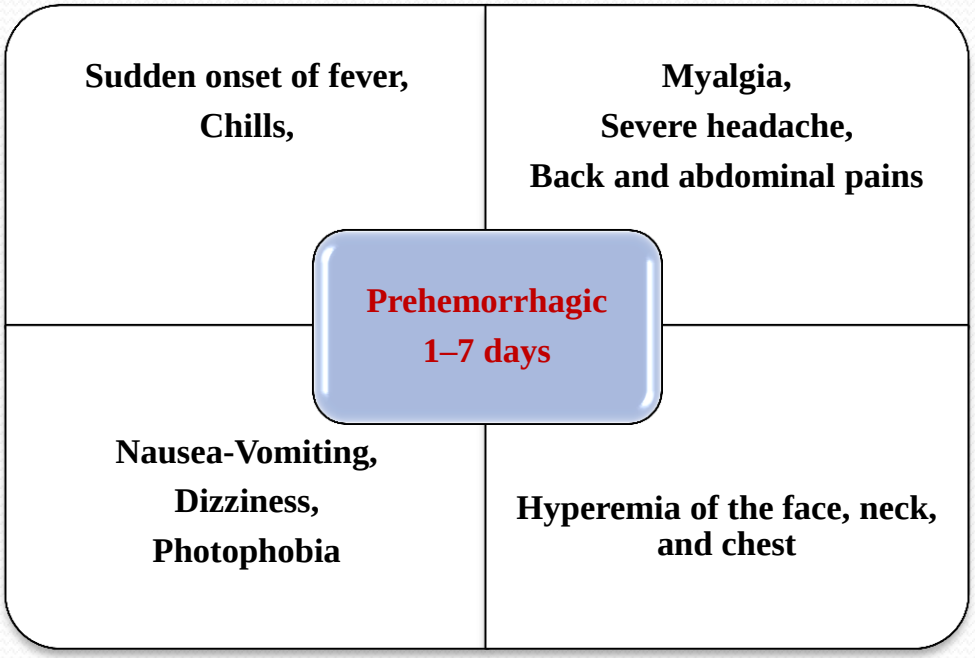
1-5 days



5-7 days

Clinical features of CCHF

Prehemorrhagic phase

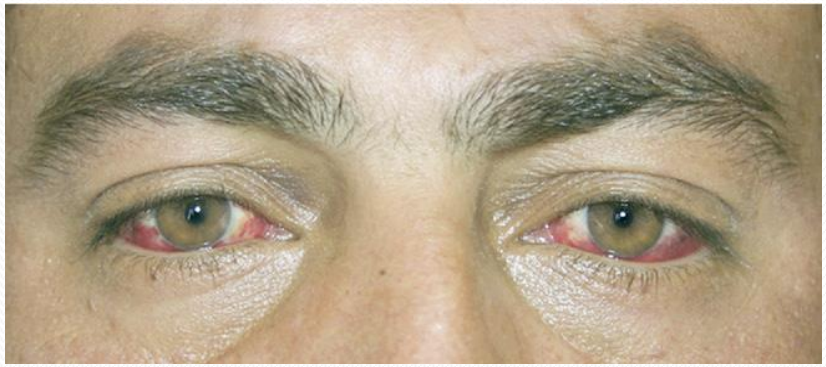


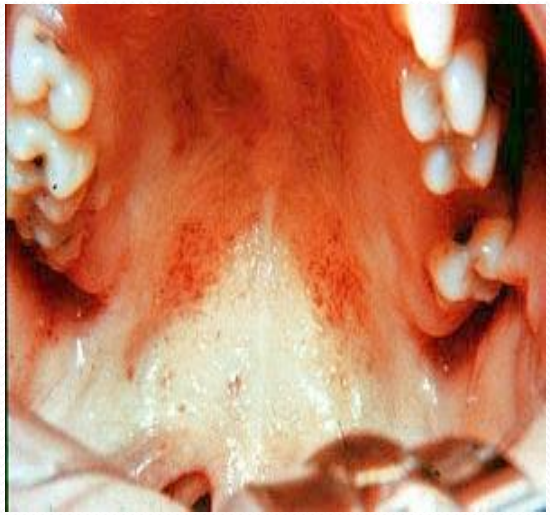
Clinical features of CCHF

Hemorrhagic phase

- Hemorrhagic period is **short**, **rapidly develops**, and usually begins at the **3rd–5th** days of disease.
- Its **most common initial manifestation is a petechial rash** of the skin, conjunctiva and other mucous membranes, which progresses to large cutaneous **ecchymoses** and **bleeding.**
- The most common bleeding sites are:
  - **Nose** (epistaxis)
  - **Gastrointestinal** tract (hematemesis, melena)
  - **Urinary tract** (hematuria)
  - **Respiratory tract** (hemoptysis)

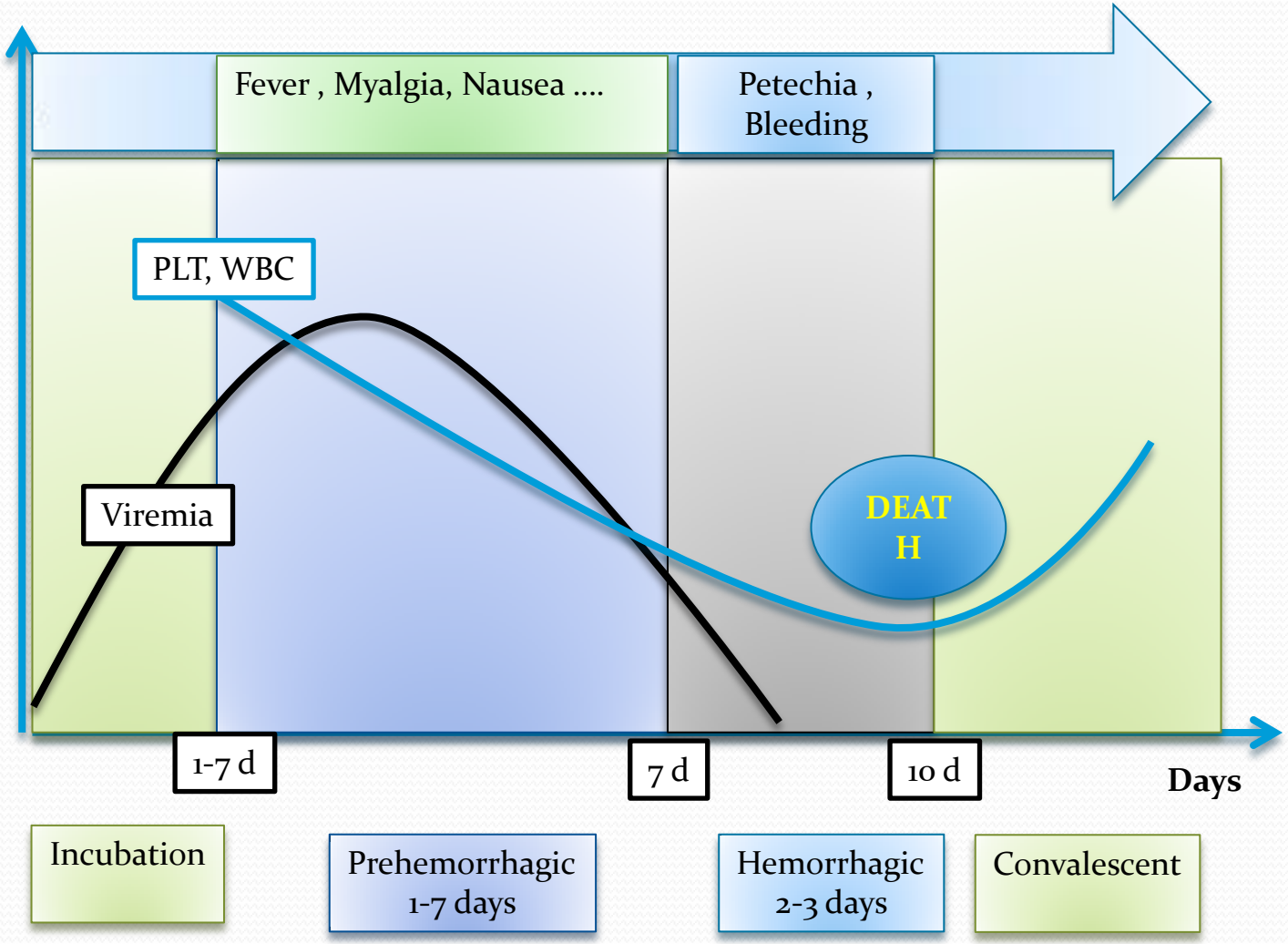
Hemorrhagic manifestations





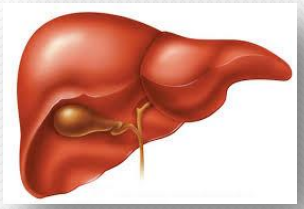
Clinical features of CCHF

- Convalescence period
  - Begins about 10–20 days after the onset of illness.
  - Full recovery may take up to a year
  - Recovering patients often experienced a variety of health problems, including :
    - Weakness,
    - Hair loss,
    - Poor appetite,
    - Hearing loss,
    - Impaired memory and vision
    - Hepato-renal insufficiency

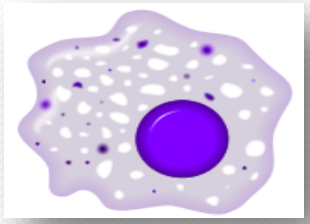

Fever , Myalgia, Nausea ....
Petechia , Bleeding
PLT, WBC
Viremia
DEAT H
1-7 d
7 d
10 d
Days
Incubation
Prehemorrhagic 1-7 days
Hemorrhagic 2-3 days
Convalescent

Pathogenesis of CCHF

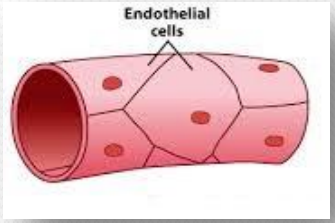
Hepatocytes



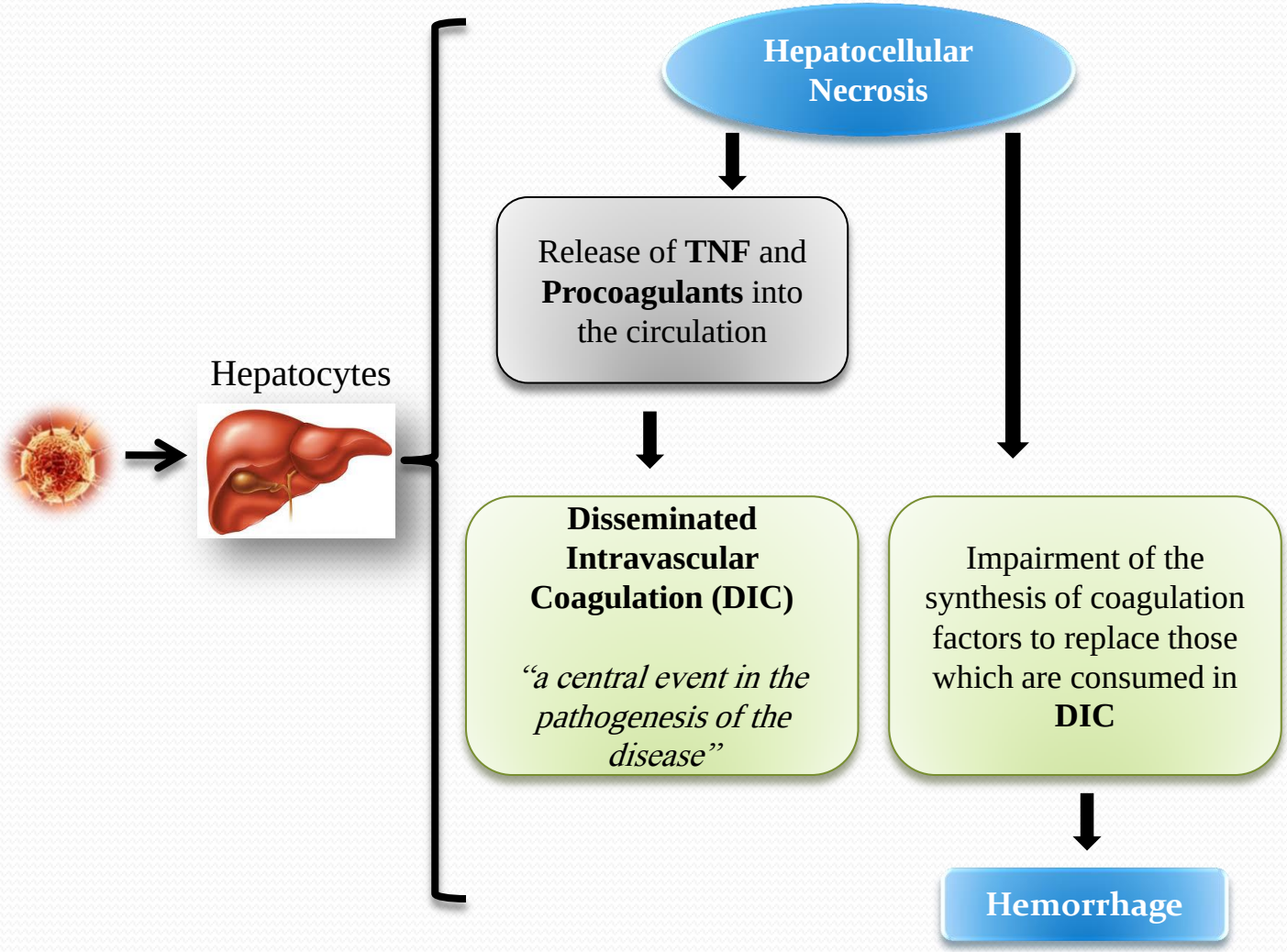
Macrophages & DCs



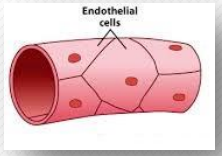
Endothelial Cells



*Are **major targets** of **virus infection***


Hepatocellular Necrosis
Release of **TNF** and **Procoagulants** into the circulation
Hepatocytes
Disseminated Intravascular Coagulation (DIC)
"a central event in the pathogenesis of the disease"
Impairment of the synthesis of coagulation factors to replace those which are consumed in **DIC**
Hemorrhage

Endothelial Cells



Widespread infection of endothelium

Capillary dysfunction

hemorrhagic diathesis
and
generation of a petechial rash

Treatment of CCHF

- Most CCHFV infections are either **asymptomatic** or result in a **nonspecific febrile illness** that does not require hospitalization or specific therapy.
- In small percentage of infection that develop to severe disease treatment is needed:

General supportive measures

Antiviral therapy

Antibody therapy

Treatment of CCHF

General supportive measures
is the essential part of the case management:

1. **Blood volume replacement**
With **intravenous fluids**

2. **Blood transfusion**
In the cases with significant hemorrhage

3. Countering coagulation abnormalities
by
administration of fresh frozen plasma and platelets,

Treatment of CCHF

- Due to its broad-spectrum activity there have been attempts to use it in the treatment of many different viral infections, particularly those with no proven therapeutic options
- The efficacy of ribavirin in the treatment of CCHF is debatable.
- Some reports have suggested its **prophylactic efficacy** for but it has not been approved for use in CCHF by FDA or European Medicines Agency (EMA).

Treatment of CCHF

Favipiravir

- Favipiravir is approved in Japan for the treatment of influenza virus infections but has shown promise against other highly pathogenic RNA viruses, including Ebola and Lassa.
- Favipiravir treatment was effective in suppressing viral replication and preventing mortality following CCHFV infection, even when treatment was started 48 hours PI.

Treatment of CCHF

Antibody therapy

- Anti-CCHF immune globulin, prepared from the plasma of disease survivors, was recommended as therapy in:
  - Crimea
  - Bulgaria
  - South Africa
  - Turkey

Vaccine

Approaches for human vaccines against CCHFV.

Vaccine type	CCHFV antigen	Immunity		Protection in preclinical model
		Antibody	T cell	
Inactivated virus (mouse brain)	Whole virus	✓	✓	?
Inactivated virus (cell culture)	Whole virus	✓	NT	✓[2]
Modified Vaccinia Ankara (MVA)	M segment	✓	✓	✓[3]
	S segment	✓	✓	X
DNA vaccine	M segment	✓	NT	NT
	Gc, Gn and NP	✓	✓	✓[4]
Transgenic plant	Glycoprotein	✓	NT	NT
Protein	Gn glycoprotein	✓	NT	X
	Gc glycoprotein	✓	NT	X
Adenovirus	M segment	✓	✓	X
Virus-like particles	Gc, Gn and NP	✓	✓	✓[5]

Key: NT, not tested; ✓, positive results; X, negative results; ?, unknown.

S.D. Dowall et al. / Vaccine 35 (2017) 6015–6023

Sever Fever with Thrombocytopenia Syndrome virus (SFTSv)

Sever Fever with Thrombocytopenia Syndrome virus

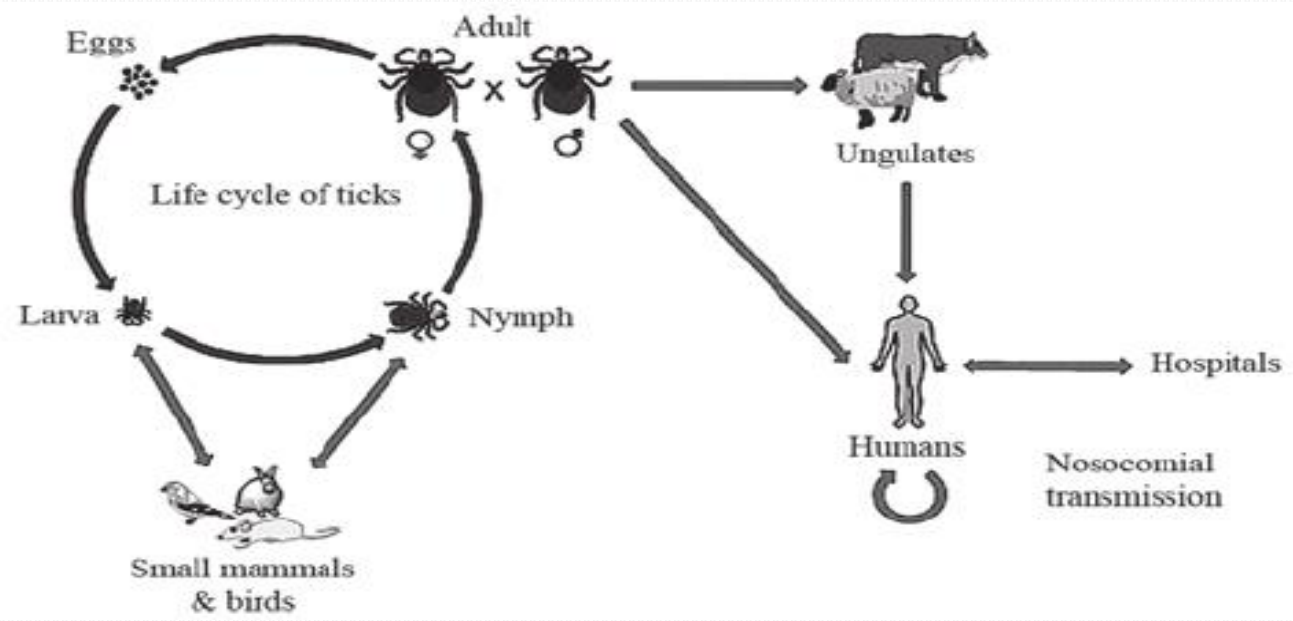
- The causative agent of SFTS is SFTSV, which is a tick-borne virus in the family *Bunyaviridae*, genus *Phlebovirus*. The first isolation of SFTSV was from an acute patient's blood in 2010 ; more strains of SFTSV were isolated later in China, Japan, and Korea

- SFTSV comprises a segmented, negative-strand RNA that includes large (L), medium (M), and small (S) segments

- SFTS is a spherical particle with a lipid bilayer envelope and a diameter of ~100 nm; it contains a tripartite single-stranded negative-sense RNA genome

Sever Fever with Thrombocytopenia Virus

- *Tick –borne virus*
- Vector: Ticks: *Haemaphysalis longicornis as the predominant vector*

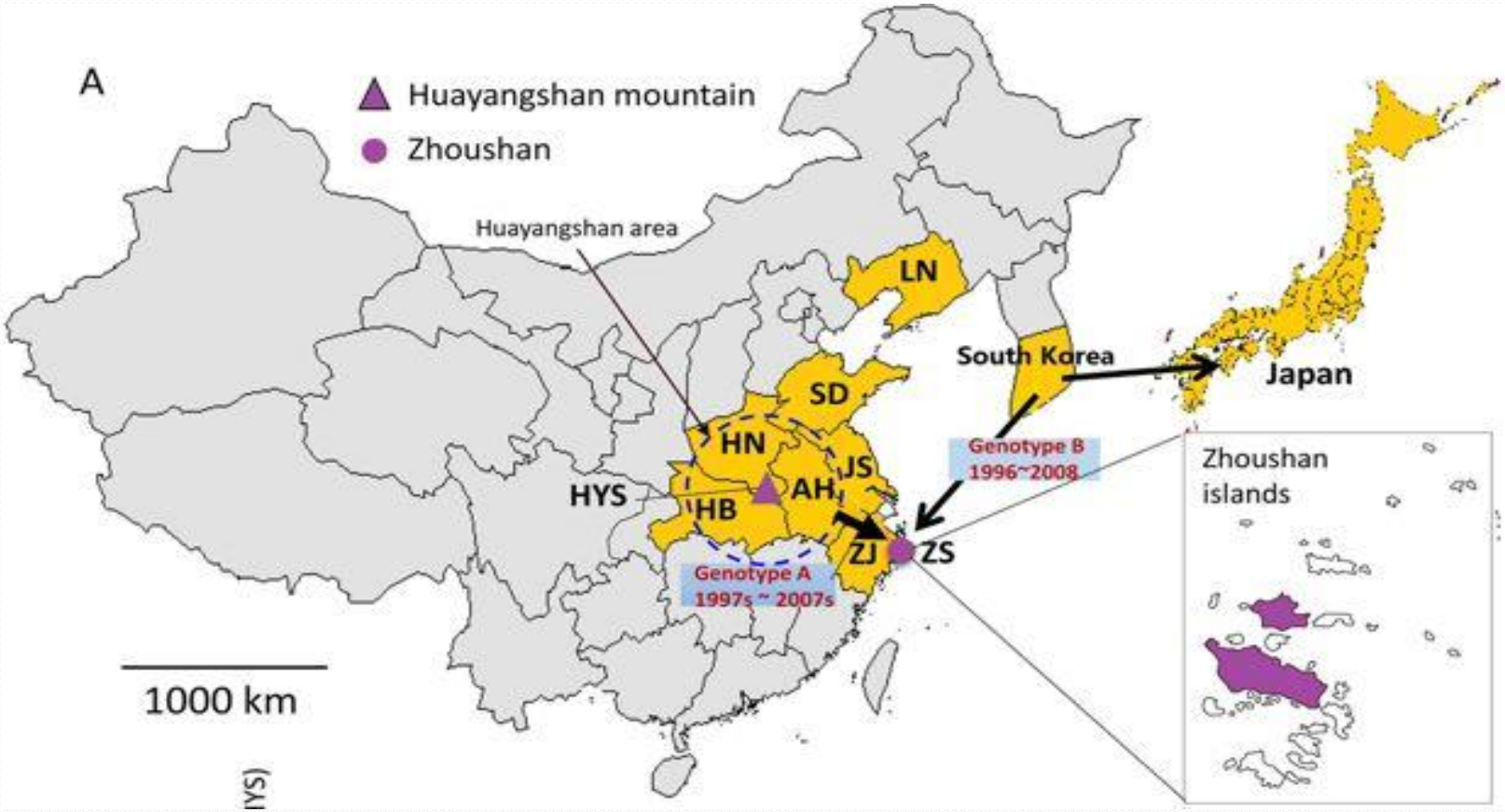


Sever Fever with Thrombocytopenia Virus

- H. longicornis is endemic to the Asia-Pacific region and has a broad host range, including wild and domestic mammalian and avian species

- Currently, Japan and South Korea reportedly exhibit high mortality rates of 27% and 23.3%, respectively. In contrast, SFTSV in China reportedly has a markedly lower mortality rate of 6.18%

Geographical distribution :
China, Japan, Korea



The disease is a severe hemorrhagic fever with very high fatality

Clinical signs and symptoms

- Fever
- Leukopenia (low white blood cells)
- Thrombocytopenia (low platelet count)
- Gastrointestinal disorders (vomiting and diarrhea)
- Hemorrhaging
- Multiple organ failure
- Death (on average 12% fatality rate and as high 30% in some areas)

Clinical characteristics in SFTS patients

- Clinical symptoms of SFTSV infection, such as high fever and thrombocytopenia, were generally reported with a 7–14 (average of 9) day incubation period
- Besides high fever and thrombocytopenia, the main clinical manifestations include gastrointestinal disorders, leukocytopenia, and hemorrhagic tendency
- Generally, the SFTS clinical course is characterized by three distinct periods based on disease progression: fever stage, multiple-organ dysfunction (MOD) stage, and convalescent stage.
- . Additional clinical aspects of SFTS include substantial elevation of serum levels of alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), creatinine kinase myocardial band fraction, and increased activated partial thromboplastin time (aPTT)

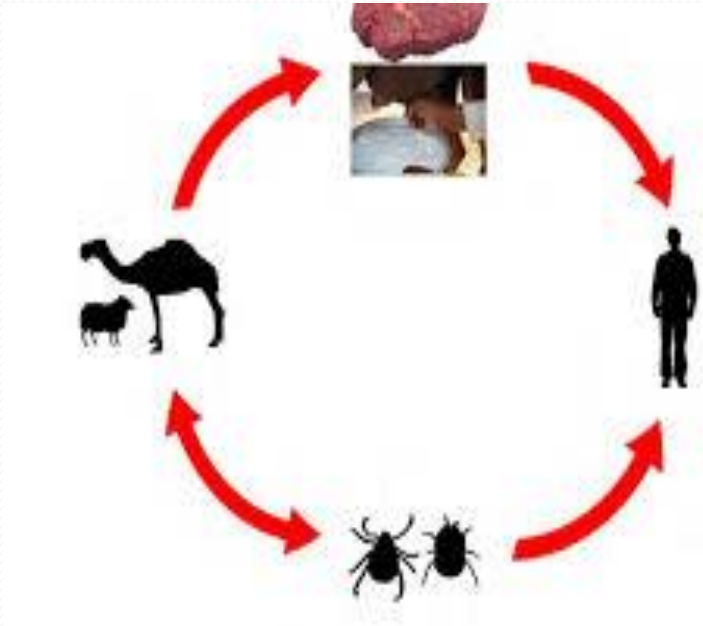
Treatment

- Administration of ribavirin, steroids, and/or plasma exchange in human patients

- T-705 (Favipiravir) therapeutic in Japan suggest that this drug may be a good candidate for the treatment of SFTSV infection

Alkhurma Hemorrhagic Fever virus (AHFV)

- Tick-borne virus

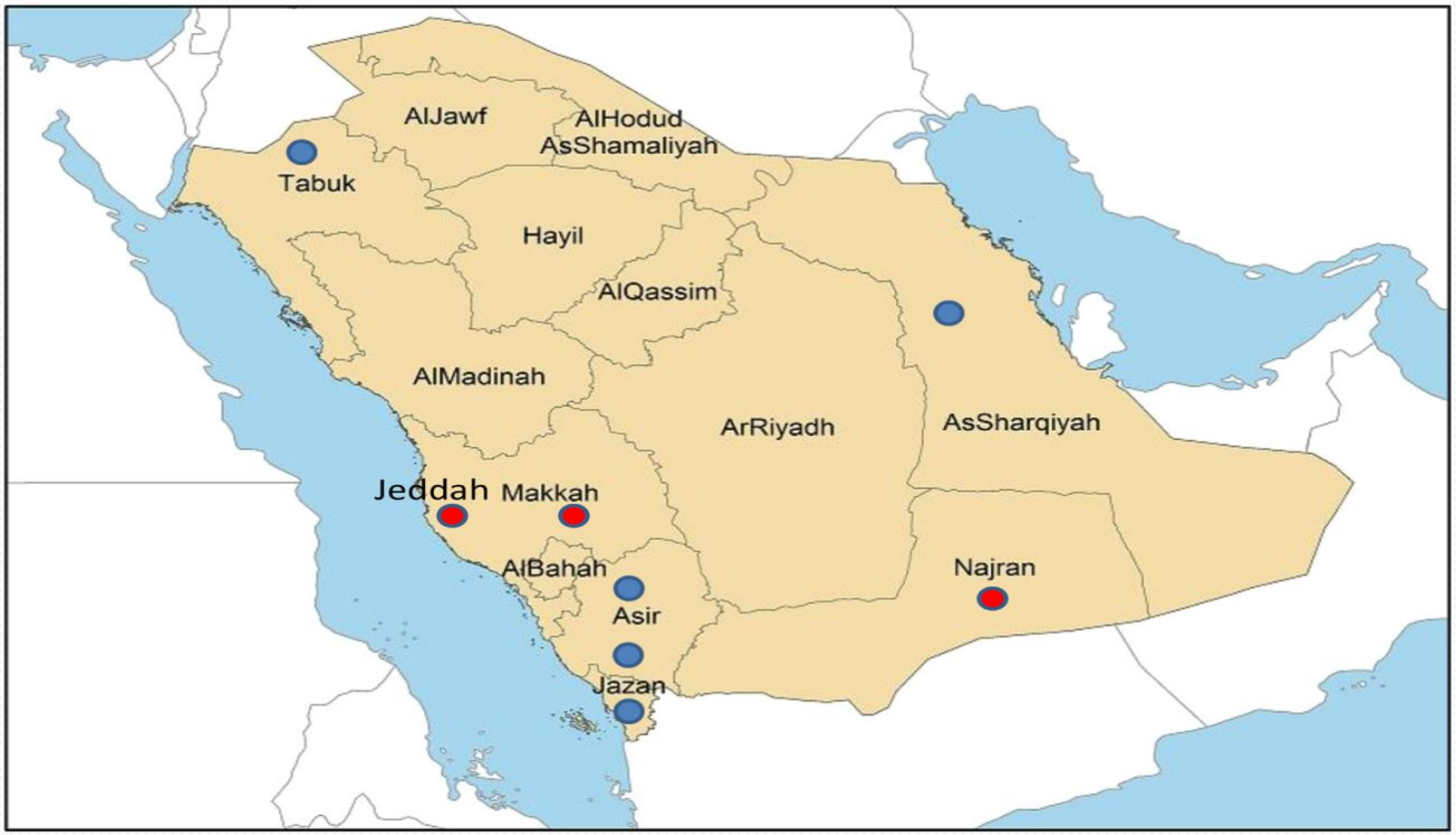


- Route of Infection: tick bite , consumption of raw milk, exposure of infected blood of slaughtered animals

Alkhurma Hemorrhagic Fever virus (AHFV)

- A new virus causing hemorrhagic fever was reported in the Kingdom of Saudi Arabia (KSA) in 1995
- AHFV is a member of the tick-borne encephalitis group, belonging to the genus Flavivirus of the family Flaviviridae.
- It was concluded that AHFV and KFDV are likely to be descendants from a common ancestor and represent two genetic subtypes of the same virus species

Alkhurma


AlJawf
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Hayil
AlQassim
AlMadinah
ArRiyadh
AsSharqiyah
Jeddah
Makkah
AlBahah
Asir
Jazan
Najran

Clinical presentations

- fever, headache, generalized body aches, arthralgia, anorexia, vomiting, leucopenia, thrombocytopenia, elevated liver enzymes, Other presentations included: hepatitis (100%), hemorrhagic manifestations (55%), and encephalitis (20%) a high case fatality rate of up to 25%

Spread of AHFV

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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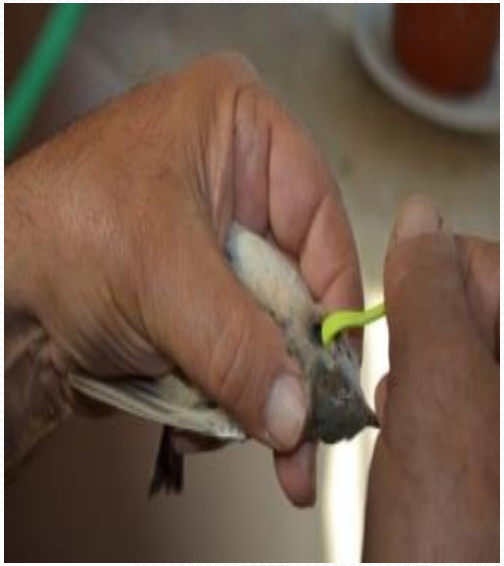
Dispatch

Alkhurma Hemorrhagic Fever Virus RNA in *Hyalomma rufipes* Ticks Infesting Migratory Birds, Europe and Asia Minor



Ticks on migratory birds found to carry newly discovered hemorrhagic fever virus

Press release
1 June 2018

In a new study, researchers at Uppsala University and other institutions have identified genetic material from the recently identified Alkhurma hemorrhagic fever virus in the tick species Hyalomma rufipes. The discovery was made after thousands of ticks were collected from migratory birds captured in the Mediterranean basin. The results indicate that birds could contribute to spreading the virus to new geographical areas.

Diagnostic

- The ability of this virus to induce hemagglutination after treatment with trypsin has potential for use as a serological and functional test for the diagnosis of AHFV.

- Polymerase chain reaction (PCR) amplifcation of a 220-bp genome fragment is used for the identifcation of AHFV

- by using the bufycoat than by using plasma or serum samples for the detection of AHFV RNA by real-time RT-PCR.

TREATMENT

- There is no specifc antiviral agent to treat AHFV. In previous reports, patients received supportive care, including intravenous fuids, and when indicated, ionotropic support, blood and fresh frozen plasma transfusions, mechanical ventilation, and anti-microbial therapy for secondary infections.


Thanks for your kind
attention